Nanotechnology in the Life Sciences

Anand Krishnan · Balasubramani Ravindran · Balamuralikrishnan Balasubramanian · Hendrik C. Swart · Sarojini Jeeva Panchu · Ram Prasad *Editors*

Emerging Nanomaterials for Advanced Technologies

Springer

Nanotechnology in the Life Sciences

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Nano and biotechnology are two of the 21st century's most promising technologies. Nanotechnology is demarcated as the design, development, and application of materials and devices whose least functional make up is on a nanometer scale (1 to 100 nm). Meanwhile, biotechnology deals with metabolic and other physiological developments of biological subjects including microorganisms. These microbial processes have opened up new opportunities to explore novel applications, for example, the biosynthesis of metal nanomaterials, with the implication that these two technologies (i.e., thus nanobiotechnology) can play a vital role in developing and executing many valuable tools in the study of life. Nanotechnology is very diverse, ranging from extensions of conventional device physics to completely new approaches based upon molecular self-assembly, from developing new materials with dimensions on the nanoscale, to investigating whether we can directly control matters on/in the atomic scale level. This idea entails its application to diverse fields of science such as plant biology, organic chemistry, agriculture, the food industry, and more.

Nanobiotechnology offers a wide range of uses in medicine, agriculture, and the environment. Many diseases that do not have cures today may be cured by nanotechnology in the future. Use of nanotechnology in medical therapeutics needs adequate evaluation of its risk and safety factors. Scientists who are against the use of nanotechnology also agree that advancement in nanotechnology should continue because this field promises great benefits, but testing should be carried out to ensure its safety in people. It is possible that nanomedicine in the future will play a crucial role in the treatment of human and plant diseases, and also in the enhancement of normal human physiology and plant systems, respectively. If everything proceeds as expected, nanobiotechnology will, one day, become an inevitable part of our everyday life and will help save many lives.

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Preface

Recent years, the world has perceived the rise of nanotechnology, a fascinating field that creates numerous divisions of the scientific community. The book covers a broad spectrum of the scientific fields such as synthesis techniques, various innovative characterization techniques, and growth mechanisms of nanomaterials, physics and chemistry of nanomaterials, diverse functionalization methods as well as their applications in biological, therapeutic, energy, food and environmental science. Also, it focuses on the applications of nanostructured materials, integrative applications such as nano and microelectronic sensor devices, as well as agriculture and environmental remediation applications. This book comprises a collection of chapters on advances in functionalized nanomaterials and discusses the early stages of development of functionalized nanostructures, including a look at the future of 2D nanomaterials and 3D objects. Further, it includes a chapter on nanomaterial research developments, highlighting work on the life-cycle analysis of nanostructured materials and toxicity aspects. The contents of this book will prove useful for researchers and professionals working in the field of nanomaterials and green technology. Researchers, in the field of nanotechnology from entrants to specialized researchers, in a number of disciplines ranging from biology, chemistry and materials science to engineering and manufacturing in both of academia and industry sectors. The book targets scientists, researchers, academicians, graduates and doctoral students working in biological sciences and waste management.

Our sincere gratitude goes to the contributors for their insights on applications of various nanomaterials in industrial and medical sector.

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Chapter 1
An Insight on Emerging Nanomaterials for the Delivery of Various Nutraceutical Applications for the Betterment of Heath

T. Karpagam, Balasubramanian Balamuralikrishnan, B. Varalakshmi, A. Vijaya Anand, and J. Sugunabai

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1.1 Introduction

An ancient Siddha medicine aphorism "unave marundhu, marundhe unavu" which means food as medicine, medicine as food well emphasizes the importance of diet for disease-free living. The role of food components in inhibiting disease and health enhancement is becoming more apparent to the researchers as well as consumers (Palzer 2009). The relationship between diet and health, and awareness on foods, from a wide range of sources, that either inherently contains health-enhancing active ingredients or included via fortification is important (Taneja and Singh 2012). Thus, there is a demand for a balanced diet and functional food products that focus on specific health benefits. Consumption of functional ingredients enriched foods keeps the body in good health. Diets rich in essential nutrients along with regular exercise decrease threats related to many diseases and maintain body weight. The case of age-related diseases, such as malignancy (e.g., gastrointestinal cancer), cardiovascular diseases, and diabetes, is more prevalent with the increase in life expectancy of humans. Escalating the use of food products from plants delays the development of these chronic diseases, and various health organizations all over the world recommend this. Plant-derived food products show a positive effect on the reduction of chronic diseases due to the presence of phytoconstituents. These are nonnutritive secondary metabolites with widespread biological functions. As bioactive metabolites, these phytochemicals ensure low effectiveness in comparison with pharmaceutical products. However, if regularly ingested in the diet, a perceptible long-term physiological effect can result without side effects (Shampa Sen and Yashwant Pathak 2016). These bioactive components are beneficial to our health and exploited for nutraceutical application. De Felice (1995) defined nutraceuticals as "food or a part of food that provides medical or health benefits, which include prevention and treatment of diseases." The term nutraceutical exists between foods and drugs, and it arose from the combination of nutrition and pharmaceuticals and was framed by Stephen L. DeFelice (Fig. 1.1), in the year 1989 (Kalra 2003). This concept is in modern food science, and the area is beyond the diet, but before the drugs (El Sohaimy 2012).

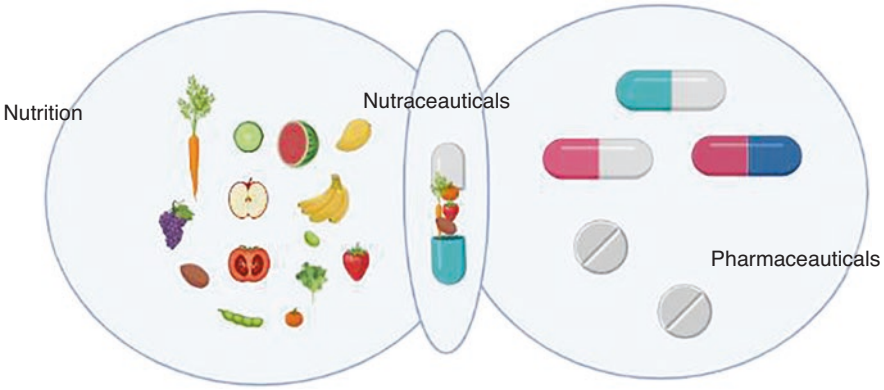


Fig. 1.1 Stephen L. DeFelice definition of nutraceuticals

1.1.1 Role of Nutraceuticals

Nutraceuticals are dietary supplements which deliver nutrients to the body. They are made accessible within a nonfood medium by supplementing phytoconstituents in the health/food product. Nutraceuticals enhance human health by introducing different dosages of active compounds from food in a higher quantity than the amount that can be by the consumption of regular food. Nutraceuticals provide resistance against several diseases and thus contribute significantly to the therapeutic performances. According to the theory of nutritional therapy, the nutraceuticals function by cleansing the body, evading deficiencies due to lack of protective food, reestablishing healthy food practices, and thus restoring healthy absorption of nutrients.

1.1.1.1 The Functional Role of Nutraceuticals

The functional role of nutraceuticals is the enhancement of nourishment for specific groups of people with impaired metabolism, in a specific physical state, who reduce the consumption of certain substances in food.

The following are the categories of nutraceuticals which include foods for special medical purposes (FSMPs):

- Nutrition for newborn and subsequent nourishment for the next stage
- Foods with cereal and foods devoid of cereal for infants and preschool children
- Low-calorie foods for decreasing obesity
- Foods deprived of or lacking phenylalanine
- Foods without gluten
- Nutrition designed for carbohydrate metabolic disorder

- Lactose-lacking foods
- Foods composed of decreased protein
- Foods for sportspersons and persons with augmented physical activity

FSMPs are recommended to consume under the direction of medical persons, and it must hold information regarding their use.

1.1.2 Role of Phytonutrients

Phytonutrients have a biological function which enhances health. They generally help plants to thwart competitors, predators, or pathogens – phytochemicals in food work by acting as a substrate and cofactors for biochemical reactions. As inhibitors of biochemical reaction, it removes the unwanted component in the intestine and augments the absorption and stability of vital nutrients. Also, they function as a selective growth factor for good flora and as inhibitors of infectious bacteria. They also deactivate harmful chemicals and act as ligands to antagonize the receptors that are present either extracellular or intracellularly (Baby Chauhan et al. 2013).

1.2 Classification of Nutraceuticals

Nutraceuticals are dietary component with health benefits. Examples include diets rich in fiber, probiotics, prebiotics, PUFA, antioxidants, vitamins, minerals, polyphenols, and spices. Natural sources, chemical nature of components, nature of the reaction, and pharmacological functions form the basis of nutraceutical classification.

The broad classifications of nutraceuticals are as follows:

(a) Potential nutraceuticals
(b) Established nutraceuticals

Clinical data on the medical benefits are needed to make the potential nutraceutical to established nutraceuticals (Pandey et al. 2010).

Classification of nutraceuticals based on its composition/functions (Akobundu et al. 2004):

1.2.1 Nutraceuticals with nutrients
1.2.2 Nutraceuticals with herbals or phytochemicals
1.2.3 Nutraceuticals with dietary supplements

1.2.1 Nutraceuticals with Nutrients

Nutraceuticals with nutrients are foods rich in nutrients and do the nutritive function, e.g., carbohydrates, fatty acids, amino acids, vitamins, and minerals. Foods comprising of carbohydrates, proteins, and lipids are necessary for the appropriate functioning of the body and its calorific requirements. Vitamins and minerals are not synthesized within the human body and play the role as protective foods. Hence they must be supplied via diet for the appropriate functioning of the body. Nutraceuticals play the role to improve health by combating against some chronic diseases (Mc Clements 2012).

1.2.2 Nutraceuticals with Phytochemicals

Nutraceuticals with phytochemicals possess herbs or botanical products. Intake of plant-based food offers enormous benefits to human health. Plants contain various phytochemical compounds, mostly polyphenols. These polyphenols are responsible for the beneficial activity. Pharmaceutical products with active ingredient have appeared in health products. These active ingredients are phytoconstituents with bioactivity (Espín et al. 2007). Important phytochemicals are anthocyanins, resveratrol, isoflavones, and polyphenols like ellagic acid, proanthocyanins, and flavanones.

1.2.3 Nutraceuticals with Dietary Supplements

Nutraceuticals act as dietary supplements composed of probiotics, prebiotics, antioxidants, and enzymes. They deliver bioactive constituents to the body, which is a mixture of several ingredients, metabolites, or constituents in the form of liquid, capsule, or tablet. The subclassification includes extracts from plants, supplements from herbs, proteins, vitamins, and minerals.

1.3 Sources of Nutraceuticals

Sources of nutraceuticals include plants, animals, and microbial.

Plant sources: Some significant plant sources include beta-glucan, ascorbic acid, gamma-tocotrienol, luteolin, cellulose, quercetin, gallic acid, indole3carbinol, pectin, perillyl alcohol, glutathione, potassium, allicin, D-limonene, daidzein, genistein, lycopene, hemicellulose, lignin, capsaicin, alpha-tocopherol, and zeaxanthin.

Animal sources: Some significant animal sources include conjugated linoleic acid (CLA), eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), selenium, and zinc.

Microbials: Some significant microbial sources include yeast, *Bifidobacterium*, *Lactobacillus*, and *Streptococcus*. Nowadays, the intake of foods is not only to satisfy the energy needs but also combat diseases and augment both physical and mental health (Menrad 2003).

1.4 Recent Trends of Nutraceuticals in the Global Market

Due to the enormous change in living style, the incidence of lifestyle-associated diseases is also growing. Life expectancy with these diseases is also growing. After gaining knowledge regarding the underlying cause of disease, now the consumers across the world are shifting from disease-causing chemical products to preventive healthcare products like nutraceuticals. Hence, the growth of the nutraceutical market is also rising. The value of global nutraceutical market was 205.39 billion USD in 2016 and is foreseen to elevate to around 294.79 billion USD by 2022, at 6.3% compound annual growth rate (CAGR) from 2017 to 2022 (Mordointelligence.com, 2017). Last year (2019), the global nutraceutical market was at 382.51 billion USD, at 8.3% CAGR which was higher than the estimation (https://www.grandviewresearch.com/industry-analysis/nutraceuticals-market, 2020). In forthcoming years, the market is expected to reach 423.2 billion USD by 2025, at a CAGR of 6.8% during 2020–2025. The tremendous increase in the global nutraceutical market is due to the increased utility of nutraceuticals by the people around the world. Improved delivery of nutraceuticals is may be one cause.

1.5 Bioavailability of Bioactive Compounds of Nutraceuticals

The efficiency of nutraceuticals depends on its bioavailability. With the increasing knowledge and understanding of the protective role of nutraceuticals, its availability into the body has become a significant concern. This essential factor must be considered by the manufacturers when producing nutraceuticals (Rapaka and Coates 2006). The quantity of a functional/bioactive compound that enters the blood circulation is called bioavailability (Esfanjani et al. 2018). Decreased bioavailability lowers the benefits of nutraceuticals inside the body. The route of administration/intake of nutraceuticals is oral, and they pass through GIT to reach the blood. Various constrain and obstructions like inadequate gastric retention, reduced permeability, solubility in the gut, and unstable conditions encountered in the GI tract reduce the activity and hence availability of nutraceuticals (Bell 2001). Apart from decreased bioavailability, it is necessary to regard other challenges like poor solubility, instability, and crystallization before incorporating these bioactive molecules into

products while manufacturing (Augustin and Sanguansri 2012). To overcome the physiological limitations of the body and to enhance the bioavailability and absorption of nutraceutical compounds as nutritionally and pharmacologically important one, the bioactive compound needs to be conjugated with the suitable delivery system, thus enhancing its bioavailability.

1.5.1 Enhancing the Bioavailability of Nutraceuticals by Nanotechnology

Many proposed targeted delivery systems have not been considered globally as a pertinent system for the delivery of bioactive compounds since each bioactive compound has its typical molecular structure requiring different systems. Nanotechnology-based targeted delivery systems are now booming to evade problem raised in the bioavailability of bioactive compounds. Development of delivery systems with nanomaterials is to boost the biological availability of functional components present in nutraceuticals. The encapsulation of bioactive compounds combats the acidity and breakdown by enzymes present in the GIT. These delivery systems offer an increased surface area and enhance the bioavailability. Reducing the particle size of delivery systems improves its efficiency, solubility, and biological activity of the compounds due to the availability of greater surface area per unit molecule (Prasad et al. 2019).

1.6 Nanotechnology

Employing and handling materials, at the nanometer scale, is called nanotechnology (Fathi et al. 2012). A nanometer is one-millionth of a millimeter. The dimensions of nanoparticles (NPs) are roughly between 1 and 100 nm (Prasad et al. 2016, 2017a, 2018). Nanotechnology shows the excellent possibility of enhancing the delivery of nutraceuticals. It facilitates controlled release, improves bioavailability, and protects the nutraceuticals during processing, storage, and distribution.

1.6.1 Nanocarriers as Nano Delivery System

The material used for the synthesis of nanoparticles (NPs) or nanocarriers is of organic or inorganic material (Bhushan et al. 2014) or a mixture of both (Fig. 1.2). Nanocarriers synthesized from organic material are comprised of polymeric and lipid-based nanoparticles, and those that are synthesized from inorganic materials are from metallic nanostructures such as quantum dots (Prasad et al. 2017b).

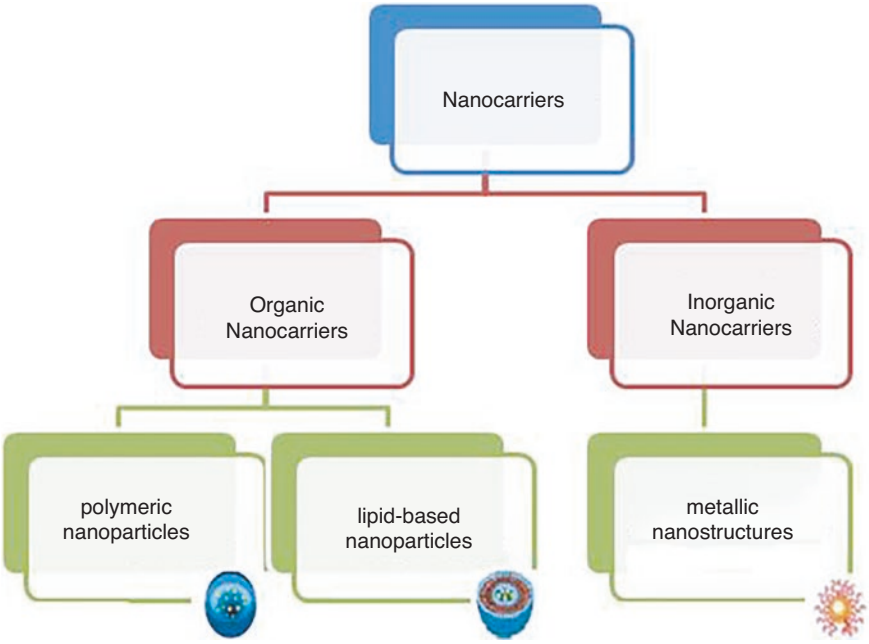


Fig. 1.2 Nanocarriers

1.6.2 Synthesis of Nanoparticles

Nanoparticles can be produced either by top-down methods (fluidization, dispergation, emulsifying technologies, or homogenization methods) or by bottom-up methods (precipitation or condensation, controlled sol-gel syntheses, evaporation) (Fig. 1.3) (Brayner et al. 2013). The size of the mechanical method of production of nanoparticles yields 100–1000 nm, while the size of nanoparticles from the chemical and bottom-up method yields 10–100 nm (Acosta 2009). Various biodegradable natural biopolymers for nanoencapsulation are frequently used (Jampilek and Kralova 2017).

Application of nanotechnology in nutraceuticals has enhanced the properties of nutraceuticals. They alter the difficulties encountered during delivery inside the body. The increased surface area of nutraceuticals is due to the decrease in size of a prepared nutraceutical, which in turn enhanced the desired delivery process inside the body. In a study by Javed et al. (2011), reformulation of silymarin into nanoliposomes increased its bio-absorption. The unique properties, such as size, shape, and internal structure, are essential while designing and fabricating nanomaterials. The fabrication monitors not only the incorporation of bioactive compounds but also on their stability, entrapment and release behaviors, and biological function (de Souza Simo˜es et al. 2017). Thus, nanotechnology offers an essential role in the delivery systems of a nutraceutical (Acevedo-Fani et al. 2017). Some of the

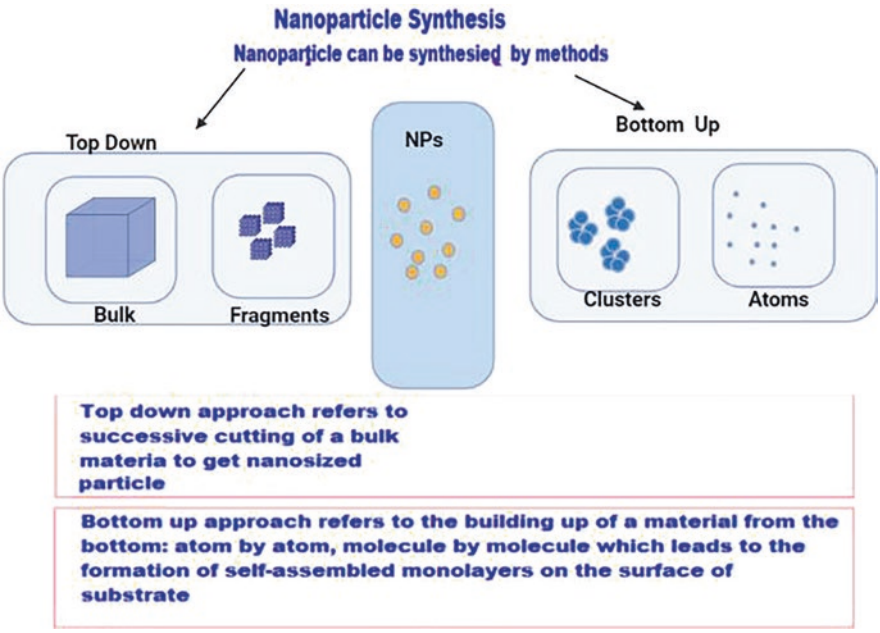


Fig. 1.3 Synthesis of nanoparticles

fabrication techniques of nanomaterials are emulsification, solid dispersion, spray drying, spray freeze drying, electro-spraying process, anti-solvent precipitation, complex coacervation, and layer-by-layer (LbL) deposition. The microscopically developed instruments that characterize nanomaterials help in better understanding of structures in nano-size and interpretation of their role (Tolles and Rath 2003). The nano-architecture endows protection and bioavailability of nutraceuticals by modifying the extent of solubility and its release (Ezhilarasi et al. 2013). Liquid crystalline mesophase is known as lyotropic formed by amphiphilic substances such as lipids along with surfactants and copolymers dispersed in a polar solvent. Under appropriate conditions, hydrophobic interactions cause them to self-assemble into stable crystals in nanometer size. Examples include micelles, hexagonal structures, lamellar structures, and cubosomes, which retain a high degree of molecular orientation in a liquid state.

1.6.3 Scenarios of Nanotechnology in Nutraceuticals

In the present scenario, nutraceutical delivery systems need to be familiar with the location, the load needed to be delivered, a decision on release, and feedback control. Advances in nanotechnologies revolved this by aiding its delivery. Aforementioned can be compared to the "smart drug delivery" presently under

medical research. Thus, nanoscience, engineering, and technology guaranteed the proper delivery of nutraceuticals. Innovation in encapsulated formulations and bioavailability of nutraceuticals are considerably augmented. Even though nanotechnology aids in the delivery of nutraceuticals, however, the essential step necessary is the selection of the loading materials for the delivery systems, which plays a vital role in the encapsulation efficiency and stability, and the available option of materials is also limited. Loading of bioactive ingredients into nanotechnology-based delivery systems is essential. The nanotechnology-based nutraceuticals can attain commercialization by overcoming the boundaries related to them (Augustin and Hemar 2009), by using food grade-based nanomaterials which offer uniformity, flavor, taste, and texture (Prasad et al. 2017c; Chausal et al. 2021).

1.7 Food-Grade Nanomaterials

Various food-grade nanomaterials for delivery of nutraceuticals are as follows:

1.7.1 Lipids as nanomaterials
1.7.2 Polymer as nanomaterials
1.7.3 Cellulose as nanomaterials
1.7.4 Protein as nanomaterials
1.7.5 Polysaccharide as nanomaterials

1.7.1 Lipid as Nanomaterials

Lipids have a tremendous capability for encapsulating nutraceuticals. Some of the examples of lipid-based nanoparticles (Fig. 1.4) are solid-lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), liposomes, nanoemulsions, and nanoliposomes systems. They encapsulate majority of the natural bioactive compounds. A high dose of different molecules can be encapsulated and used on distinct sites using these lipid-based nanomaterials.

Solid-lipid nanoparticles (SLNs): The first-generation lipid-based nanocarriers are solid-lipid nanoparticles (SLNs). The lipids used in the synthesis are fatty acids, monoglycerides, diglycerides, and triglycerides. They remained in the solid state at body temperature and are stabilized by emulsifying agents (Müller et al. 2000). The SLNs are highly lipophilic, which enables the transportation of core material. Synthesis of SLNs is shown in Fig. 1.5, and list of constituents necessary for the synthesis of nutraceuticals encapsulated in SLNs is shown in Table 1.1.

Advantages of solid-lipid nanoparticles: Solid-lipid nanoparticles have a combination of advantages of liposomes, nanoemulsions, and polymeric nanoparticles. SLNs have good tolerance, high bioavailability, and biodegradability. There is no formation of toxic breakdown products in SLNs (Cacciatore et al. 2016). Therapeutic

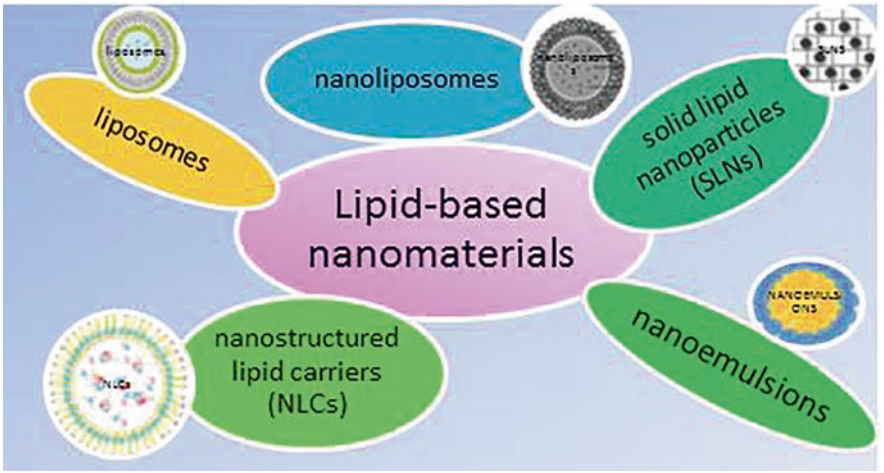


Fig. 1.4 Lipid-based nanomaterials

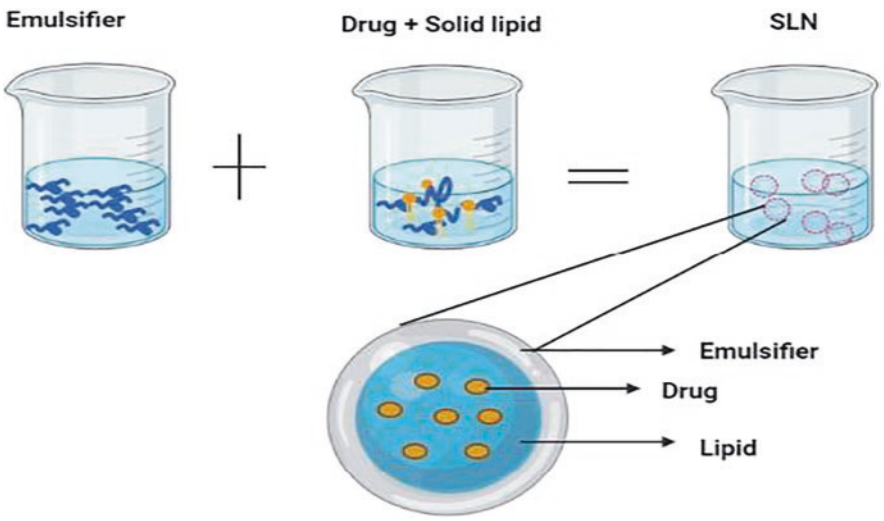


Fig. 1.5 Synthesis of solid-lipid nanoparticles

application of SLNs in different ailments is shown in Table 1.2. The significant benefits of SLNs are the following:

- Organic solvents are not necessary for their preparation.
- The physical stability is high.
- The drug release and drug targeting is well organized.
- The active substances are stable.
- Both lipophilic and hydrophilic compounds are encapsulated with SLNs.

Table 1.1 Constituents used for the synthesis of solid-lipid nanoparticles

Types of lipids used in the synthesis of SLNs	The emulsifier used in the synthesis of SLNs	Techniques for the synthesis of SLNs
Triglycerides Partial glycerides Fatty acids Steroids Waxes (cetyl palmitate)	Pluronic F 68 Pluronic F 127 Polysorbate Lecithin Sodium cholate Tyloxapol Taurodeoxychocolic acid sodium Sodium glycocholate Butyric acid and butanol (Campos et al. 2014; Severino et al. 2012)	High shear homogenization Hot homogenization Cold homogenization Ultrasonication Solvent emulsification Microemulsion Supercritical fluid Spray drying method and double emulsion method (Mukherjee et al. 2009)

Table 1.2 Therapeutic application of solid-lipid nanoparticles

Bioactive compound encapsulated in SLNs	Therapeutic uses of SLNs
Rosmarinic acid (RA)	Protects against Elevated blood pressure Myocardial infarction (MI) Aging Atherosclerosis Diabetes Neurodegenerative disorders like Huntington's disease Parkinson's and Alzheimer's diseases (Klyachko et al. 2012) Autoimmune disorders (Caccamo et al. 2012) Malignancy (Riemann et al. 2011; Tasset et al. 2011) Inflammatory disease (Lee et al. 2011) and excess O_2 in tissues and organs (hyperoxia) (Gao et al. 2012)
β-Carotene	Can suppress the production of free radical Offers protection against lipid peroxidation (Souyoul et al. 2018)
Nicotinamide (NA)	Has antioxidant and anti-inflammatory activity (Takechi et al. 2013) Protects the blood-brain barrier (BBB) Protects against neurodegenerative disorders
Quercetin	Can decrease serum lipids in hyperlipidemia Can widen the narrowed coronary arteries Acts as anticarcinogenic agent Stops platelet aggregation Provides antioxidant and anti-inflammatory activity Suppresses anaphylactic effects and elevates the level of hemoglobin in anemic condition (Wang et al. 2007)

- Simple in preparation hence scale up is also simple, so large-scale production is possible.
- Deliverance systems with safe ingredients.
- Sterilization is possible (Weber et al. 2014).

Limitation of solid-lipid nanoparticles: Although SLNs have many advantages, there are some potential disadvantages also. The main disadvantage is its drug-loading capacity which is low (Yoon et al. 2013), expelling of the drug from the carrier as a result of the polymorphic transitions, which depends on the physical and chemical structure of the active substances (e.g., hydrophilic molecules), and this mostly happens during storage. Another drawback is initial burst release and its dispersion (Makwana et al. 2015), with a large amount of water. Nanostructured lipid carriers (NLCs): Nanostructured lipid carriers (NLC) are the second-generation delivery system. In this system, partly crystallized lipids are present in the aqueous layer along with emulsifiers. It is one of the appropriate systems for nutraceutical delivery.

The main advantages of NLCs are as follows:

- The drug-loading efficiency is high.
- They have stable bioactive compounds with increased bioavailability (Muller and Keck 2004).
- More cost-effective to fabricate.
- Has low crystallinity and less dense lipid packaging.
- They provide augmented shelf life and controlled release of encapsulated materials.

Organic solvents are not necessary since it is water-based and are easy to scale up (Doktorovova et al. 2014). NLCs have the capability of transporting both lipophilic and hydrophilic drugs at the same time. NLCs can be added directly to transparent/opaque pasteurized products (e.g., fruit juice and milk). However, they are supplemented to foods prior to pasteurization. They can be spray-dried or freeze-dried. NLC has all the necessary characteristics for the use as nanocarriers for food and nutraceuticals. A combination of solid lipid and liquid lipid (or oil) is used to circumvent lipid crystallinity.

Limitation of nanostructured lipid carriers: Even though NLCs have many advantages as a nano delivery vehicle, they also have certain limitations:

- Toxic effects on the cells which depend on the matrix
- Irritating and sensitizing action of surfactants

Types of NLCs: The types of NLCs depend on the composition of the lipids mixed and fabrication techniques used. The principal mechanism involved is to arrange for a nanostructure for the lipid matrix, in turn, and escalate the load of bioactive compounds and decrease the discharge of these compounds during storage. The three different types of NLCs (Westesen et al. 1997) are imperfect, amorphous, and multiple. Production of NLCs using high-pressure homogenization (HPH) is used for quantitative production of SLNs and NLCs. It is a beneficial, trustworthy, and powerful technique. The procedure involves top-down methodology wherein a very high shear stress pushes the lipid with high pressure (100–2000 bars), which disrupts large particles to submicron or nanometer size. Five to ten percent of lipids is used for the production. When compared to other techniques used for preparation, HPH does not show scaling up problems. Homogenization can

be performed either at a higher temperature (hot homogenization) or at a lower temperature (cold homogenization) (Schwarz et al. 1994). Different approaches used for the preparation and its constituents necessary are depicted in Table 1.3. Nanoemulsions: Emulsions are combination of oil, water or aqueous buffer, surfactant, and cosurfactant. Nanoemulsions are colloids with oil droplets dispersed in an aqueous medium. Hence they can solubilize drugs or bioactive compounds which have an affinity for lipid environment, thus enhancing their delivery. The isotropic systems of nanoemulsions are kinetically stable systems of oil and water (both the liquids do not mix) and become stable by forming an interfacial film using surfactant and cosurfactant. They can also encapsulate hydrophilic drugs (Tshweu et al. 2013) and can enhance the bioavailability of encapsulated compounds (Tshweu et al. 2014). The sizes of nanoemulsions are in the range of 5–200 nm and are transparent (Solans et al. 2005). They give protection from hydrolysis (Ozturk 2017) and can increase the therapeutic activity of essential oil (Katata-Seru et al. 2017).

The different types of nanoemulsions are water-in-oil (W/O) type, oil-in-water (O/W) type, and bi-continuous water-in-oil-in-water (W/O/W) type. The different techniques for the production of nanoemulsions are low and high energy type (Fig. 1.6).

Low energy type involves spontaneous emulsification and phase inversion temperature with the change in solubility, and high energy type are microfluidics, high-pressure homogenizers, or ultrasound equipment methods. O/W nanoemulsions can encapsulate lipophilic nutraceuticals and form stable systems for oral delivery. The food-grade nanoemulsions have been prepared by homogenization, mixing, and shearing (Aditya et al. 2017). The factors that prevent the oral availability of lipophilic bioactive agents are absorption, accessibility inside the body, and transformation (Aboalnaja et al. 2016). The encapsulation of lipophilic bioactive agents to nanoemulsions could help in diffusion across the membrane that will improve oral availability (Sivakumar et al. 2014). The size of nanoemulsions is small and globular with augmented surface area resulting in improved digestion rate. It also protects the bioactive compounds from oxidation and decreases their breakdown in the GIT (Frede et al. 2014). Thus, nanoemulsions can protect and deliver both lipid-soluble and water-soluble bioactive agents through the oral route and dermal route, similar

Table 1.3 Constituents used for the synthesis of nanostructured lipid carriers (NLCs)

Types of lipids used in NLC	The emulsifier used in NLC	Techniques used in NLC
Glycerides	Sodium dodecyl sulfate	High-speed homogenizer
Fatty acids	Sodium oleate	Hot homogenization
Waxes (cetyl palmitate)	Span 20, 80, and 85	Cold homogenization
	Tween 20 and 80	Ultrasonication
	Egg phospholipid	Phase inversion
	Sodium taurodeoxycholate	Microemulsion
	Sodium glycocholate	Evaporation solvent injection
	Phospholipon 80 H	Membrane contractor technique (Sanap and Mohanta 2013)

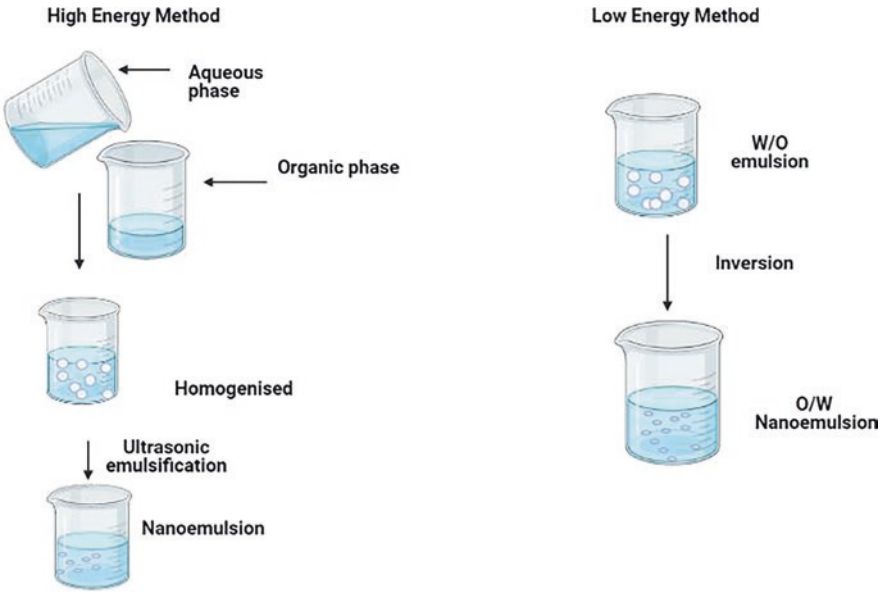


Fig. 1.6 Preparation of nanoemulsions (Typical low-energy (bottom-up) methods and high-energy (top-down) methods for producing nanoemulsions)

to that of pharmaceuticals. Although nanoemulsions have many advantages, they also have limits. The main disadvantage is the stability of nanoemulsions. Although nanoemulsions are stable for years, due to their minimal size, the Oswald ripening could disrupt them, making their role inadequate. Most of the time, they are made only at the time of usage. Liposomes and nanoliposomes: Liposomes are used as a carrier for the transportation of active components inside the body by oral absorption or preventing breakdown in the acidic environment present in GIT. The phospholipids arranged with their heads in the aqueous environment and their tails toward each other (Fig. 1.7).

These structures have trapped aqueous-soluble components and protect them from aggressive environments. Interactions between the membrane of liposome and cell membranes enhanced cellular uptake through endosomal mechanisms. Because of small size, liposomes provide improved bioavailability of entrapped components by their large surface area to the biological tissues. Examples of antioxidants encapsulated using liposomes are shown in Fig. 1.8. Resveratrol-loaded liposomal formulations showed improved bioavailability and are used as therapeutic agents to treat neurodegenerative diseases like Parkinson's disease (Wang et al. 2011).

Liposomes are the well-designed optimal drug carrier system for a broad range of bioactive substances. The biological advantage of liposome is due to the amphipathic nature of phospholipids used for encapsulation. They are small in size, compatible, and degradable within the body and also lack toxicity.

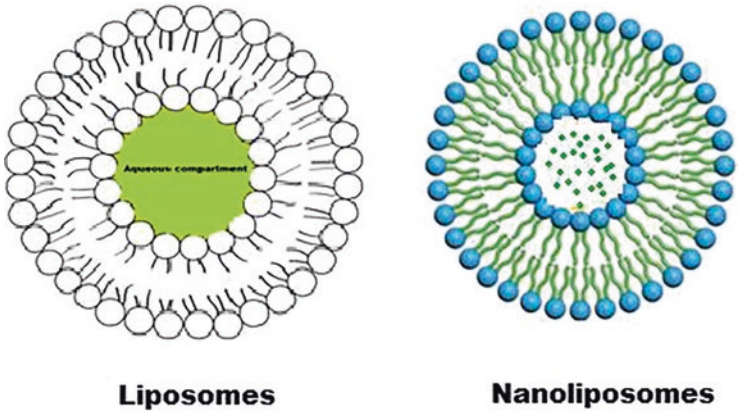
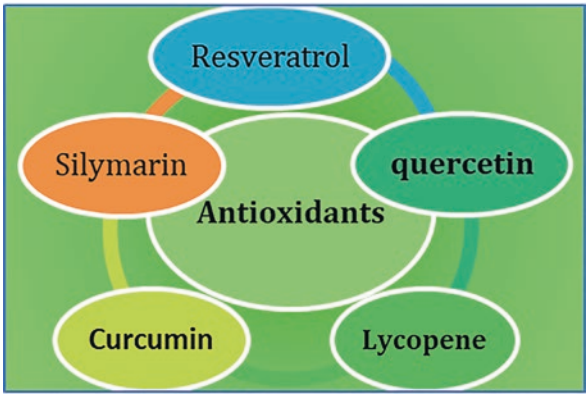


Fig. 1.7 Liposomes and nanoliposomes

Fig. 1.8 Examples of antioxidants encapsulated using liposomes



Some of the advantages of liposomal delivery are as follows:

- Increased biological availability and bio-absorption.
- Liposomal delivery vehicle protects the bio-component against the acidic environment of the GIT and enhances mucosal absorption.
- It augments intracellular delivery.
- Can entrap hydrophilic and lipophilic components.
- The dose can be lowered with the same effect by liposomal delivery and thus cost-effective.

Limitations of liposomal delivery are as follows:

- Possibility of large particle size with decreased core material during the manufacturing
- Lack of stability

Nanoliposomes: Nanostructured delivery systems are promising candidates that permit efficient and targeted delivery of bioactive compounds. Lipid carrier system includes liposomes and nanoliposomes (Fig. 1.7). Nanoliposomes are liposomes at nanoscale lipids as encapsulating agents. Both liposomes and nanoliposomes have common physicochemical structure, with kinetically stable characteristics. However, nanoliposomes offer additional surface area because they are nanometer in size (the smaller the size, the higher the surface area) and the solubility is also more with enhanced biological availability, sustained release, and site-directed targeting of the bioactive agents at an increased level than liposomes. Nanoliposomes are colloidal structures formed by a mixture of phospholipids which have an excellent emulsifying property along with the other constituents in water (Danaei et al. 2018). Dispersion of lipid and phospholipids for the synthesis of liposomes and nanoliposomes consumes energy (Mozafari 2005). Nanoliposomes are exploited as a useful drug carrier in the delivery of nutraceuticals. The routes of delivery of nanoliposomes are oral as well as parenteral (Shoji and Nakashima 2004). Stable polymers are used to protect the nanoliposomes.

Advantages of nanoliposomes are as follows:

- Nanoliposomes provide benefits in delivering and targeting of bioactive compounds by encapsulation (Chaudhry et al. 2017).
- Nanoliposomes are metastable. This stability resists the change in size in an aqueous medium when compared with other lipid encapsulating agents.
- Another benefit of nanoliposomes is that they can encapsulate lipophilic, hydrophilic, and amphiphilic molecules.
- Another added benefit is that they can encapsulate concurrently two different bioactive components differing in their solubility and be used as bifunctional nanosomes with synergistic function (Gowda et al. 2017).

1.7.2 Polymer as Nanomaterials

Biodegradable polymers are used for the transportation of nutraceuticals and synthesized in the form of nanoparticles (Vorhies and Nemunaitis 2009). By encapsulating the nutraceuticals, they are protected from the acidic environment of GIT. Thus, polymers are used as the means to deliver nutraceuticals. Biodegradable polymers are broken down either by biological processes or by hydrolysis. Biodegradable polymers are composed of natural and synthetic polymers (Fig. 1.9) (Nicolas et al. 2013). They are designed to break down within the body by biochemical processes. The breakdown products are also biologically endurable. These polymers deliver nutraceuticals. They are also biocompatible. Natural biodegradable polymers are biologically originated molecules. They can undergo chemical modifications to break down and are biocompatible. Within the body, the polymer can metabolize and clear them. Collagen, gelatin, albumin, gliadin, zein, and casein are examples of polymers of proteins, and carrageenan, alginate, chitin, chitosan,

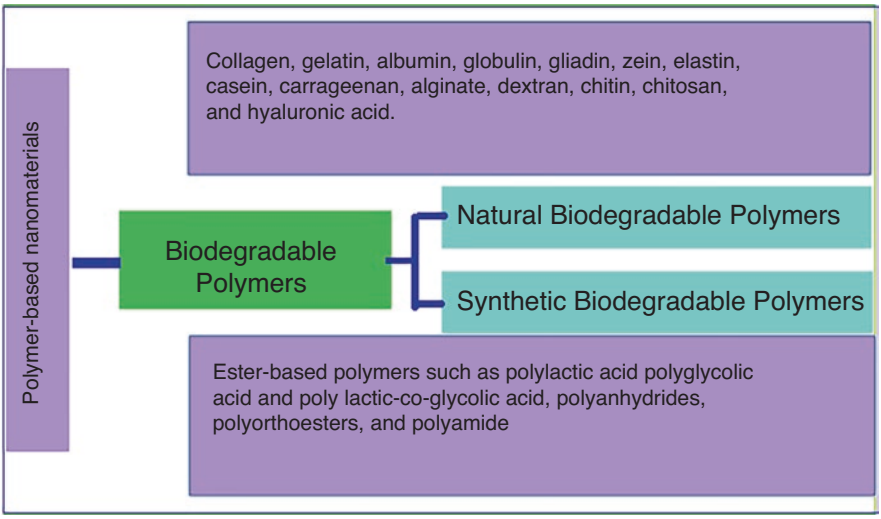


Fig. 1.9 Polymer as nanomaterials

and hyaluronic acid are examples of polymers of polysaccharides. These natural polymers have some limitation like poor mechanical properties and have complex structure. Natural polymers are extensively used most of the time because they are commercially available. The synthetic biodegradable polymers enhance the release of nutraceuticals. Synthetic polymers have additional benefits when compared to natural polymers in the sustained release of encapsulated active compounds for many days. The limitations of synthetic polymers are toxicity and chronic inflammation (Coelho et al. 2010). Toxicity and immunogenicity must be taken into account when using synthetic polymers for the delivery of nutraceuticals.

Examples of synthetic polymers are polylactic acid (PLA), polyglycolic acid (PGA), poly (lactic-co-glycolic) acid (PLGA), polyanhydrides, polyorthoesters, and polyamide. These have many substantial applications in medicine (Makadia and Siegel 2011). PLA, PGA, and PLGA are polymers of esters and are also extensively used. The composition of PLA is lactic acid. It is biodegradable by hydrolysis. The composition of PGA is glycolic acid. It is a sturdy polymer with fiber-forming properties. The limitation of PGA is that it cannot be made into films or rods since it is not soluble in polymer solvents (Makadia and Siegel 2011). The polymer properties of PLGA are due to the composition of two different monomers (lactic and glycolic acid) (Makadia and Siegel 2011). Polyanhydrides are made into microspheres and tubes for sustained release of nutraceuticals. Polyorthoesters under dry conditions are stable. The drug release rates of polyorthoester are from days to months (Engesaeter et al. 1992). The polyamide application is limited due to its ability to induce an immune response.

1.7.3 Cellulose as Nanomaterials

The nanomaterials made from cellulose are synthesized from renewable sources. They are light in weight and biocompatible and possess excellent strength. The physicochemical properties of cellulose have made these nanomaterials attractive for its role in nutraceutical. Examples of nanomaterials made from cellulose used for various applications are enzyme immobilization, active compounds, microorganisms, stabilizers, and additives.

The application of nanomaterials made from cellulose depends on its origin and extraction conditions (Grishkewich et al. 2017). Precise acid hydrolysis of cellulose produces rod-shaped crystalline nanoparticles. During this process, hydrogen bonds break down, thus dissolving the amorphous region of the fiber. The dimension also varies depending on the resources. For example, nanomaterial obtained from hardwood has 3–5 nm width and 100–300 nm length, while those that are obtained from a marine animal have a 15–30 nm width and length of 1000–1500 nm (Grishkewich et al. 2017). Incorporation of chemical and mechanical methods like microfluidization, high-pressure homogenization, high ultrasonic treatment, and cryo-crushing is involved in the processes of formation of cellulose nanomaterial (Khan et al. 2017). Cellulose nanomaterials are made up of mixtures of amorphous and crystalline cellulose chains having width range of 4–20 nm and length in micrometers. They are capable of forming intertwined linkage and semicrystalline structure, with excellent flexibility and mechanical strength. *Lactobacillus* species and *Bifidobacteria* are beneficial bacteria. These organisms are present naturally in GIT, which are beneficial to the body. They are exploited as nutraceuticals for health benefits. The main disadvantage of it is its decreased shelf life. The shelf life can be enhanced by using cellulose nanomaterials as encapsulating material (Huq et al. 2017). Vitamins and antioxidants are encapsulated with nanofibers and nanocrystals of cellulose acetate and cellulose. Appropriate delivery of antioxidants prevents long-term complications of metabolic diseases such as nephropathy and neuropathy by shielding the ill effects of oxidative damage. Vitamin C is an excellent nonenzymatic antioxidant which suppresses reactive oxygen species. It can be encapsulated using chitosan oligosaccharide (Akhlaghi et al. 2015). The encapsulated vitamin C showed stability and potent scavenger of reactive oxygen species when compared with nonencapsulated vitamin C. Cellulose nanocrystals can also be used for preparing nutraceuticals for other scavengers of reactive oxygen species. The oxidation-reduction reaction of ascorbic acid and hydrogen peroxide is brought out using cellulose nanocrystals as an encapsulant. This was in turn enhanced by γ-irradiation of cellulose nanocrystal suspension, and then the suspension can be made to react with ascorbic acid and hydrogen peroxide, and then gallic acid was added. The enhanced features of cellulose nanocrystal derivative showed enhanced antioxidant activity compared to nonencapsulated substances (Criado et al. 2016).

1.7.4 Protein as Nanomaterials

Proteins are biomolecules with one or more polypeptide chains of amino acids, and they provide essential amino acid to the human body. They are a part of natural ingredients, e.g., milk, eggs, gelatin, silk protein, whey protein, and casein. Even though proteins are one of the main dietary components, they are used for encapsulating nutraceuticals. Proteins play an outstanding role as encapsulant. They are flexible biopolymers. They are used as nanocarrier system due to their biocompatibility, encapsulation efficiency (Fathi et al. 2018), low cytotoxicity, biodegradability, controlled release of bioactive agents, and site-specific drug delivery (Chakraborty and Dhar 2017). As delivery vehicles, various kinds of animal proteins (Fig. 1.10) are used including gelatin (Payne et al. 2002), collagen (Swatschek et al. 2002), casein, albumin (Tomlinson and Burger 1985), and whey protein (Picot 2004), and plant proteins used are glycinin from soy (Lazko et al. 2004), zein from corn (Liu et al. 2005), and gliadin from wheat (Ezpeleta et al. 1996).

Of the above protein-based nanomaterial for nutraceutical deliveries, collagen and gelatin are widely used since they are biodegradable and non-immunogenic. The articulation of collagen into sponge, particles, gels, and films facilitated the delivery of nutraceuticals (Friess 1998). Next to collagen, albumin is a widely used polymer because it is nontoxic, non-immunogenic, biologically compatible, and degradable (Bae et al. 2012).

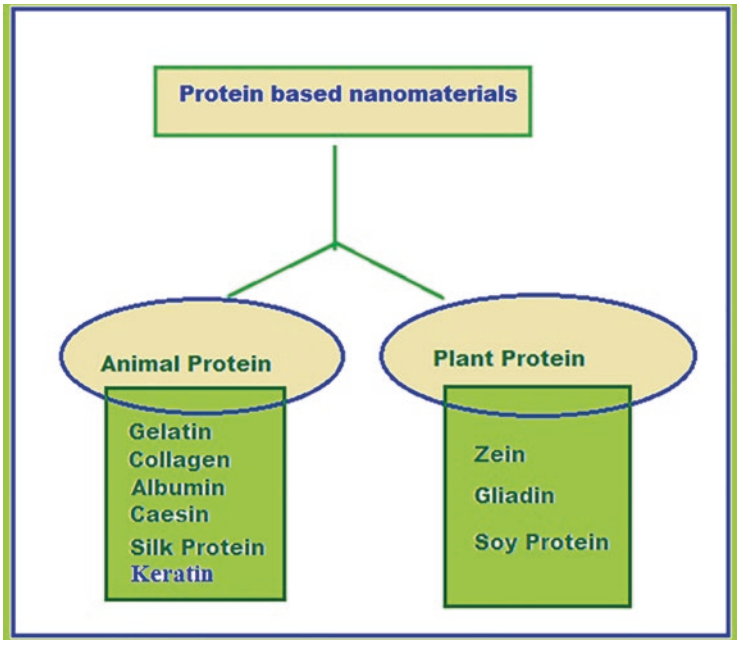


Fig. 1.10 Protein-based nanomaterial

Gliadin and zein are prolamins, and these plant proteins are abundant in proline. They are present in cereal grains (wheat (gliadin), corn (zein)) and used as an oral delivery system. SOD and catalase are antioxidant proteins. Within the body, they scavenge free radicle and thus have a therapeutic role. These antioxidants are encapsulated with gliadin or zein, to protect them from the acidity of GIT (Lee et al. 2013). Protein as nanoparticles can be prepared with ease, and the size distribution can also be supervised (Mac Adam et al. 1997). They can be modified, forming complexes with polysaccharides, lipids, or polymers. Since they have distinct primary structure, a wide variety of nutrients can be incorporated by modifying the surface. To the primary amino groups or sulfhydryl groups, the bioactive can be covalently added (Weyermanna et al. 2005). Nanoscale phenomena of proteins are also due to denaturation and aggregation properties, which pave the way to design them. These related properties make them promising agent for entrapping nutraceuticals. Nanostructured proteins have improved properties for the incorporation of nutraceuticals (Ramos et al. 2017). Submicron sizes are obtained by strong bonds and weak forces (Clark and Ross-Murphy 1987). The possible mechanism leading to the formation of these nanoaggregates involves electrostatic interactions, hydrophobic interactions, and intermolecular disulfide bonds. To increase the bioavailability of nutraceuticals, the surfaces of nanocarriers are coated with proteins which can modify the adhesive properties of it and their behavior in the GI tract. Coated proteins can bind to sugar-bearing sites on epithelial cells in the GIT (Goldstein et al. 1980). Coating of protein on nanoparticles provides added protection to the nutraceutical. Broadly proteins are used as nanocarriers for the delivery of nutraceuticals (Chakraborty and Dhar 2017). The whey proteins are utilized mainly as functional components in prepared foods as they are cost-effective and generally safe and ensure significant function (Gunasekaran et al. 2006). Furthermore, proteins possess beneficial biological properties against diseases such as cancer, viral infection, and indigestibility. It also modulates the immune system (Dissanayake and Vasiljevic 2009). These essential properties make them promising encapsulating agents.

1.7.5 Polysaccharide as Nanomaterials

Polysaccharides are polymer of monosaccharide, and they do both structural and functional role. The polysaccharides obtained from plants are pectin, inulin, fiber, and starch and from animals are chitosan, glycogen, and chondroitin sulfate. The microorganism present in the colon breaks these polysaccharides into monomers. When polysaccharides are used as a nanomaterial, they protect the nutraceuticals from the harsh environment of the GI tract. When they reach the colon, they get hydrolyzed and release nutraceuticals present within them. The primary therapeutic role of these systems is to deliver probiotics such as bifidobacteria and lactobacilli. Polysaccharides are one of the main classes of biological polymers. They are bioactive, hydrophilic, biologically degradable, biologically compatible, cost-effective,

and without toxicity and possess a wide range of properties. These can be altered to enhance the stability of bioactive compounds (Sinha and Kumria 2001). Polyelectrolytes and non-polyelectrolytes are the types of nanomaterials made from polysaccharides. The polyelectrolytes are classified based on their intrinsic charge into cationic, anionic, and neutral. Examples of cationic polyelectrolytes are chitosan; examples of anionic polyelectrolytes are alginate, pectin, hyaluronic acid, and heparin; and examples of neutral polyelectrolytes are pullulan and dextran subgroups. Based on sources of origin, polysaccharides are mainly classified as (a) algal origin (alginate); plant origin such as guar gum, and pectin; (b) microbial origin, e.g., xanthan gum, dextran; and (c) animal origin, e.g., chondroitin, chitosan (Zheng et al. 2015; Augustin and Hemar 2009). The majority of the natural polysaccharides are used for nanoencapsulation of different types of bioactive. The types of polysaccharides used for nanoencapsulation depend on safety and cost. Different methods are utilized for the synthesis of nanoencapsulation of bioactive components depending upon the physical and chemical characteristics of both bioactive and polysaccharides. They can encapsulate both hydrophilic and hydrophobic bioactives. Their structural flexibility and site-specific targeting make them as suitable carriers for the controlled and targeted delivery of nutraceuticals for GIT (Sinha and Kumria 2001).

1.8 Conclusion

The significance of nutrition containing all necessary nutrients, along with antioxidants, vitamins, and minerals in appreciable amount, is necessary for health. Intake of nutraceuticals with bioactive ingredients will prevent the people from ailments and improve their health. For this purpose, nanoencapsulation of active compounds synthesized by using various biodegradable natural/semisynthetic-based nanocarriers that include polymeric nanoparticles, micelles, liposomes, nanoliposomes, nanoemulsions, solid-lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), nanoemulsions, nanomaterials made from cellulose, protein, and polysaccharides is carried out. These nanomaterials have improved stability and sustained release of nutrients. Many nano delivery systems have not been considered as a universally appropriate system because the bioactive compounds have individual characteristics which necessitate new types of diverse systems. To conclude, this chapter gives an understanding of nutraceuticals, its types, nanocarriers and nanomaterials, and their encapsulation efficiency. In the upcoming years, nanomaterial generation for nutraceutical applications can benefit them in the global market.

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Chapter 2
Nanoscale Smart Drug Delivery Systems and Techniques of Drug Loading to Nanoarchitectures

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2.1 Introduction

The term "nanomedicine" refers to a wide variety of nanomaterials and structures used for treatment and diagnosis. Nanoparticles are colloidal in nature with size ranges from 10 to 1000 nm. It can include nanosized polymers, dendrites, micelles, liposomes, particles, and capsules. They are constructed from organic or inorganic (or both) compounds and perfectly apt for optimized drug delivery with negligible adverse effects (Kim et al. 2010).

Requirements for a good drug delivery system are as follows:

1. The half-life in blood circulation should be considerably long enough for the accumulation of drug at the target site.
2. They should be able to carry significant quantity of drug compound.
3. Either the drug delivery system or its degradation products should not have adverse toxic outcomes.
4. The shelf life must be significantly long to permit storage and transport.
5. It should be economic, or the cost can be directly proportional to effectiveness of the drug.

Disadvantages of conventional drug delivery system are as follows:

1. The drug is quickly degraded or inactivated in the body prior to reach its target site.
2. The drugs lack the capacity to cross physiological barriers such as cell membranes, placenta, blood-brain barrier, etc.
3. Poor specificity and hence distribution of drugs to all types of tissues and organs. All these lead to decreased therapeutic efficiency or undesirable side effects.

Nanomedicines have more advantages over conventional medicine. Nanoparticles can be used for both treatment and diagnosis simultaneously. Theranostic nanoparticles carry both drugs for targeted therapy and imaging molecules for simultaneous diagnosis of diseases. The physiochemical characteristics of nanoparticles can directly influence the function and make them advantageous over many conventional medicines. Physiochemical properties of nanocarriers depend on compositions (organic, inorganic, or hybrid), size (nanoscale in dimension ranging from 10 nm to 1000 nm), shape (sphere, rod, highly branched, multilayer), and surface characters (active groups, electrostatic charges, shelling methods, or binding of ligands) (Tran et al. 2017).

The size of nanoparticles is basically very tiny, ranging from 1 to 1000 nm. They have typical structural, optical, and electrical characters which many larger molecules do not have. They have better solubility, so that they are able to change insoluble or sparingly soluble therapeutic agents into soluble aqueous suspensions; thus, the need for toxic organic solvents for the drug formulation is eliminated. The small nanosize of these particles increases circulation time and bioavailability. Hence, the circulation time of nanoparticles is definitely longer than any conventional drugs. Generally, nanoparticles coated with hydrophilic polymers show prolonged

circulation time in the blood, so they are a better choice for increasing the efficiency of drugs having shorter half-life periods. The dissolution kinetics of drug is improved; commencement of therapeutic function is enhanced so the drug dosage can be reduced. Coating of nanoparticle with suitable material can make them to escape from the recognition and elimination by the immune system. Nanoparticles are available in different shapes (rods, cylindrical, spherical, hemispheres, discs, tubes, cones, and wires). Nanoparticles can also be porous, hollow, or solid (Husain 2017). These features influence the loading, interactive, and transport efficacy of nanoparticles. For instance, a hollow nanoparticle may be a smart carrier for both therapeutic drug and diagnostic imaging compounds. Nanoparticles have large surface area due to nanosize. The sum of surface area increases exponentially as particle size diminishes. The meaning of increase in surface area is that a larger fraction of atoms are positioned on the surface relative to the inner core. This makes nanoparticles more reactive compared with traditional bulky drugs. Amplified surface area also leads to better solubility in aqueous environment and better bioavailability of nanoparticles. The larger surface area of nanoparticles permits them to possess wide varieties of surface characters, including binding with biomolecules or charged groups.

Due to smaller dimension, nano drug carriers can cross biological barriers (blood-brain barrier, etc.) easily by enhanced permeability and retention effect (EPR) and deliver drugs to sites that are not normally reachable by conventional therapeutic agents. The increased permeability of nanoparticles allows delivery of drugs to inflamed tissue and delivery of cancer drugs into tumors by passing via neovessel pores of diameter less than 1 μm (Jong and Borm 2008). The use of novel nanotechnology-based drug delivery systems has paved the way to enhance the pharmacokinetic characters of drugs than conventional drugs. Pharmacokinetics deals with the proportion of dosage of a drug and its concentrations in biological fluids over a period. The factors influencing pharmacokinetics are rate and extent of drug absorption, distribution, metabolism, and excretion processes (ADME studies). The measureable pharmacokinetic factors of nanoparticles are maximum serum concentration (C_{max}), volume of distribution (V_d) area under the curve (AUC) of serum concentration-time profile, time to maximum serum concentration (T_{max}), half-life ($t_{½}$), and clearance (CL). Plant-derived compounds or synthetic compounds encapsulated or entrapped into nanoparticles gave good results to overcome their undesirable pharmacokinetic characters and improved stability of the loaded drugs (Abdifetah and Na-Bangchang 2019).

2.2 Nanoscale Drug Delivery Strategies

Nanoparticles/nanocarriers are nanosized, colloidal particles, normally ranging below 1000 nm in size, characterized by having larger surface area to size ratio. These particles are made of natural or synthetic biodegradable polymers, and the therapeutic drug is loaded by encapsulation or entrapped/embedded within

polymeric matrix or adsorbed or conjugated onto the surface. These drug-loaded nanoparticles are better drug delivery system than conventional carriers. Nanoparticle-based drug delivery in nanomedicine depends on two factors, enhanced encapsulation/entrapment/adsorption of the therapeutic compounds and delivery and release of drugs to the target site.

2.2.1 Passive and Active Targeting

Nanotechnology-based drug delivery strategy follows two main techniques: *passive* and *active targeting*. The fundamental principle for accumulation of nanoparticle into target site is the same for both approaches. According to EPR (enhanced permeability and retention) effect, nanocarriers extravasate from blood capillaries via interendothelial membrane openings by passive diffusion and reach target tissues. This kind of passive transfer mechanism is referred to as paracellular transport pathway. This pathway is based on nanoparticle concentration gradient between the blood and target tissue interstitium which drives nanoparticles to diffuse passively across the endothelium via interendothelial gaps/openings and assists accumulation in target tissue (Fig. 2.1a).

To perform active targeting mechanism, nanoparticles are attached with specific ligands on particle surface and these ligands are known as targeting ligands. These targeting ligands may be biomolecules such as RNA/DNA, antibodies, or peptides which can selectively bind to distinct cell membrane receptors on target cells with good attraction. Due to very high specific cellular interaction by the nanoparticles, the active targeting approach is widely employed in nanomedicine, thus reducing the chance of nonspecific cellular interaction by nanoparticles (Fig.2.1b) (Rosenblum et al. 2018).

2.2.2 Cellular Internalization of Drug Nanocarriers by Endocytosis

Polymer-based nanoparticles bind to target cellular surface and deliver therapeutic compounds which enter into the cell by simple diffusion. Also, intact polymeric nanoparticles can penetrate into the target cell by endocytosis process. These nanoparticles attach to the cell surface receptor and form endosomes. Once reaching the cytoplasm, these endosomes are lysed by enzymes or by the applied external stimulus; thereby, the drug-loaded nanoparticles and the drug are released in the cytoplasm. Thus, cellular internalization of drug nanocarriers takes place (Fig. 2.2) (Wang et al. 2012).

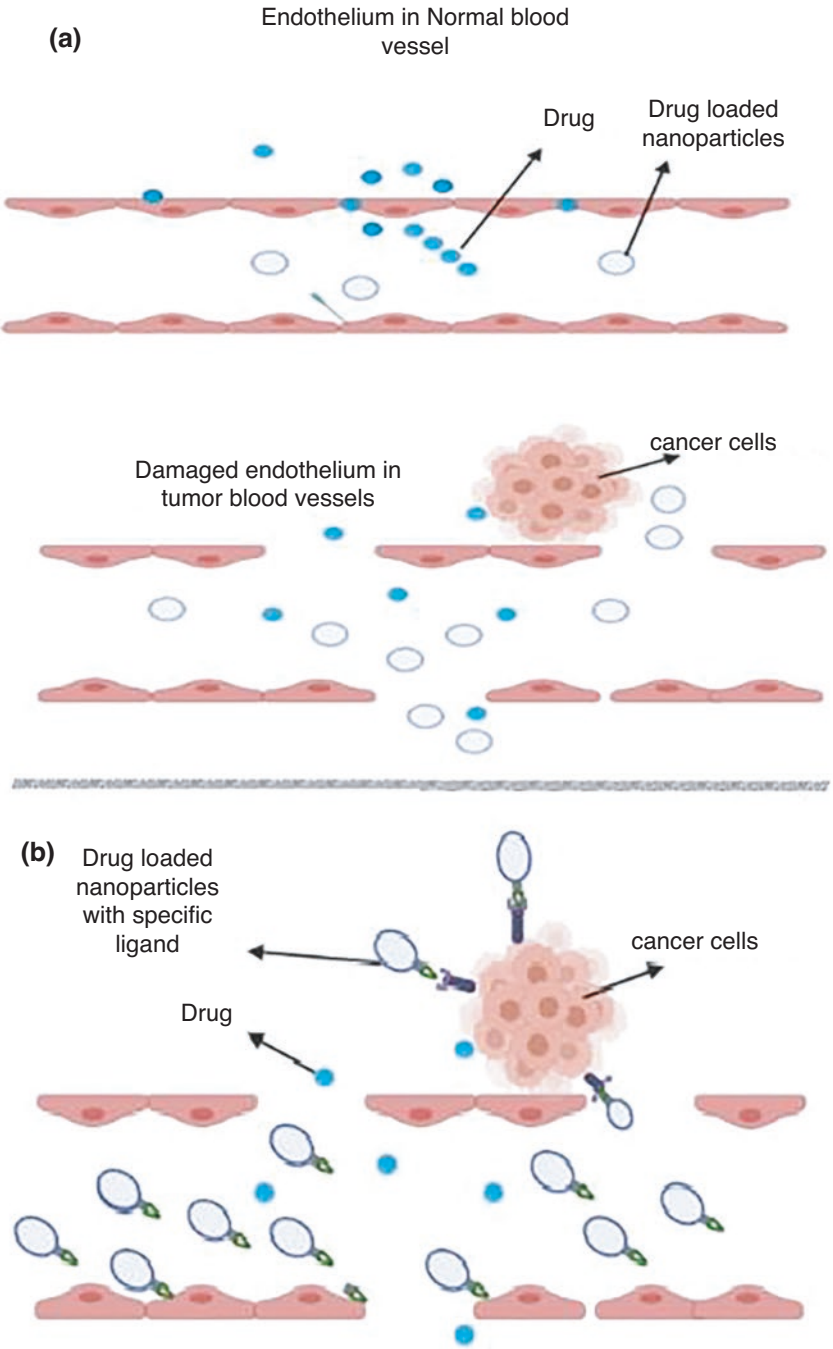

Fig. 2.1 (**a**) Mechanism of passive targeting. (**b**) Mechanism of active targeting

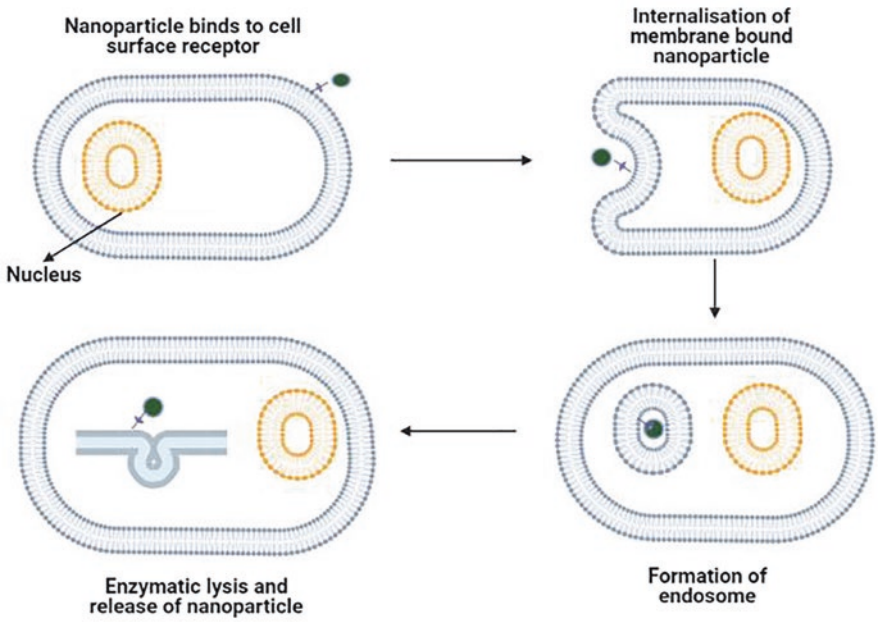

Fig. 2.2 Cellular internalization of drug nanocarriers by endocytosis

2.2.3 Release of Drug from Nanoparticles

The molecular nature of the nanoparticles (e.g., organic, inorganic, or hybrid compounds), the site where drugs are loaded to nanoparticles (shell region or matrix region), and the strength (strong covalent or weak non-covalent interactions) of binding of drug with nanoparticle are the three main parameters which dictate drug delivery profile (Mattos et al. 2017). The most prominent advantage of nano drug delivery system is the accurate rate of drug release at the target site. When the drug-loaded nanoparticle reaches the target site, the drug molecule has to be released from the nanocarrier at definite controlled rate. This can be achieved either *spontaneously* or by applying proper *stimulus.* The spontaneous release involves few mechanisms like gradual diffusion along with the degradation of delivery system or by solvent extraction or by chemical process. For stimulus-responsive nanosystems, the stimulus applied or used may be internal or external stimulus. The stimulus-responsive prototypes involve the application of *physical stimuli* like temperature, light, ultrasonic vibrations, magnetic field, *and* ionic strength; *chemical stimuli* like redox and pH; or *biological stimuli* like enzymes, etc. (Fig. 2.3) (Ding and Li 2017).

Smart stimuli-responsive drug delivery systems (SDDS) are the basis for fabricating several controlled drug delivery systems (DDSs). SDDS have drawn much focus and attraction because of controlled drug release with an effective

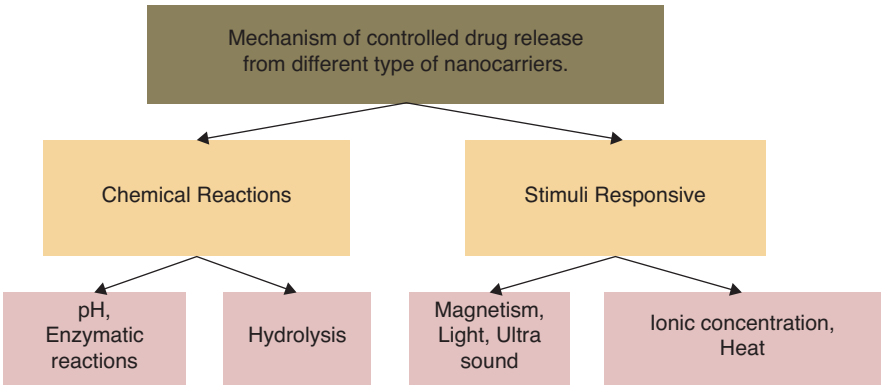

Fig. 2.3 Mechanism of controlled drug release from different types of nanocarriers

concentration for an extended duration, thus avoiding the need for repeated dosing and thus reducing the side effects. Also, SDDS prevent premature degradation of chemotherapeutic agents and induce their absorption into solid tumors (Hu et al. 2017; Ma et al. 2017).

2.3 Nanoparticle Drug Delivery Systems

Nanocarriers like nanotubes, nanoshells, nanopores, nanoliposomes, solid lipid nanoparticles, nanocapsule, dendrimers, fullerene, quantum dots, nanosphere, nanocrystals, gold nanoparticles, mesoporous silica nanoparticles, etc. are reliable novel drug delivery systems. Moreover, nano robotics and nanochips are modern systems developed for drug delivery (Couvreur 2013).

2.3.1 Classification of Nanoparticles Based on Composition

Generally nanoparticles are classified based on their composition, namely, *organic*, *inorganic*, and *hybrid* (Fig. 2.4). The organic or polymeric nanoparticles are not toxic and biodegradable. Dendrimers, solid lipid nanoparticles, nanogels, and hollow spheres like micelles and nanoliposomes are examples for organic nanocarriers. The carbon-based organic nanoparticles are fullerenes, graphene, and carbon nanotubes which are entirely made of carbon only.

The inorganic nanocarriers are principally composed of metals (silver, gold, iron, copper, aluminum, cadmium, cobalt, and zinc) or metal oxides (titanium oxide, iron oxide, magnetite, silicon dioxide, cerium oxide, and zinc oxide). Metal oxide-based nanocarriers show advanced properties than their metallic counterparts. Examples

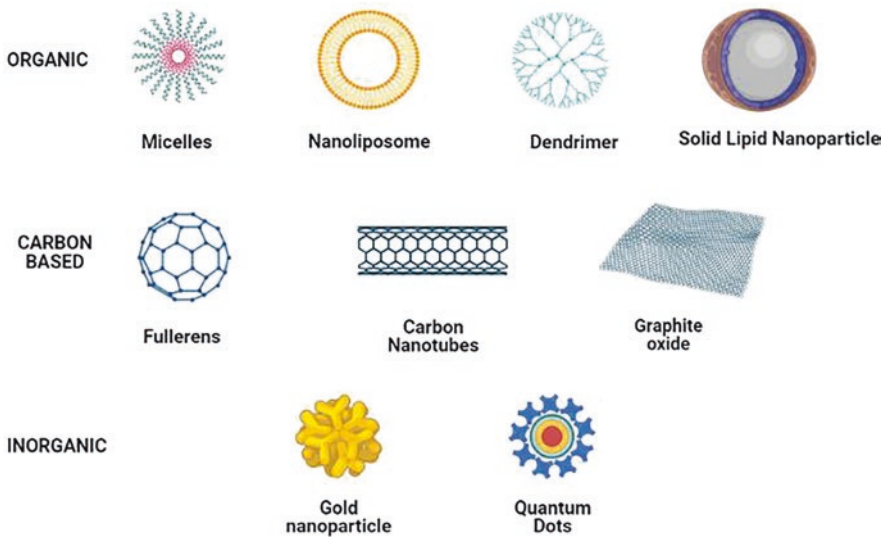

Fig. 2.4 Classification of nanoparticles for drug delivery applications

of metal oxide-based nanocarriers include quantum dots (QDs), mesoporous silica nanoparticles (MSNs), superparamagnetic iron-oxide nanoparticles (SPION), etc. (Domenico et al. 2019).

2.4 Organic Nanoparticles as Drug Carriers

The nanocarriers composed of organic compounds are endowed with excellent biological compatibility, enhanced drug carrying ability, high colloidal stability, and optimum size. Organic nanoparticles are well suited to carry a range of hydrophilic or lipophilic/hydrophobic drugs. Based on method of synthesis, nanocarriers are classified into two main types: amphiphilic systems obtained by self-assembly processes (such as nanovesicles and nanomicelles) and those nanocarriers prepared by *specific synthesis processes* (e.g., dendrimer nanoparticles, chemical cross-linked nanogels, CNTs, fullerenes, graphenes, etc.,) (Lombardo et al. 2015). Amphiphilic macromolecules contain both *hydrophilic* and *hydrophobic* (*lipophilic) r*egions. Hydrophilic regions that interact with surrounding aqueous medium may be negatively or positively charged or neutral. *Lipophilic* regions are usually made of long hydrocarbon chains. Self-assembly interactions involved are non-covalent mild interactions, namely, van der Waals forces, hydrogen bonding, hydrophobic attractions, hydration and electrostatic interactions, *pi-pi* bonding, coordination bonding, steric interactions, depletion, and restoration reactions (Degiorgio and Corti 1985).

2.4.1 Lipid-Based Amphiphilic Drug Delivery Systems

2.4.1.1 Nanoliposomes

Vesicles are made of natural or synthetic lipids known as liposomes. They are self-assembled amphiphilic systems. In water, they form a flexible bilayer vesicle with the hydrophilic regions facing the aqueous phase while hydrophobic regions are embedded inside by self-assembly process (Khosa et al. 2018). Generally, the degree fluidity of a lipid bilayer is based on two factors: composition and temperature. As the temperature increases, a bilayer composed of phospholipids transform from a rigid crystalline gel form to more mobile liquid form. Hence, desired fluidity of vesicle can be attained by adjusting composition and temperature. Fluidity plays an important role in uptake and discharge actions of cells (Kiselev and Lombardo 2017). Nanosized liposomes are called nanoliposomes. They contain hydrophilic head regions and lipophilic tail regions. Nanoliposomes are engineered to carry and deliver small drug molecules, imaging compounds, peptides, proteins, DNA and RNA, etc. Usually hydrophilic medicaments are loaded in hydrophilic regions of nanoliposomes, and lipophilic medicaments are loaded in hydrophobic tail regions. Nanoliposomes can easily escape from decomposition and clearance by macrophages present in the liver. They can execute both passive targeting and active targeting strategy for the delivery of therapeutic compounds (Kumar et al. 2010). Nanoliposomes principally get accumulated in the target tissue by passive targeting and discharge loaded drugs for longer duration. Active targeting is attained by attaching antibodies, proteins, peptides, and ligands on the outer region of nanoliposomes. In active targeting, nanoliposomes specifically reach the target diseased organs or tissues and enhance the sustained release of drug compound for longer duration. Active targeting is very specific in action since healthy cells are unaffected and diseased cells alone exposed to the drug (Riaz et al. 2018). This is the advantage of active targeting over passive targeting. For example, nanoliposomes engineered with C6-ceremide ligand are specifically targeted toward overexpressed leukemic cells and hence can be used as therapeutics for leukemia (blood cancer) (Kumar et al. 2012). Nanoliposomes composed of polyethylene glycol modify the pharmacokinetic characters of drug compounds resulting in prolonged half-life time for drug clearance (Dadashzadeh et al. 2008).

Nanoliposomes are able to present slow and steady release of an encapsulated drug at the target tissue resulting in enhanced efficacy. Many stimulus-responsive drug release nanoliposome models have been developed. Shi et al. (2017) developed light or photo-stimulated nanoliposomes (PNLs) against drug-resistant human breast cancer (MCF-7/MDR) cell lines and MCF-7/MDR mice tumor models. The PNLs are designed to carry two compounds, a photosensitizer and an anticancer drug molecule. The photosensitizer (hematoporphyrin monomethyl ether) molecule was incorporated in the outer lipid bilayer, and an anticancer medicine doxorubicin was encapsulated in the inner region of the nanoliposome. When photosensitizer molecule is activated by light, it leads to enhanced cytotoxicity and decreases drug

resistance in tumor models. This reaction is carried out in synchrony with a photo-initiation reaction and fast release of anticancer medicine. Thus, combining effective chemotherapy and photodynamic therapy showed much improved antitumor activity and attained notable tumor suppression in drug-resistant tumor models.

2.4.1.2 Solid Lipid Nanoparticles (SLNs)

SLNs are innovative colloidal lipospheres of size less than 1000 nm. They exist in the form of nanoscale lipid emulsions, in which the lipid in oily (liquid) state is replaced by a solid lipid. SLN has exclusive biophysical characteristics such as tiny size with large surface area, excellent drug loading capacity, and the significant interaction of phases at the interface, all of which makes it an efficient drug delivery device. SLN lipospheres are basically solid at human normal body temperature (98.6 °F) (Pardeike et al. 2009). SLNs are composed of a variety of lipids, including mono-, di-, and triacylglycerols like tristearoyl glycerol, partial acylglycerols like Imwitor, long chain fatty acids like stearate and palmitate, and steroids like cholesterol and waxes like cetyl palmitic acid. They have outer shell and inner core regions. The lipids present in SLN are mostly physiological lipids which makes it advantageous in reducing the danger of acute as well as chronic toxic consequences. The lipid dispersions are generally stabilized by using a wide range of emulsifiers or combination of emulsifiers (Cavalli et al. 1993). The inner solid hydrophobic lipid core is loaded with drug compound which is solubilized in solid lipid matrix of high melting point. This core is enclosed by single layer of phospholipid. The loaded drug can be triggered easily for successive release from SLNs. Stabilizing surfactants are mixed to SLNs to convert it to an administrable emulsion.

Release of loaded drug from SLNs is carried out by disruption or degradation of solid matrix of SLN and diffusion of drug. Basically, three drug loading models are applicable for SLNs: homogenous matrix model, drug enriched shell in core shell model, and drug enriched core in core shell model (Fig. 2.5) (Pardeshi et al. 2012). Many kinds of stimulus-responsive SLNs have been designed to attain efficient drug release at target site. The stimulus applied can be either external or internal type. The main factor which affects the release of the drug from SLNs is particle size. Small size particles with larger surface area showed fast drug delivery profile when compared with large size SLNs. Another factor which affects the rate of drug release from SLNs is the site of drug loading on SLNs, for instance, rapid release of drug could be noticed when drug is loaded on outer shell (drug enriched shell in core shell model) than in inner core (drug enriched core in core shell model) (Rabinarayan and Padilama 2010).

Drugs in SLN are inserted in both regions: the matrix and shell (homogenous matrix model). This type of drug incorporation enables versatile dual drug release (immediate and sustained release) from SLN. Drugs loaded on the shell region of SLN will release first followed by the release of drugs from matrix region. The drug released from the shell is rapid and results in immediate drug effect. Afterward, depending on the composition of the matrix lipid, the matrix degrades or erodes and

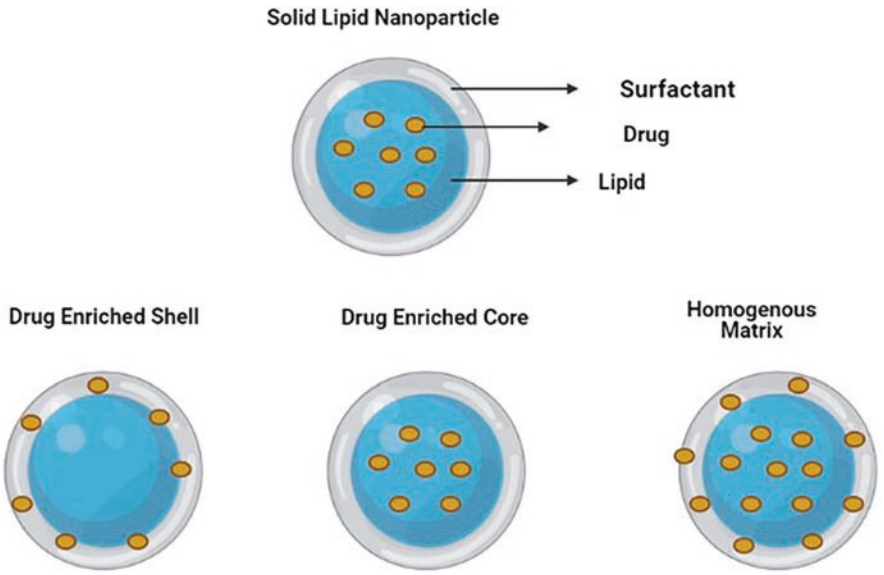

Fig. 2.5 Models of drug loading into SLN

leads to sustained or controlled drug release, thus enabling gradual drug effect. Thus dual drug release profile is obtained with SLNs. The release of drug from SLNs is based on the diffusion of drug compounds through lipid matrix and in vivo breakdown of lipid matrix by the action of lipase enzymes present in cells (Westesen and Siekmann 1996). Muller et al. (1993) studied on the in vitro degradation of SLNs in solutions of pancreatic lipase. The rate of lipid degradation was analyzed by quantifying the concentration of liberated free fatty acids by turbidimetry technique. The rate of lipid degradation was depending on the composition of the lipid matrix. The kinetics of breakdown is very high for triacylmyristic acid (triglyceride) moderate for acetylpalmitic acid (wax) and comparatively slower for triglycerides with very long chain fatty acid, for example, tribehenin.

High temperature or high concentration of surfactant can lead to burst discharge of drug from SLNs. So, the synthesis of SLN is generally carried out at room temperature to prevent burst discharge and partitioning of drug compound in aqueous phase but helps the partitioning of large amount of drug in lipid phase. Thus, at low temperatures, slow and controlled drug release is obtained from SLN without immediate or burst release of drug. Based on solid-liquid transition character of SLN upon applying heat, thermoresponsive SLNs have been developed by Rehman et al. (2017). Different combinations of fatty acids (laurate and oleate, laurate, and linoleate) were used to develop SLNs. The drug release profile was studied, and the results proved that rapid or immediate discharge of loaded 5-fluorouracil drug was >90% observed at 39 °C featured to the liquefaction of lipid core, whereas 22–34% of drug discharge was observed at 37 °C where solid core is retained.

In another research work, pH-responsive cholesterol-polyethylene glycol-coated SLNs were prepared and loaded with anticancer drug doxorubicin. The electric charge attraction between the positively charged doxorubicin and anionic (negatively charged) lipid core laurate (by protonation) plays an important role on drug release pattern. The release pattern was investigated, and it was reported that these stimulus-responsive particles showed rapid discharge of doxorubicin at pH 4.7 (intracellular pH) compared to slow drug discharge at pH 7.4 (extracellular pH). The rapid release of doxorubicin from SLN at low intracellular pH is due to the weakening of electrostatic attraction between the lipid core and the drug doxorubicin (Chen et al. 2015).

2.4.2 Polymer-Based Drug Delivery Systems

Many biodegradable synthetic and biological polymers are utilized for the synthesis of polymeric nanoparticles. Widely used synthetic polymers are polylactide (PLA), poly (D, L-lactide-co- glycolide) (PLGA), poly (glycolic acid) (PGA), and polyethylene glycol (PEG). These polymers have characteristic functions in drug delivery processes. They can provide controlled discharge of therapeutic agents by crossing the biological and also pathology barriers of the tissues, hydrolysis under in vivo conditions, and having high biocompatibility and less immunogenic and negligible toxicity. These properties make them good drug delivery system. PLGA is highly degradable and nontoxic because the hydrolytic products of this polymer are lactic acid and glycolic acid, which are degraded and eliminated naturally from the body (Tyler et al. 2016). Alginate is a natural polysaccharide polymer made of mannuronic and glucuronic acid monomers. It is an anionic mucoadhesive biopolymer used in nanoparticles to carry drugs (Maitra and Shukla 2014). Chitosan polymer is another natural, mucoadhesive, degradable, and biocompatible molecule with positively charged functional groups to which drugs can be bound (Yoo and Park 2001).

2.4.2.1 Polymer-Based Micelle and Vesicles

Micelle-like nanocarriers are made of amphiphilic polymers formed by the *self-assembly* process. The micelles contain inner hydrophobic (lipophilic) core and outer hydrophilic shell regions. The inner region forms a nanoenvironment for the loading of hydrophobic drugs and considerably improves the solubility and hence bioavailability of lipid-based drugs. Meanwhile, the outer shell forms a stabilizing interface between the lipophilic core and the aqueous phase; this helps in improving colloidal stability and suppressing aggregation and decreases unnecessary interactions between other components in the blood. The micelles

of dimension less than 200 nm can escape from detection and clearance by reticuloendothelial cells and exhibit increased EPR effect at target tissues (passive targeting) (Yin et al. 2016).

In many polymeric micelles used for efficient drug delivery purpose, the core contains hydrophobic PLA or PLGA polymers, and the hydrophilic shell is made with the most hydrophilic polymer polyethylene glycol. For example, in PEG-PLGA copolymeric micelles, lipophilic PLGA core can proficiently encapsulate several kinds of drugs, while the hydrophilic PEG shell inhibits the binding of proteins and phagocytic cells, thus prolonging exist time in the blood (Cho et al. 2016). *Chitosan*-derived self-assembled *amphiphilic micelles* exhibit mucoadhesive characteristics, suitable to target at the epithelial tight junctions. Chitosan-derived nanomicelles are extensively used for continued drug delivery to different kinds of epithelia, such as buccal, intestinal, nasal, eye, and pulmonary. Chitosan-based nanocarriers can allow either parental or nonparental routes of administrations and be used for the treatment of skin and gastrointestinal tract diseases, lung diseases, and eye infections (Yoo and Park 2001).

Polymersomes are *vesicles* made of amphiphilic polymers, characterized by the presence of bilayer arrangement with an aqueous interior core. The water-soluble therapeutic agents can be encapsulated in the aqueous core, and lipophilic drugs can be integrated into the internal region of the bilayer structure. *Critical micelle concentration* (*CMC*) is defined as the concentration of surfactants above which micellar structure is formed by self-assembly process. Polymer-based vesicles and micelles retain their structural integrity above the CMC value. Below the CMC, the assembly of nanoarchitectures dissociate into component polymeric chains, which leads to loss of their drug carrying ability (Mikhail and Allen 2009). Stimulus-responsive polymersomes are engineered which are enabled to elicit controlled drug release and improved imaging sensitivity at tumor and intracellular microenvironment. Weak acidic pH, range of temperatures, many specifically overexpressed enzymes, and redox species are the most used key endogenous stimuli for the triggered drug release at the target tissues.

For example, temperature-sensitive polymeric nanocarriers are used in drug delivery applications for cancer treatment. Lower critical solution temperature (LCST) is the temperature below which the polymers are dissolved incompletely in water phase. Below LCST, polymer holds water through hydrogen bonds. However, at temperatures above LCST, the hydrogen bonds are disrupted rendering the polymer hydrophobic to precipitate out. Poly (N-isopropylacrylamide) (PNIPAm) is the most frequently used thermoresponsive polymer with LCST at 33 °C (Wei et al. 2009). Thermosensitive micelles are made of thermoresponsive polymers, which can undergo a sharp variation in their solubility in water with change in temperature. When the solubility is disrupted by temperature, the micellar structure is destabilized. Thus, the micellar structure can be destabilized by altering the surrounding temperature slightly above or below the LCST. This phase change is utilized for the controlled release of encapsulated drug by applying heat or cooling the environment for a definite period (Ward and Georgiou 2011).

2.4.2.2 Polymer-Based Nanogels

Polymeric nanogels are three-dimensional networks of size ranging from 100 to 200 nm. The cross-link between polymer chains may be chemical or physical in nature. The very peculiar character of nanogels is swelling in water. When diffused in water medium, they form semisolid states by swallow of large amount of water (hydrogels).

To synthesize chemically cross-linked hydrogels (Fig. 2.6), the hydrophilic polymer solution is treated with a bifunctional cross-linking agent. Few examples of chemical cross-linking agents used are glutaraldehyde and mono- and polycarboxylic acids. These agents can cross-link both proteins and polysaccharides (Sosnik and Seremeta 2017; Reddy et al. 2015),

while the cross-linking in physically cross-linked hydrogels is accomplished by the formation of non-covalent bonds (hydrogen bond, ionic, van der Waals forces, hydrophobic interactions) between polymers. Complex of polyanionic polymer with polycationic polymer has been used in many drug delivery approaches. The degree of cross-linking interactions (hydrogen bonding or ionic boning) between polymer chains is based on a variety of parameters such as polymer concentration, nature of solvent used, and solution temperature and pH. By using optimum conditions, these cross-linking interactions can be disrupted, and the controlled delivery of entrapped drug at target tissues is performed by these hydrogels (Hennink and van Nostrum 2002).

The small size of nanogels enables them to undergo rapid structural modifications in response to surrounding changes. Stimulus-responsive nanogels show

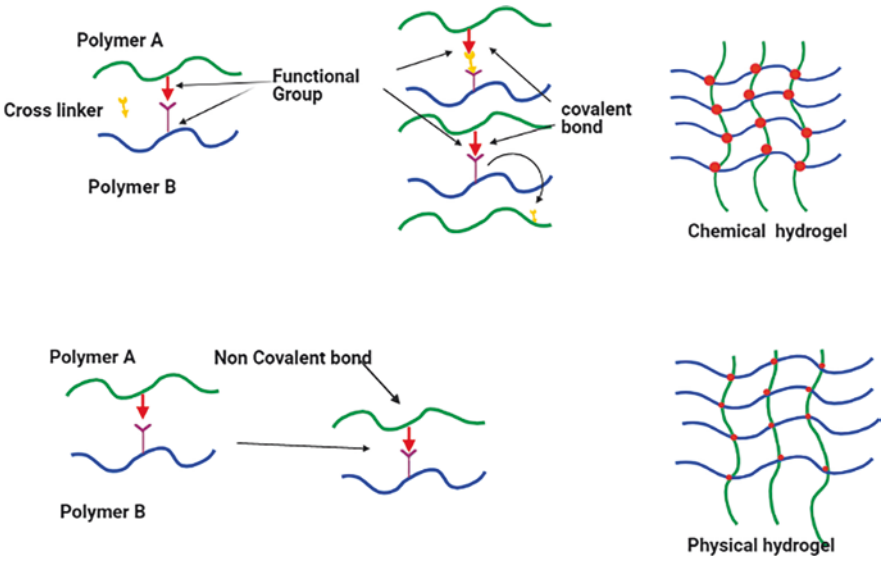

Fig. 2.6 Chemical and physical hydrogel

structural transitions in response to internal/external stimuli such as temperature, pH, electric field, and light (Soni and Yadav 2016). In disulfide-based cross-linked nanogels, the disulfide bond is stimuli-sensitive and biodegradable by biochemical reductants such glutathione or thioredoxin I/II. This system was used for the controlled release of doxorubicin (Chacko et al. 2012). Nanogels containing doxorubicin are studied for the treatment of cancer in the form of pH- and temperature-sensitive nanogels made of maleic acid poly-(*N*-isopropylacrylamide) polymers. Doxorubicin is liberated from these nanogels following a slight decrease in pH or through temperature stimulus (Sharma et al. 2016). Nanogel carriers are used to deliver large proteins and small peptides to the target tissues. Various types of nanogels used in the controlled delivery of drugs, protein, and peptides are listed in Table 2.1 (Kousalová and Etrych 2018).

Alginate is an anionic mucoadhesive biopolymer, used in nanogel formulations to encapsulate cells and proteins. It is biocompatible and nonimmunogenic in nature. Alginate is a naturally occurring polysaccharide consisting of mannuronic acid and glucuronic acid monomers. At room temperature and biological pH, alginate polymers produce a cross-linked gel complex in the presence of calcium ions. The gel structure can be distorted by removal of calcium ions from alginate gel by using chelating agent. Upon destabilization, the encapsulated drug is released from calcium alginate hydrogels and delivered to target tissue. This kind of stimulus-responsive controlled drug release strategy is used in various medicinal applications like scaffolding for cell cultures, drug delivery, and animal tissue engineering (like wound dressing) (Maitra and Shukla 2014). Nanogels of size 10–100 nm is used for systemic drug administration, since they can pass from small blood vessels via gaps in the endothelial membrane and reach tissues (passive targeting). Passively targeting nanogels are used for neoplastic disease treatment (Rigogliuso et al. 2012). Encapsulated paclitaxel in nanogels was actively targeted to the liver, breast, or prostate tumors using galactosamine, transferrin, anti-HER2, or parts of mAbs (anti-HER_2 scFv F5) as ligands selective for those cancer cells (Kousalová and Etrych 2018). Nanogels are an especially attractive tool for delivery of nucleic acid

Table 2.1 Stimulus-responsive nanogels for controlled delivery of drugs

Nanogel composition	Type of stimulus	Uses
Poly(N-isopropylacrylamide-copolyethylenimine-co-N,N′-methylenebisacrylamide)	Temperature and pH	5- Fluorouracil-loaded nanogel used for mastocarcinoma therapy
Poly(N-isopropylacrylamide-cobutylacrylate-co-N,N′-methylenebisacrylamide)	pH	Methotrexate-loaded nanogels used for therapy for breast and lung cancer, leukemia, and lymphoma
Poly(methylacrylic acid-co- N,N´-ethylenebisacrylamide)-coated Fe3O4 nanoparticles	pH and temperature	Controlled delivery of α-chymotrypsin using a magnetic field
Self-assembled cholesterol-bearing pullulan	Heat and light	Controlled delivery of bone anabolic agents, e.g., recombinant hormones and cytokines

drugs (plasmid DNA) and are hence widely used for gene therapy-based treatment such as in cancers, hemophilia, and viral infections (Ginn et al. 2013). DNA delivery using nanogels is advantageous over nonencapsulated DNA because of their enhanced cellular uptake and extended period of circulation in the blood (Peer et al. 2007). Cationic nanogels composed of PEO and poly (ethylenimine) are used to increase the transport of oligonucleotides across the GI tract epithelial layer and blood-brain barrier. Nanogels composed of polymer-protein conjugates have desirable drug carrier characteristics such as longer plasma half-life and improved protein stability.

2.4.2.3 Dendrimer-Polymeric Nanocarriers

Dendrimers are three-dimensional, treelike highly branched polymeric nanostructures of diameter ranging from 2.5 to 10 nm. Dendrimers exist in various shapes like spheres and flattened spheroids (disks) and ameba-like and starfish-like structures. The polymeric branch points are covalently bonded to middle core. The branching units are arranged into typical symmetric concentric layers around the core; these layers are known as generations. Each branching unit terminates with different kinds of functional groups exposed on the surface of the nanoparticle (Fig. 2.7) (Duncan and Izzo 2005). Dendrimers are prepared by *specific synthesis* process. The dendrimers are made of synthetic or biopolymers.

For medical applications, polyamidoamine (PAMAM) class and polypropyleneimine class dendrimers are generally used. A few other kinds of dendrimers are peptide dendrimers, glycodendrimers, polyethyleneimine (PEI) dendrimers, etc. Dendrimers are applied for the transport of DNA in cancer treatment or viral infections in various tissues and organs. Dendrimers display desirable drug delivery characteristics like monodispersity, presence of numerous functional groups, definite structure, and multivalency which makes them versatile nano drug carriers for various diseases especially for cancer treatment.

Controlled drug release from dendrimers depends on two factors.

(a) Chemical modification of dendrimer: For example, the drug indomethacin loaded on G4-NH2 dendrimer showed slow and controlled drug release when compared to the rapid discharge noted with G4-COOH dendrimer. Thus, the chemical modification of functional groups determines the strength of interaction of drugs with dendrimers which in turn determines the drug release kinetics from dendrimers (Chauhan 2018).
(b) Physical loading: The second parameter which determines the rate of release of therapeutic agent from dendrimers is physical loading which means dendrimer-to-drug molar ratio. For example, the drug release kinetics of cisplatin from dendrimer was observed to be directly related to the cisplatin/dendrimer molar ratio (Kulhari et al. 2015).

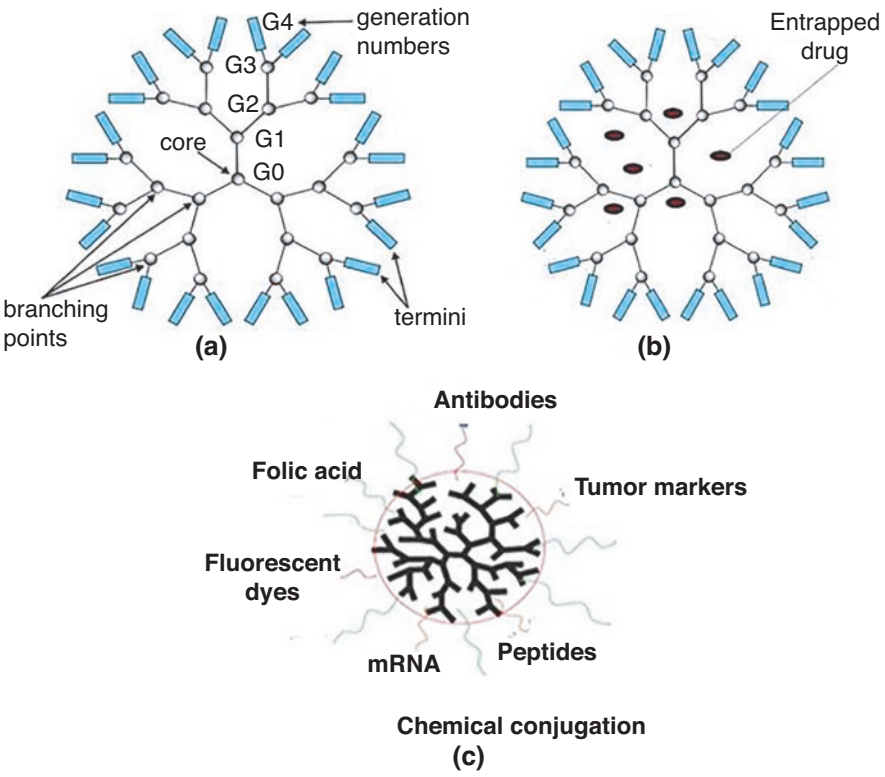

Fig. 2.7 (**a**) Structure of dendrimer nanocarrier. (**b**) Physical entrapment of drugs in dendrimer internal gaps. (**c**) Chemical conjugation of drugs through surface functional groups

Stimulus-responsive controlled drug release strategy depends on the in vivo breakdown of covalent bond linking drug and dendrimer by suitable enzymes or favorable physical environment like pH, temperature, etc.

Figure 2.8 depicts the use of dendrimers as gene delivery vectors. For gene therapy purpose, polyamidoamine (PAMAM)-based dendrimer is widely used. The possible mechanism for gene therapy by dendrimer is as follows: At first, the plasmid DNA (drug) is loaded on to dendrimer to form dendriplex (dendrimer and DNA complex) under in vitro conditions. Then, the dendriplex is mixed with cells under in vitro condition or is applied directly into animals in vivo or ex vivo by which dendriplex can reach the target cells by the blood circulation. On interaction with cell membrane, the dendriplex gets internalized into cytoplasm by endocytosis process. Now, the dendriplex experiences the change in pH from 7.4 (extracellular pH) to 5.5 (intracellular pH); this variation in pH triggers deprotonation of dendrimer functional groups which leads the dissociation of dendrimer and DNA from dendriplex and also results in diffusion of H+ and Cl− and water into the endosomes, leading to osmotic swelling and burst of endosome. This pathway of release of free nucleic acid into cytoplasm by dendrimer destruction is known as endosome escape

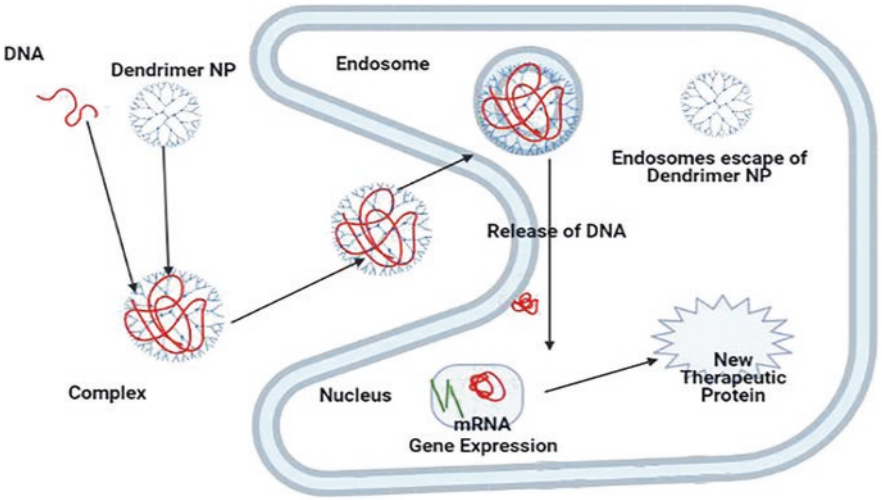

Fig. 2.8 Schematic presentation of application of dendrimers for gene therapy

pathway. In this pathway, the cargo of endosome is released into cytoplasm prior to the fusion of endosome with lysosome. Finally, the DNA from cytoplasm reaches the nucleus resulting in expression of gene. Thus, pH acts as internal stimulus for controlled targeted drug release (Palmerston Mendes et al. 2017).

2.4.3 Carbon-Based Drug Delivery Systems

These nanoparticles are made with carbons only which include carbon nanotubes, graphene, fullerenes, etc. Carbon-based nanodevices have distinctive, electric, optical, thermal, and mechanical characteristic, finding application in medicine as carriers of drug and imaging agents (Tonelli et al. 2015). Carbon-based nanomaterials have potential toxicity, but by suitable surface modifications, these nanomaterials are made susceptible to enzymatic degradation, thus rendering them nontoxic and more biocompatible (Bhattacharya et al. 2013).

2.4.3.1 Carbon Nanotubes (CNTs)

The CNTs are nanometer-scale tubelike structures made of carbon atoms in sp2 hybridization. The tube wall in CNTs consists of single (SWCNTs) or multiple (MWCNTs) layer of graphene sheets. CNTs comprise versatile drug delivery systems. CNTs show strong absorption in the near IR light and Raman scattering, photo-acoustic characteristics which render them as versatile device for in vivo biomedical applications like diagnosis and therapy (Kushwaha et al. 2013). The surface

of raw CNTs is highly hydrophobic in nature and is insoluble in aqueous medium. To overcome this dilemma, functionalization of CNTs is carried out to increase its solubility. Functionalization is the process of binding required functional groups onto the walls of CNTs by chemical synthesis method to produce functionalized CNTs (f-CNT). To enhance the solubility, generally carboxylic or ammonium groups are incorporated to carbon nanotubes. f-CNTs are used for various biomedical applications like transport of small proteins, DNA/RNA, and drug molecules. The functionalization of CNTs not only improves solubility but also increases biocompatibility of loaded drugs and encapsulation tendency hence used for multimodal drug delivery and imaging. CNT-drug composites are easily eliminated from the body (Spitalsky et al. 2010).

Drugs can be incorporated onto CNTs either by mild non-covalent bonds (pi-pi bonding, van der Waals attractions, and hydrophobic interactions) or by covalent bonds. CNTs covalently attached cisplatin (drug) and with epidermal growth factor (ligand) are designed and actively targeted toward overexpressing EGF receptors present on head and neck squamous cancer cells. Thus, they are used for the treatment of malignancy (Bhirde et al. 2009). The CNTs can easily transport DNA molecules across plasma membrane, thus finding application in gene therapy. Genes can be loaded either at the tips or inside of CNTs. Al-Jamal et al. (2011) reported successful targeting of siRNA to the CNS by stereotactic administration of MWCNTs, resulting in the protection of neurons in experimental animals. Sacchetto et al. (2014) provided evidence that when PEG-treated SWCNTs were loaded with antisense oligonucleotides and administered to intra-particular region of chondrocytes in mice, they showed undisturbed cartilage homeostasis and no systemic side effects. Carbon nanotubes are used for the delivery of prodrugs (precursors of active drug). The prodrug can be converted to active form once delivered inside the cancer cells, for example, drug cisplatin. By using carbon nanotubes, the prodrug is delivered in the inactive form of platinum (oxidation IV state) which is then reduced to the active form of platinum (oxidation II state) selectively inside the cancerous cell only. Thus, the active drug does not interact with noncancerous cells, thus leading to targeted drug delivery (Hirsch et al. 2006). CNTs can even act as anticancer agents by themselves. Once CNTs entered cancerous cells, external electromagnetic radiation such as radiofrequency or NIR radiation were applied to heat up the carbon nanotubes and thus kill the cancer cells by the generated heat (Tomalia et al. 2007).

Heister et al. (2012) studied drug loading, dispersion stability, and stimulus-responsive targeted drug release of cancer drugs with oxidized SWCNTs (oxSWCNTs) and reported that pH 8 for doxorubicin and pH 9 for mitoxantrone were optimum for binding to oxSWCNTs by non-covalent interactions at 4 °C in the dark. Further, dispersion stability was improved by PEGylation of oxSWCNTs with various PEG formulations. It was also standardized that drug/oxSWCNTsPEG weight ratio of 1:2 was optimum for quantitative drug binding. The drug/oxSWCNTsPEG was tested for the density of drug loaded by suitable techniques, for example, by UV-VIS spectrophotometric analysis (at 479 nm for doxorubicin or at 550 nm for mitoxantrone). It was also reported that drug liberation of both

doxorubicin and mitoxantrone from oxSWCNTsPEG and drug uptake by HeLa cells were significant at pH 5.5, which is the estimated pH for any drug delivery system that would involve in the endosomal pathway. The endosomal pathway is an endocytotic, energy-requiring engulf mechanism, by which the drug/oxSWCNTsPEG complexes were engulfed into endosomes and subsequently the drug was released from carrier due to the low endo-lysosomal pH. The drug freed from carrier would then be translocated to the nucleus to carry out its cytotoxicity function by interfering with DNA synthesis (Heister et al. 2012).

2.4.3.2 Fullerenes

Fullerenes are another promising nanomaterial for drug delivery and imaging. Fullerenes are made of carbon atoms joined to three other carbon atoms by covalent bonding resulting in hollow sphere or ellipsoid tube structures. Fullerenes are also named as "buckyballs" (Fig. 2.9). The size of fullerenes ranges from those containing 20 carbon atoms to 100 carbon atoms. However, the most widespread fullerene is C_{60} made with 60 carbon atoms. C_{60} are hydrophobic in nature and aggregate very quickly in aqueous phase (Prato 1997). To overcome this problem, several methods are used to make C_{60} more hydrophilic and make it as an effective drug delivery system. Fullerenes are converted to highly hydrophilic functionalized nanostructures by treating with amino acid, carboxylic acid, polyhydroxyl group, amphiphilic polymers, etc. (chemical functionalization process) (Chen et al. 2001). Fullerenes and C_{60} derivatives lack immunogenetic action which supports their wide use in biomedical field.

Fullerenes are used for transport of antiviral, antibacterial, and chemotherapeutic drugs. C_{60} derivatives have potential antiviral activity. Dendrofullerene 1, a derivative of C_{60}, has strong antiprotease activity. It can precisely fit into the hydrophobic pocket of HIV protease enzyme and hinder the binding substrate molecules at the active site of enzyme (Schuster et al. 2000). Amino acid derivatives of fullerene C_{60} interfere with multiplication of HIV and human cytomegalovirus (Kotelnikova et al.

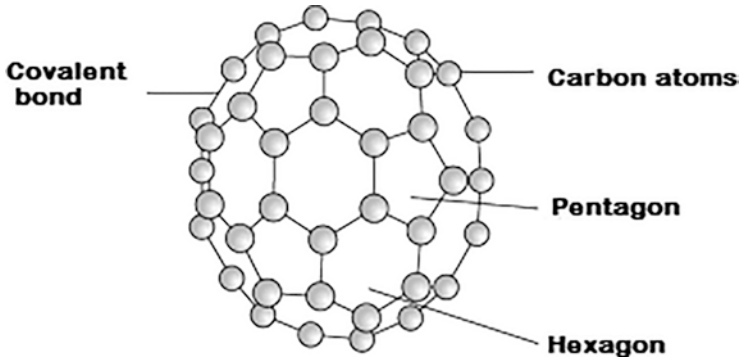

Fig. 2.9 Fullerenes

2003). Monoclonal antibodies targeted against melanoma tumors are conjugated with multiple C_{60} buckyballs to develop a new system of active targeting and simultaneous multiple drug delivery to tumors (Darshana Nagda et al. 2010). Buckyballs do not break down in the body and are excreted intact. This property has significant use to deliver anticancer drugs that are harmful to normal cells. For example, buckyball drug delivery nanoparticles that carry hazardous radioactive elements would allow for the complete excretion of radiation from the body following cancer treatment (Chan 2007). The conventional drug delivery methods have disadvantage of uncontrolled drug release in circulation and the slow release of drug at target tissue. Many stimulus-responsive drug release models are developed with C_{60} derivatives. Shi et al. (2016) engineered an "on- off" model of controlled drug release system with C_{60} derivative. In this, doxorubicin was covalently bonded to C_{60} through a reactive oxygen species (ROS)-sensitive thioketal linker (C_{60}-DOX), and then the hydrophilic shell was fixed to the external surface of C_{60}-DOX, to get C_{60}-DOX-NGR. The hydrophilic shell can impart enhanced stability in body fluids and also provides efficient tumor targeting. C_{60}-DOX-NGR was able to strongly hold doxorubicin (off state) even at weak acidic pH (pH 5.5). C_{60}-DOX-NGR can be switched to "on state" when large amounts of reactive oxygen species were generated by C_{60}, resulting in breaking of ROS-sensitive thioketal linker, thereby leading to burst release of doxorubicin. The "off-on" state of C_{60}-DOX-NGR could be accurately remote-controlled by irradiating with a 532 nm laser beam (at a low power density) with a high spatial/temporal resolution (combined phototherapy with chemotherapy). This new C_{60}-based drug delivery system with "off-on" switch showed efficient anticancer activity and a low toxicityunder in vivo and in vitro conditions.

A biocompatible, hydrophilic fluorescent fullerene derivative, C_{60}-TEG-COOH, was prepared by treating C_{60} with tetraethylene glycol. C_{60}-TEG-COOH was then coated on MSN which had been treated with 3-aminopropyltriethoxysilane to obtain an amino-modified MSN (MSN-NH_2). The anticancer drug doxorubicin hydrochloride (DOX) was loaded on the surface of the MSN-NH_2 at pH = 7.4 to get MSN@C60-DOX complex. This nanostructure can act as pH-sensitive drug delivery and fluorescence cell imaging system. This complex showed high cytotoxicity to HeLa cancer cell lines. The release of doxorubicin hydrochloride is stimulus responsive and could be encountered under a mild acidic environment (lysosomal pH = 5.0) due to the protonation of C_{60}-TEG-COO−, which disrupts the association between C_{60}-TEG-COOH and MSN and leads to controlled drug release (Tan et al. 2016).

2.4.3.3 Graphenes

Graphenes/graphene derivatives can be functionalized easily and possess large surface area, and delocalized pi electrons hence provided new openings for new drug delivery applications (Tonelli et al. 2015). Graphenes exhibited adequate drug loading, efficient in vivo drug distribution, and drug release (Novoselov et al. 2012). Graphene-based biological stimulus-responsive controlled drug release models were designed. The drug doxorubicin was chemically attached to "PEI-PEG

polymer-graphene oxide" by means of a matrix metalloproteinase 2 (MMP2)-cleavable peptide linker. Matrix metalloproteinases are a family of enzymes largely secreted by cancer cells. Normally, the intrinsic fluorescence property of doxorubicin is quenched by graphene oxide. On reaching cancer cells, doxorubicin-loaded graphenes are acted upon by MMP2 enzymes, and then the peptide linker is cleaved and releases doxorubicin precisely at tumor cells. The unbound doxorubicin emits fluorescence for tumor cell imaging, thus making a versatile dual purpose theranostic system (Qin et al. 2014).

2.5 Inorganic Nanoparticles as Drug Carriers

Inorganic nanocarriers consist of two parts: core and shell. The core is generally made of inorganic component like gold, quantum dots, silica, iron oxide, etc., and the shell is composed mostly of organic polymers (or metals) to which biomacromolecules can be attached.

2.5.1 Gold Nanoparticles (Au NPs)

Gold nanoparticles are metallic nanostructures having size ranges from 1 to 8 μm and exist in diverse shapes such as nanosphere, nanorod, nanocage, and nanoshells (Fig. 2.10). AuNPs are nontoxic drug carriers. Optical and electrical characteristics of AuNPs are dictated by its shapes and sizes. A combined resonance oscillation of electrons on the surface of gold nanoparticle stimulated by incident light at given wavelength is called surface plasmon resonance (SPR) effect. SPR effect converts light energy to heat energy. AuNPs are attractive nano drug carriers because of the presence of the surface plasmon shapes and sizes, which allow them to convert the incident light to heat and spread the generated heat to destroy the tumor cells (Sreejivungsa et al. 2016).

AuNPs generally use three main pathways for cellular internalization which includes receptor-mediated endocytosis, phagocytosis, and fluid-phase endocytosis (Nalawade et al. 2012). Gold NPs for drug delivery are depicted in Fig. 2.11.

Many AuNP-based stimulus-responsive smart drug delivery systems have been developed. Drugs are linked to AuNP surfaces by ionic or covalent bonding or physical absorption. The controlled drug release at target site can be achieved through internal biological stimulus (pH or glutathione) or applied external stimulus (light) (Kong et al. 2017). The controlled discharge of therapeutic agent at target cells is based on the strength of conjugation between drug and AuNPs and methods of drug discharge inside the cells. Weak non-covalent interactions are used for binding hydrophobic drugs, which does not need any more alteration in order to be released. Some prodrug compounds are linked to AuNPs by strong covalent interactions requiring exposure to internal or external stimulus for the release. The fine-tunable

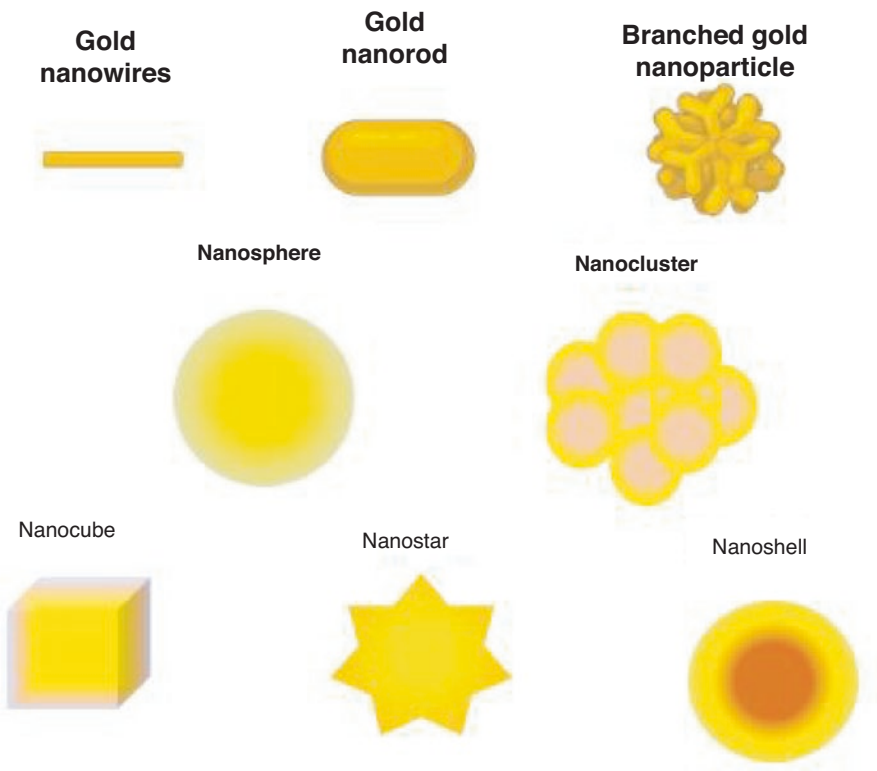

Fig. 2.10 Morphology of synthesized gold NPs

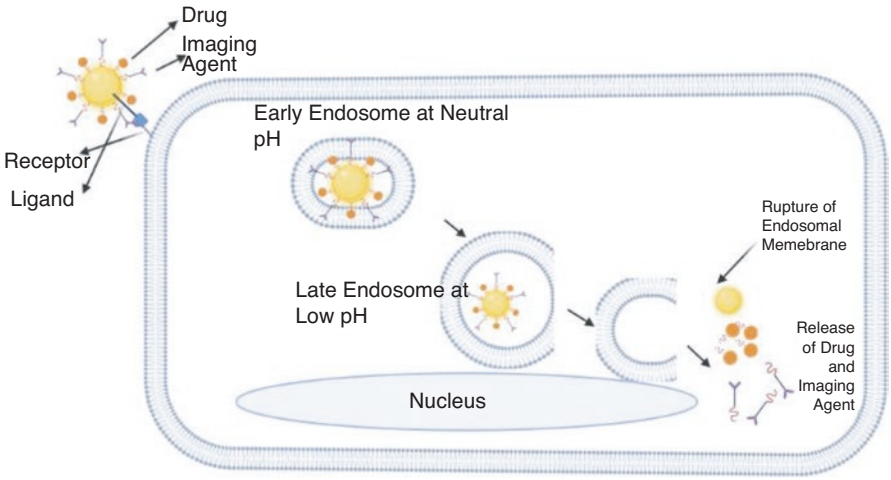

Fig. 2.11 Theragnostic gold NP-based systems for tumor treatment and imaging

optical properties of gold nanoparticle surface are utilized for the release of drug by applying internal or external stimuli.

Photo-regulated release of the prodrug depends on the absorption of light by AuNP-prodrug complex which leads to photo-cleavage of AuNP-prodrug complex with simultaneous release and activation of prodrug (Li et al. 2013). You et al. 2010 administered near IR light on novel AuNPs and achieved targeted controlled drug release by SPR effect. AuNano cages coated with thermosensitive polymers were designed to carry drugs, and by applying near IR light, controlled drug release was attained (Gou et al. 2010). In another approach, pH-dependent controlled release of doxorubicin (DOX) was studied. Doxorubicin was linked to 30 nm gold nanoparticles via a pH-sensitive linker. This kind of DOX-AuNP conjugation permits the intracellular controlled discharge of doxorubicin from gold nanoparticles once AuNPs accumulated inside acidic cell organelles. This approach gave better therapeutic benefits in drug-resistant tumor cells because of rapid intracellular accumulation of doxorubicin (Wang et al. 2011).

Another internal stimulus for controlled drug release is the higher intracellular concentration of glutathione. It is a nonenzymatic approach adopted for the effective delivery of therapeutic agents into target cells. The basic concept involved is the existence of difference between intracellular glutathione concentrations (high) compared with intercellular glutathione concentrations (low). Drug delivery nanoparticles designed with disulfide linkages can sense difference in glutathione concentrations and selectively release the drug molecule inside the target cell (cancer cell) where the intracellular concentration of glutathione is high. In another study, smart theranostic functionalized AuNPs were designed, i.e., the DOX was linked to gold nanoparticles via Au-S bond by using an octapeptide which can be selectively cleaved by overexpressed protease enzyme present in tumor tissues. Once the bond is cleaved, DOX can be precisely released at the tumor site, and thus normal cells are not exposed to the drug. The animal studies proved that after injection of this kind of smart theranostic AuNPs to the tumor mice, the overexpressed protease in tumor tissue and high intracellular glutathione concentration have led to the fast liberation of doxorubicin from the gold nanoparticles. This showed not only inhibition of growth of tumor but also simultaneous fluorescence imaging of tumor (Chen et al. 2013).

2.5.2 Nanoshells

The size of nanoshells ranges from 100 to 200 nm and finds wide applications in theranosis. Two types of nanoshells are commonly used: metallic nanoshells and E-LbL nanoshells. Metallic nanoshells contain silica core and a thin metallic shell (e.g., gold). Nanoshells with silica core and gold shell are particularly used in whole-blood immune analysis. For immune analysis purpose, nanoshells are linked with specific antibodies that function as recognition molecules for specific target compounds (Hirsch et al. 2003a). Silica-gold nanoshells of size 120 nm are

conjugated with antibodies or peptides on surface used to kill cancer cells. The antibodies on the nanoshell are bound to the cancer cell receptor. The location of the tumor is then exposed to infrared laser radiations, which heat up the gold shell adequately, and the tumor cells are selectively killed by the generated heat (Hirsch et al. 2003b). E-LbL nanoshells are synthesized by electrostatic layer-by-layer molecular self-assembly method. Nanoshells with silica core encapsulated by E-LbL method with electrolyte compounds like gelatine B or carboxymethylcellulose were prepared. This nanoshell was loaded with the peptide drug, Phor21-bCG (ala). The drug release profile and its efficiency to kill breast tumor cells were found to be improved in vitro (Hirsch et al. 2003a). The drug release profile and its efficiency to kill breast tumor cells were found to be improved in vitro (Hirsch et al. 2003a).

Nanoshells are also implanted in a polymeric hydrogel to develop nanoshell-hydrogel composite material. This composite nanodevice is designed for pulsatile drug release at the target tissues when stimulated with external stimulus. For example, gold nanoshells are conjugated into temperature-responsive hydrogels to prepare a novel kind of drug delivery device that disintegrates on exposure to laser radiation (Sershen et al. 2000). Upon irradiation with laser light, SPR effect takes place which results in photo-to-heat energy transition in embedded gold nanoshells. The liberated heat then shrinks the volume of the hydrogel and releases the drug at target site. Thus, the nanodevice is collapsed by external remote stimulus (laser light). This mechanism is utilized for efficient pulsatile drug release by nanoshell-hydrogel composite material. If the total quantity of drug load is not liberated during the first irradiation cycle, successive burst release of the drug can be obtained by applying next round of irradiations. Once the laser irradiation is terminated, the drug ejection is carried out by diffusion, and the quantity of discharged drug is lesser than that caused by laser radiation. Also, once the laser light is switched off, the hydrogel will begin to enlarge again and resume to its equilibrium state. Next, irradiation given at this moment will cause the hydrogel to disrupt again, resulting once again in burst release of the "drug" moiety. This type of pulsatile discharge of a therapeutic agent is absolutely used in insulin therapy (De Villiers and Lvov 2007).

2.5.3 Quantum Dots (QDs)

QDs are tiny semiconductor crystal particles of size less than 10 nm, made with atoms of group II and VI of periodic table (CdS, CdTe, and ZnS) that can be stimulated to emit different colors of fluorescence upon irradiated with light. The biomedical applications include drug delivery and cellular imaging. Mostly QDs consist of three regions: very tiny central core of diameter from 2 to10 nm made of semiconductor compounds (e.g., CdSe), enclosed by another semiconductor compound (ZnS); next, this double-layer structure is encapsulated by a cap made up of various kinds of compounds (Fig. 2.12). QDs made with CdSe core and ZnS shell are the most common nanoplatform used for biomedical applications. Due to

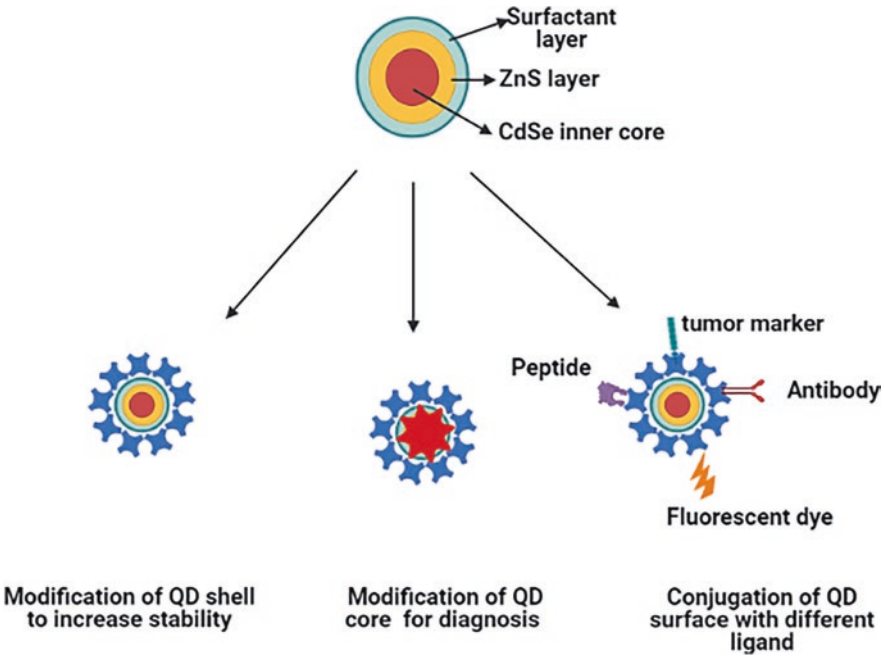

Fig. 2.12 Designs of QD nanocarriers for nanomedicine applications

their nanosize and quantum effects, they elicit peculiar optical (photophysical) characteristics that permit visualizing and monitoring the malignant cells in real time, during the drug transport and drug delivery at the target tissues (Matea et al. 2017).

QDs are labeled with biocompounds and used as extremely sensitive probes. QDs are used for imaging of sentinel node in cancer patients for diagnosis of stage of tumor and scheduling of therapy. CdSe-based QDs can be used for detection of malignant tissues because when irradiated with UV rays, they glow. This phenomenon helps in selective surgical removal of tumor. The surgeon administers these QDs into cancerous tumors and can visualize the glowing tumor; thus, the tumor can be precisely removed with ease, for example, used in the diagnosis and therapy of malignant breast tumors.

Another application of quantum dot is in the diagnosis of viral infection. Fast and accurate diagnosis of respiratory syncytial virus is essential for control of infection and development of antiviral agents. QD nanoparticles conjugated with antibodies are used for rapid and sensitive detection of this virus and also quantify the relative level of expression of viral surface protein. Many controlled drug release models have been developed with QDs. The intact QD-drug complex is transported to the target organs or tissues, and the therapeutic agents are either liberated when the polymeric particle is collapsed when it encounters a low pH or just diffuse out from polymeric particle. For instance, Bagalkot et al. (2007)

engineered and experimented a new QD-aptamer(Apt)-doxorubicin (Dox) conjugate (QD-Apt(Dox)) as a theranostic tool for prostate tumor imaging and treatment. The ideology is that the QD was functionalized with an RNA aptamer (A10 PSMA aptamer) which is then followed by intercalation of the drug DOX. This intercalation quenches the fluorescence emission from both QD and DOX via a fluorescence resonance energy transfer (FRET) mechanism. FRET usually monitors the transfer of energy between two light-sensitive molecules, in this case between QD and doxorubicin. The target site for the aptamer is cell surface domain of the prostate-specific antigen (PSA). Selective engulfment of QD-Apt(Dox) complex into prostate tumor cells takes place by endocytosis process. The release of doxorubicin from the QD-Apt(Dox) complex takes place due to low pH in cancer cells, and once released, DOX and QD both regain fluorescence which is then monitored by FRET mechanism. This system enables sensing, imaging, and killing of prostate cancer cells (Fig. 2.13).

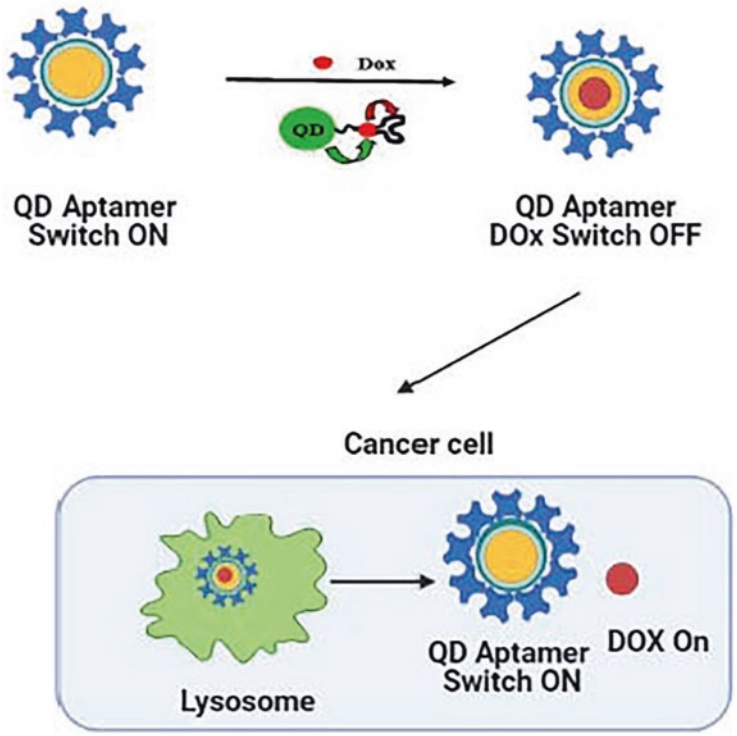

Fig. 2.13 Drug delivery by QD-Apt(Dox) FRET system

2.5.4 Superparamagnetic Iron-Oxide Nanoparticles (SPIONs)

Magnetic particles of dimension 10–20 nm exhibit a very high level of the magnetization up to saturation, and this phenomenon is known as a super paramagnetism effect (Wahajuddin and Arora 2012). SPIONs, like magnetite (Fe_3O_4) and maghemite (Fe_2O_3), are successfully proven for targeted drug release by applying magnetic energy (external stimulus). Modifying SPION surface with different ligand molecules like proteins, antibodies, peptides, and anticancer agents permits specific binding to their target receptors that are expressed only on tumor surface (Watermann and Brieger 2017). For example, SPIONs conjugated with polymers or lipids have been proven to induce a controlled drug delivery by applying external magnetic energy (Alonso et al. 2016).

A novel 100-nm-long nanoparticle chain was prepared by chemical conjugation of three magnetic iron-oxide nanospheres. One of the spheres was attached with DOX-loaded liposome. Once the nanochain enters into the malignant cells, magnetic nanospheres were vibrated by the applying radiofrequency field which leads to the burst release of drug from liposome. Then the free form of the drug spreads all over the malignant tissues. Thus, the drug release is controlled by applying field of radiofrequency as external stimulus (Peiris et al. 2012).

2.5.5 Mesoporous Silica Nanoparticles (MSNs)

Silica (SiO2)-based nanomaterials find wide applications in medicine due to their undemanding synthesis techniques and porous architecture attributes. MSNs are considered as perfect nanoparticles for drug carrier applications due to their firm architecture, adjustable pore size and volume, larger surface area, definite surface characters, and excellent biocompatibility (Tan et al. 2016). Comparatively a sufficient quantity of drug can be incorporated into MSNs, thus aiding in drug accumulation at target tissues by passive targeting. Hence, MSNs are well suited for theranosis (Angelova et al. 2015).

A variety of MSN-based systems have been designed for stimulus-responsive controlled drug release. The stimuli generally used for triggered drug release include physical (temperature, light, pH, magnetic, electrical, and mechanical), biological (enzymes), or chemical (chemical reactions) (Hu et al. 2016). The stimulus-responsive controlled delivery of drugs from MSNs is effort by smart capping agents known as gatekeepers that modify the surface of the mesopore. A wide variety of gatekeepers in use are polymers, proteins, supramolecular assemblies, and inorganic nanoparticles. Upon exposure to stimulus (pH, temperature, light, and redox), the smart capping agent and the gatekeeper material are displaced, which leads to the discharge of therapeutic agents from the mesopores (Tan et al. 2016). This kind of release ensures "Nil premature delivery" and drug release is under the control of specified stimulus only. Moreover, the framework of silica in MSN can

readily dissolve to silicic acid, under physiological conditions, which is a nontoxic compound (Croissant et al. 2017).

Sun et al. (2018) studied targeted drug delivery and cytotoxicity of a new core-shell-type nanoparticle (CSNP) on MCF-7 human breast tumor cell lines. This core-shell NP has been developed to deliver doxorubicin (drug) and indocyanine green (photosensitizer compound) simultaneously to cancer tissues. Irradiation of core-shell NP with near IR rays stimulates photothermal conversion effect. This system elicits a collective chemo- and photothermal therapy for cancer treatment. In another system, electrostatically self-joined core-shell NPs have been synthesized by amino-functionalized MSNs (MSN-NH2) as the positively charged internal core and DSPE-PEG2000-COOH and DSPE-PEG2000-FA modified phosphatidyl choline as the negatively charged external shell. This self-assembled core-shell NPs upon irradiation with near IR stimulus at 808 nm evidence the controlled drug release under in vitro condition on breast cancer MCF-7 cell lines.

A novel kind of redox-sensitive controlled drug delivery nanodevice with mesoporous carbon nanoparticles (MCNs) with custom-made fluorescent carbon dots (CDs) as gatekeeper was designed (Zhang et al. 2016). The mesoporous carbon nanoparticles were modified with a disulfide group. This makes the nanodevice responsive to higher intracellular glutathione concentration. The fluorescent carbon dots are attached to outside of the mesoporous carbon nanoparticles through an electrostatic attraction, act as gatekeeper or cap, and close the mesopores. This capping of mesopore prevents the outflow of doxorubicin which is filled inside the mesopore channel. When this nanodevice is exposed to high concentration of glutathione at the biological conditions, the integrity of the nanodevice is collapsed by the cleavage of the disulfide linkage; at the same time, stripping the carbon dots to open the gate thus facilitates the fast discharge of the encapsulated anticancer drug. The fluorescence of CDs is quenched (switched off) when attached to the surface of mesoporous carbon NPs, and it restores fluorescence (switched on) when disconnected from the surface of the mesoporous carbon NPs. Thus, the fluorescent carbon dots serve as both a gatekeeper to ensure controlled drug discharge and a fluorescent probe for the monitoring of the drug release profile. Thus, by combining therapy and imaging, this kind of drug delivery nanodevice can be hopefully used for controlled drug delivery under the control of in situ stimulus in the cells.

A thiolated hydrophobic surface of mesoporous NP was made by treating with octadecanethiol via disulfide bond. On this modified mesoporous NP, Pluronic P123 was coated via hydrophobic interactions. Pluronic123 is a triblock copolymer made with hydrophilic poly (ethylene oxide) blocks and lipophilic poly (propylene oxide) blocks. Thus, a nano assembly consisting of P123 and octadecyl group-modified mesoporous NP was constructed. Before coating mesoporous NP, the drug was loaded into the mesopores. The disulfide linkages function as "gatekeeper control switch" to confer the redox stimuli-sensitive drug release system. Almost all cancer cells have 100–1000 times greater intracellular glutathione concentration than extracellular concentration. When this nano assembly is entered into the malignant cells, disulfide linkage can be broken by excess glutathione concentration inside tumor cells, and then the hybrid coating would collapse opening the pores and fast

release of therapeutic agents at the specific target cell. The benefit of this kind of drug carrier systems is that they could inhibit tumor growth and at the same time suppress tumor metastasis (Sha et al. 2018). Neetu et al. (2011) designed and experimented a polymeric mesoporous NP to deliver doxorubicin (DOX). The controlled drug release from these nanoparticles is stimulated by specific proteases present in cancer tissues.

2.6 Techniques for Drug Loading to Nanoparticles

2.6.1 Drug Loading to Polymeric Nanoparticles

Nanoencapsulation/entrapment techniques are widely adopted for the synthesis of drug-incorporated polymeric NPs of size 1–1000 nm. Based on drug loading, nanoparticles are categorized into two types, viz., nanocapsules and nanospheres. Nanocapsules are vesicular type in which the therapeutic agent is limited to a cavity containing an internal liquid core enclosed by a polymeric membrane, but sometimes the drug may also be adsorbed to the outer surface of capsule. Nanospheres are provided with matrix-type architecture. Therapeutic compounds may be either adsorbed on the surface of sphere or embedded in the polymeric matrix (Fig. 2.14).

Different kinds of techniques have been devised to synthesize drug-loaded nanoparticles; these techniques are categorized into two classes based on if the nanoparticle synthesis needs a polymerization reaction or synthesis is carried out with readymade or pre-synthesized polymers. Further, polymerization techniques

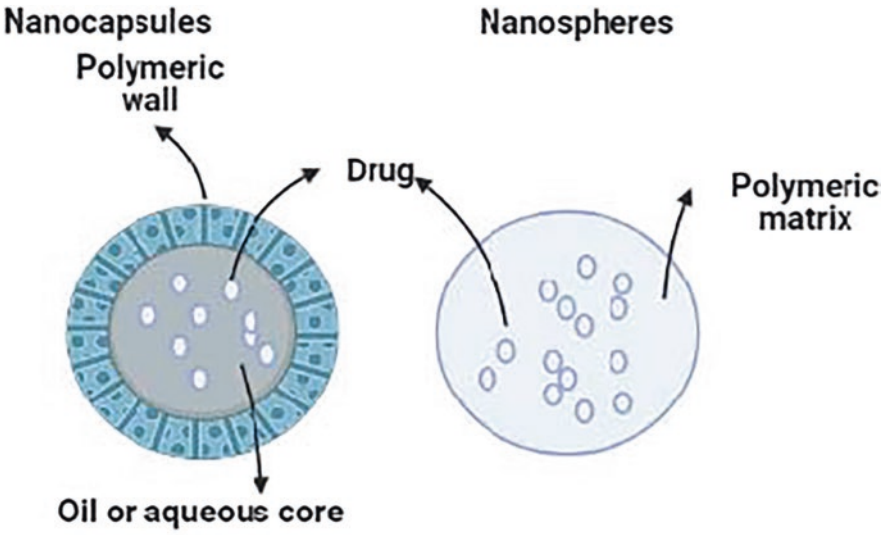

Fig. 2.14 Drug loading to polymeric nanoparticles

can be categorized into two: emulsion and interfacial polymerization, and the emulsion polymerization is further classified in to two types – organic and aqueous – based on the type of continuous phase used. Nanoparticles are synthesized directly from synthetic or biopolymers and by desolation of polymer (Couvreur et al. 1995).

2.6.1.1 Nanoparticles Synthesized by Polymerization Method

In this method, either organic solvent or water can be used as continuous phase for the synthesis of polymeric nanoparticles. The outline of *continuous organic phase* technique is shown in Fig. 2.15 (Lowe and Temple 1994; Harmia-Pulkkinen et al. 1989).

The outline of continuous aqueous phase technique is shown in Fig. 2.16 (Kreuter et al. 1979). Polymethylmethacrylate (PMMA)-based polymeric nanospheres can be used as proper adjuvants for immunizing agents, and also the synthesis of this nanoparticle is easy. The monomeric MMA are polymerized by radical emulsion polymerization method usually in the absence of emulsifiers to obtain PMMA nanospheres (Kreuter et al. 1979). A variety of therapeutic agents and imaging compounds can be efficiently entrapped into PMMA nanospheres (e.g., DOX) (Rolland et al. 1986).

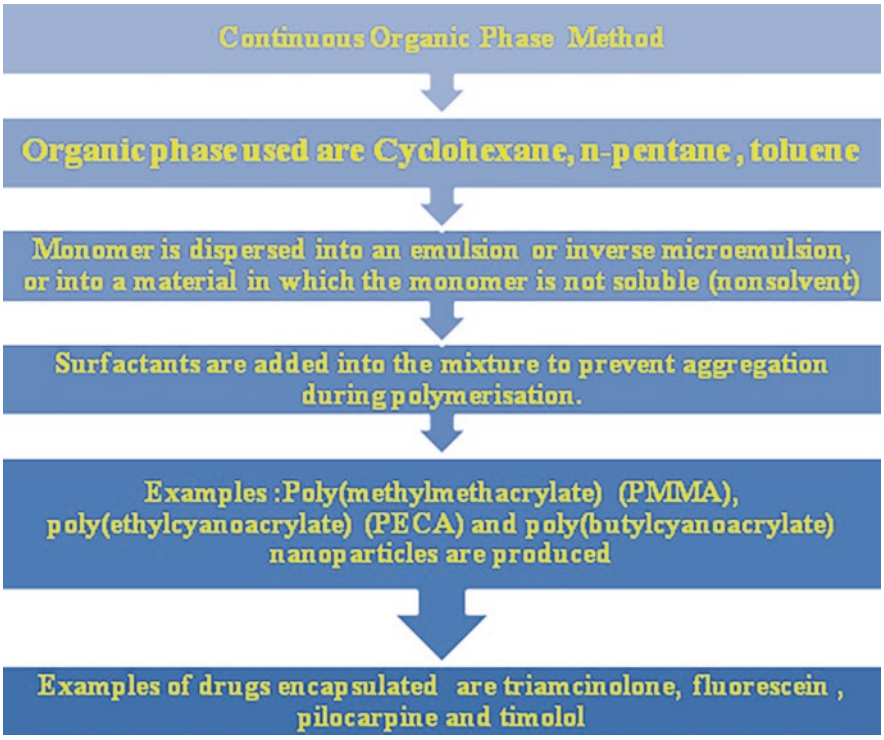

Fig. 2.15 Emulsion polymerization-continuous organic phase technique

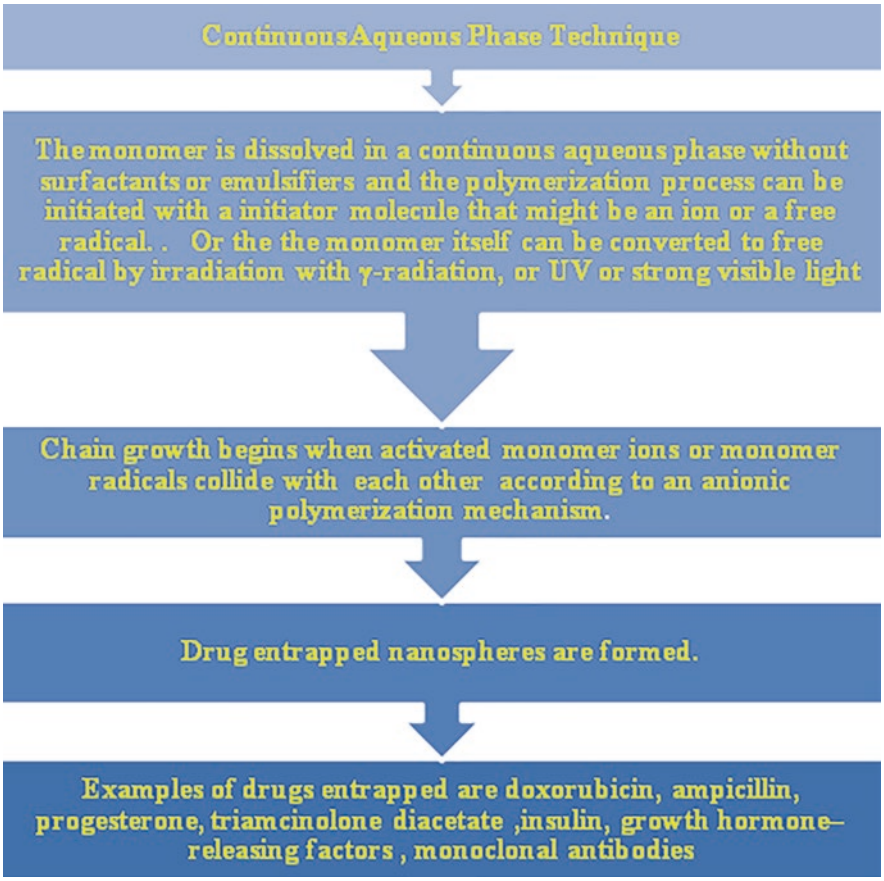

Fig. 2.16 Emulsion polymerization-continuous aqueous phase technique

Synthesis of poly (alkylcyanoacrylate) (PACA) nanoparticles has the advantage that polymerization can be initiated by anionic process at room temperature, and these polymers are highly biodegradable. Hydrophilic drugs, for example, ampicillin and doxorubicin, are encapsulated with good efficiency (Seijo et al. 1990). Sparingly water-soluble drugs, e.g., progesterone, triamcinolone diacetate, are successfully entrapped into PACA nanoparticles by dissolving the drug in a suitable solvent or surface-acting agent prior to mixing to the aqueous polymerization medium. Insulin, (Michel et al. 1991), GHRF, and monoclonal Abs have been entrapped into PACA nanospheres successfully (Grangier et al. 1991; Kubiak et al. 1988).

By interfacial polymerization technique, poly (alkylcyanoacrylate), poly (ethylcyanoacrylate) (PECA), poly(isobutylcyanoacrylate), and poly (isohexylcyanoacrylate) nanoparticles are successfully produced. The protocol for the synthesis of poly (alkylcyanoacrylate) nanoparticle is shown in Fig. 2.17 (Ammoury et al. 1991). The drug encapsulation efficiency obtained by this technique is significantly high, for example, 95% for insulin (Couvreur et al. 2002).

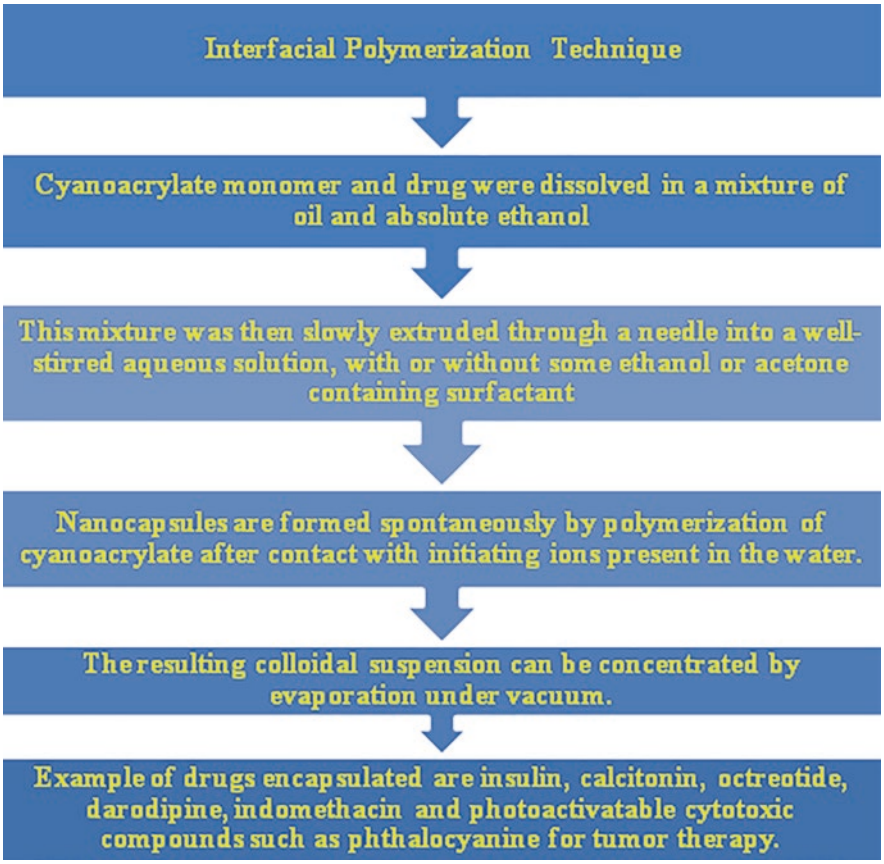

Fig. 2.17 Interfacial polymerization technique – synthesis of poly (alkylcyanoacrylate) nanoparticles

By interfacial polycondensation method, polymeric nanoparticles of size smaller than 500 nm can be synthesized. The nanoparticles were prepared by polycondensation of hydrophobic (phthaloyldichloride) and hydrophilic (diethylenetriamine) monomers with or without surface-acting agents. Urethane and ether urethane monomers were subjected to interfacial polycondensation to prepare nanocapsules to encapsulate α-tocopherol (Bouchemal et al. 2004).

2.6.1.2 Nanoparticles Synthesized from Synthetic Polymers

Emulsification/solvent evaporation technique takes place in two stages. In initial stage, the polymeric solution is emulsified into an aqueous phase. In the next stage, polymer solvent is evaporated which stimulates the precipitation of polymeric nanospheres (Figs. 2.18 and 2.19). Liposoluble drugs alone can be entrapped

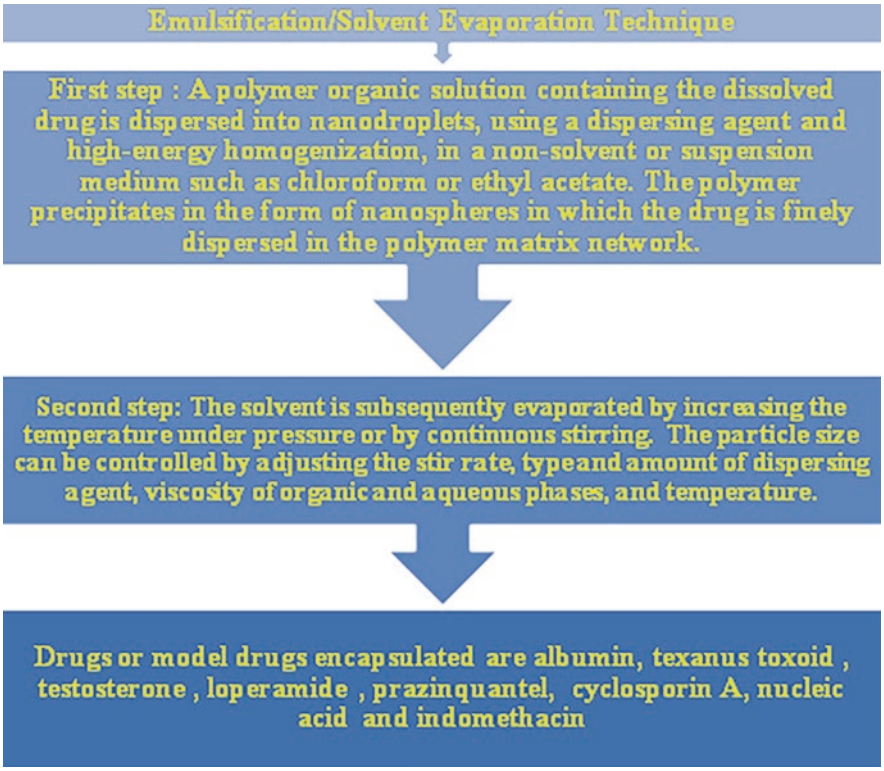

Fig. 2.18 Emulsification/solvent evaporation method

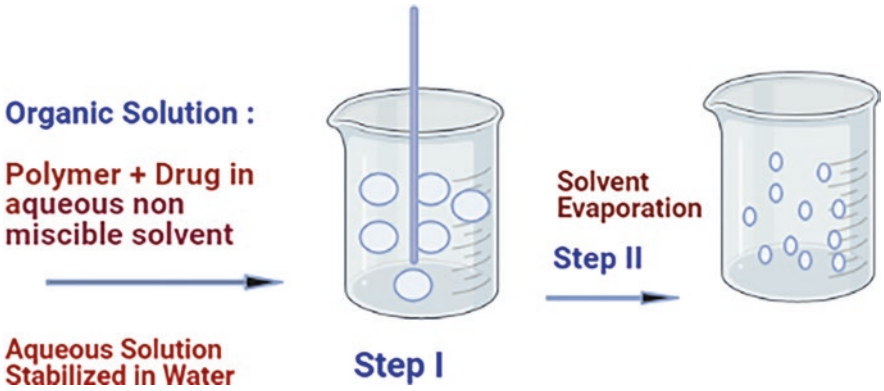

Fig. 2.19 Emulsification-evaporation method

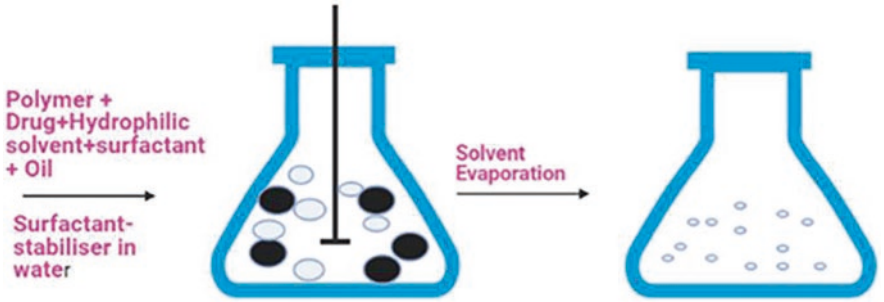

Fig. 2.20 SD technique

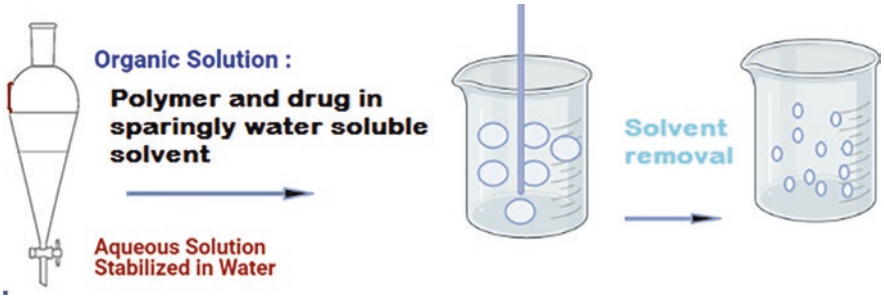

Fig. 2.21 ESD method

into nanoparticles by this method. Another disadvantage is the high energy requirement in homogenization. Often used polymers are poly lactic acid, poly(lactic-co-glycolic acid), poly(E-caprolactone), and poly(h-hydroxybutyrate) (Pinto Reis et al. 2006).

Solvent displacement (SD) and interfacial deposition (ID) methods both have nearly same principle. Both drug loaded nanospheres and nanocapsules are formed by solvent displacement method (Fig. 2.20) but by interfacial deposition method nanocapsules are only formed. SD precipitation of polymer in organic solution takes place in the presence or absence of surfactants (Ganachaud and Katz 2005). This technique is essentially adopted for loading of hydrophobic drugs into nanoparticles because of the use of solvents miscible with aqueous phase. Even though drug entrapment efficiency is high, this method is inefficient to encapsulate hydrophilic drugs (Barichello et al. 1999). Nanoparticles prepared with amphiphilic cyclodextrins are suitable for the parenteral injection of the sparingly soluble fungicidal agents like bifonazole and clotrimazole (Memisoglu et al. 2003). ID is an emulsification/solidification technique resulting in the synthesis of nanocapsules. A compound of oily nature, miscible with the solvent of the polymer but not miscible with the mixture is used. The polymer precipitates at the interface between the finely dispersed oil drops and the aqueous phase, resulting in the synthesis of nanocapsules of size 230 nm (Couvreur et al. 1995).

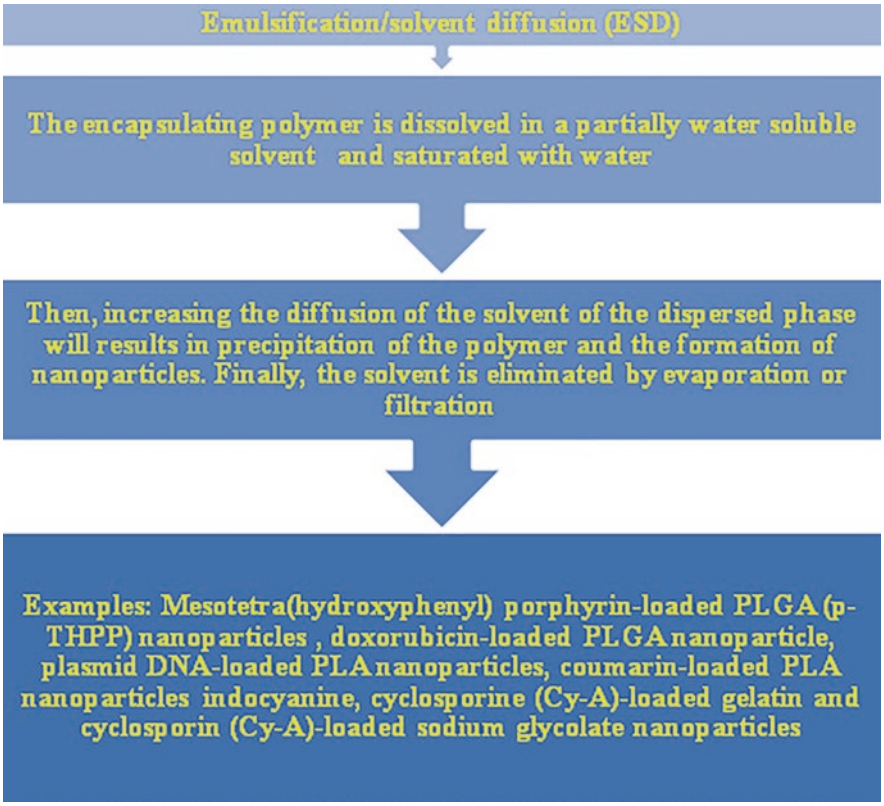

Fig. 2.22 ESD method

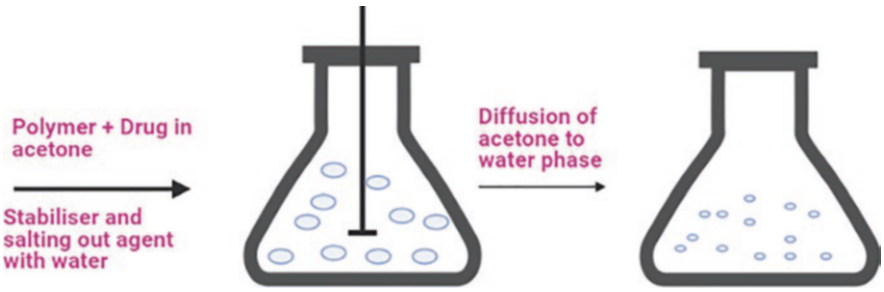

Fig. 2.23 Salting-out method

The protocol for *emulsification/solvent diffusion (ESD) technique* is illustrated in Figs. 2.21 and 2.22. This method is suitable to encapsulate lipophilic drugs (Pinto Reis et al. 2006).

The salting-out technique is similar to emulsification method with few modifications. Polymers along with drugs are first dissolved in a solvent (acetone),

which is quickly emulsified into water-based gel consisting of a salting-out agent and a colloidal stabilizer. The salting-out agent may be an electrolyte or nonelectrolyte material. Electrolytes generally used are $MgCl_2$, $CaCl_2$, and $Mg(CH_3COO)_2$, and nonelectrolyte used is sucrose. The chief stabilizers used are PVP (polyvinyl pyrrolidine) or HEC (hydroxyethylcellulose). The emulsion (oil/water) is diluted with an adequate quantity of water to increase the distribution of acetone into the aqueous layer which stimulates the synthesis of nanospheres (Fig. 2.23). This technique is useful for the loading of lipophilic drugs (Quintanar-Guerrero et al. 1998).

2.6.1.3 Nanoparticles Synthesized from Natural Polymer

Albumin nanospheres can be synthesized by homogenizing the oil with albumin droplets and stabilized by heat at 175–180 °C for 10 minutes. It was then treated with ethyl ether to decrease the viscosity of the oil phase, which was then separated by centrifugal force. The thermal-stable drug molecules only can be entrapped by the heat treatment of albumin. This disadvantage is obviated by emulsifying albumin in cottonseed oil at 25 °C, subsequently denaturing the albumin protein by suspending it again in ether along with the cross-linking agents 2,3-butadiene. Centrifugal force was applied to separate, followed by lyophilization to get dried particles. The drug release profile of doxorubicin was rapid than particles synthesized by thermal treatment (Patil 2003).

The gelatin nanoparticles are synthesized as follows: Gelatin protein was emulsified to get gelatin droplets. Then they were hardened by refrigeration which resulted in gelation. By filtration, gelatine droplets were recovered and then cross-linked with formaldehyde. Thus, gelatine nanoparticles of dimension from 100 to 600 nm with an average of 280 nm were synthesized. This is well suited for the entrapment of heat-sensitive drugs into gelatine nanoparticles (Yoshioka et al. 1981). Similarly, gliadin nanoparticles were synthesized from vegetable protein gliadins from wheat gluten. This is used to competently encapsulate lipophilic drugs, for example, alpha-tocopherol (Duclairoir et al. 2002).

Alginate nanoparticles were synthesized as follows: Sodium alginate, a natural hydrophilic polymer, can be converted to gel form by treating with multivalent cations like calcium. Alginate nanoparticles of size 1 to 5 μm are generally prepared by dropwise expulsion of sodium alginate into $CaCl_2$ solution by using an air atomizer (Fig. 2.24) (Reis et al. 2005).

Chitosan nanoparticles (CNPs) are suitable nanocarriers to encapsulate many protein drugs like BSA, toxoid vaccines (tetanus and diphtheria), antimutagenic agents insulin and DNA/RNA. Two methods are adapted to produce CNPs. In the first method, CNPs are synthesized by treating chitosan with tripolyphosphate (polyanion) to form a chitosan-polyanion complex which showed a quasi-spherical shape with size ranging from 200 to 500 nm. The second method is based on stimulating gelation in an emulsification-based technique. Gel transition of a chitosan

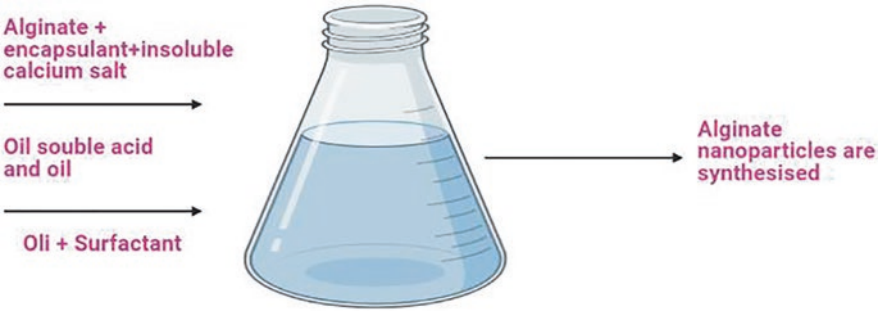

Fig. 2.24 Synthesis of alginate nanoparticles by emulsification-internal gelation method

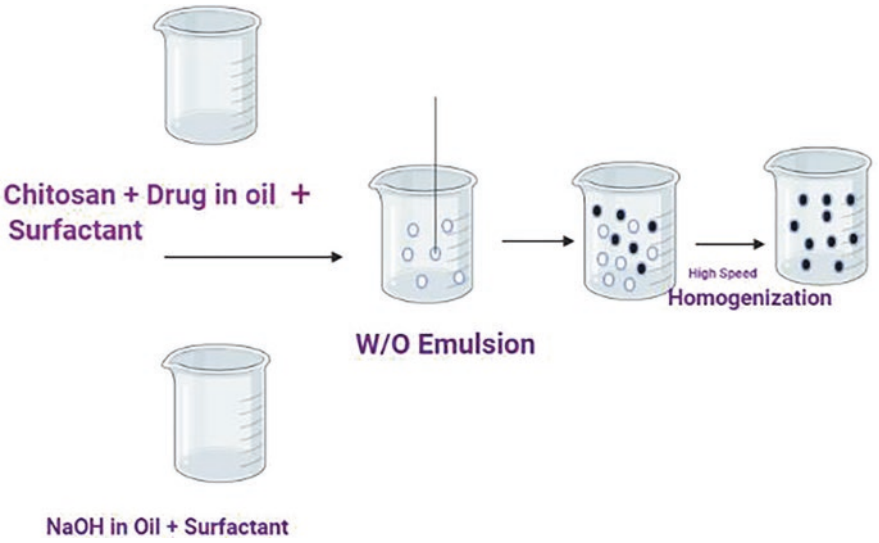

Fig. 2.25 Synthesis of chitosan nanoparticles by the emulsification method

solution dispersed in oil emulsion resulted in the synthesis of CNPs of size around 400 nm (Fig. 2.25) (Vauthier and Couvreur 2000).

Chitosan is a mucoadhesive polymer. So, chitosan-coated nanoparticles interacted much with mucus to extend the duration of drug release at these sites and save the entrapped drugs from enzyme action, thus enhancing transmucosal drug release (Sailaja and Amareshwar 2011). For example, chitosan significantly increases the absorption of insulin across the nasal epithelium, hence used in insulin aerosol therapy (Illum et al. 1994).

Agarose nanoparticles (ANPs) are suitable for therapeutic delivery of proteins and peptides. Agarose in water can be converted to hydrogels when cooled at a temperature less than the gel forming temperature (318–368 °C). Temperature-based gel formation process forms helicoid structures in three-dimensional meshes which

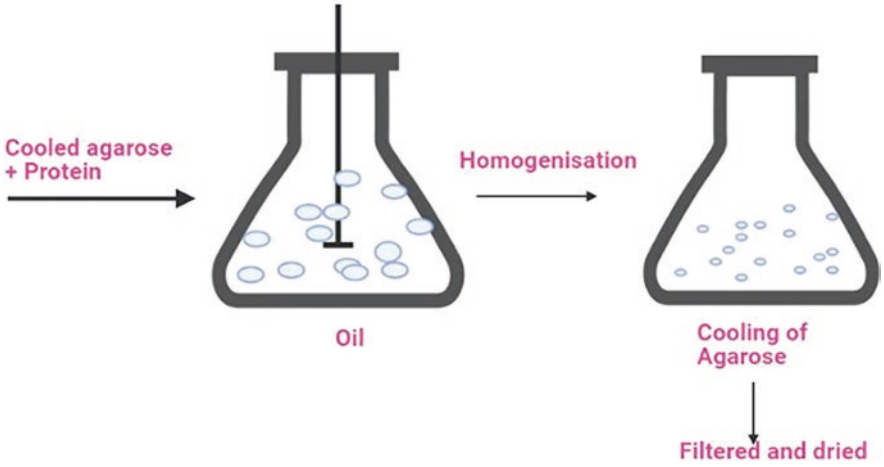

Fig. 2.26 Synthesis of agarose nanoparticles by the emulsification method

can hold large quantity of water. These gels are water loving, inert, and biologically compatible and can form matrix for proteins and peptides to entrap them during synthesis. ANPs formed by an emulsion-based technique are shown in Fig. 2.26. This technique needs the synthesis of agarose solution in corn oil emulsion at 408 °C.

Peptides and proteins are first added to the agarose solution. Dispersed nanodroplets can be obtained by homogenization. The gel formation of agarose is next stimulated by mixing the emulsion in corn oil at low temperature and stirred. The liquid nanodroplets are then gelled and entrap the protein drug. Thus, protein-loaded agarose hydrogel nanoparticles are synthesized (Vauthier and Couvreur 2000).

2.6.2 Drug Loading Techniques to Various Nanostructures

Let us discuss few drug loading techniques used to incorporate drugs into specific nanocarrier structures.

2.6.2.1 Drug Loading to Micelles

Drugs can be encapsulated inside the polymeric micelles by three main methods: 1. direct dissolution, 2. solvent evaporation, and 3. dialysis. By direct dissolution method, the copolymer and the drugs are kept in an aqueous medium and they are combined by self-assembly process to form drug-loaded micelles. In the solvent evaporation method, the copolymer and the chosen drug are kept in a volatile solvent, and the solvent evaporation forms the drug-loaded micelles. In the dialysis method, drug-loaded micelles are formed when both the drug and the copolymer in organic solvent are mixed and placed inside dialysis membrane bag (Mourya et al. 2011).

2.6.2.2 Drug Loading to SLN

Basically three drug loading models are applicable for SLNs which are Homogenous matrix model, Drug enriched shell in core shell model and Drug enriched core in core shell model (Pardeshi et al. 2012) as shown in Fig. 2.5. In the first prototype, the core contains drug as unstructured clusters. It is applicable for incorporating extreme hydrophobic drugs. This kind of drug loading can be achieved either by hot or cold homogenization method.

The hot homogenization process takes place at temperatures higher than the melting temperature of the lipid. By using a high shear mixing equipment, pre-emulsion which has drug-loaded lipid melt and the aqueous emulsifier phase (temperature is maintained in the same level) is prepared. Desired nanosize of SLN can be attained by lowering the viscosity of the lipid. To lower the viscosity of the lipid, a high processing temperature can be used, but high temperature may lead to degradation of both drug and lipid molecules (Lander et al. 2000). Better results are achieved after numerous repetitions (three to five times) through the high-pressure homogenizer.

The colloidal hot oil in aqueous emulsion is prepared after many rounds of homogenization; on cooling, it crystallizes the lipids to nanospheres and thus solid lipid nanoparticles are formed (Fig. 2.27). Degradation, partitioning, and loss of drug into aqueous medium are the disadvantages of hot homogenization technique. To obviate drawbacks, cold homogenization was developed. The initial step is

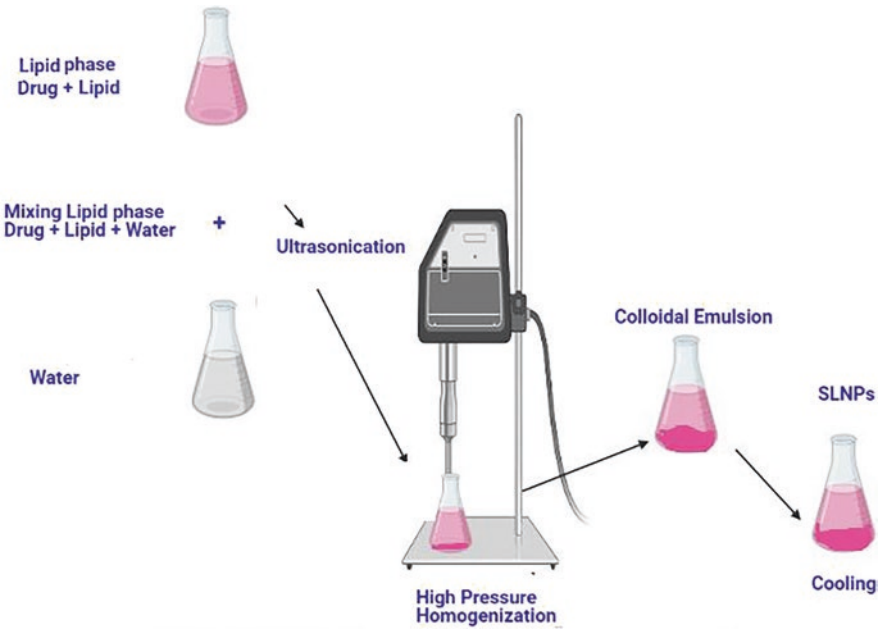

Fig. 2.27 Proposed protocol of hot homogenization technique

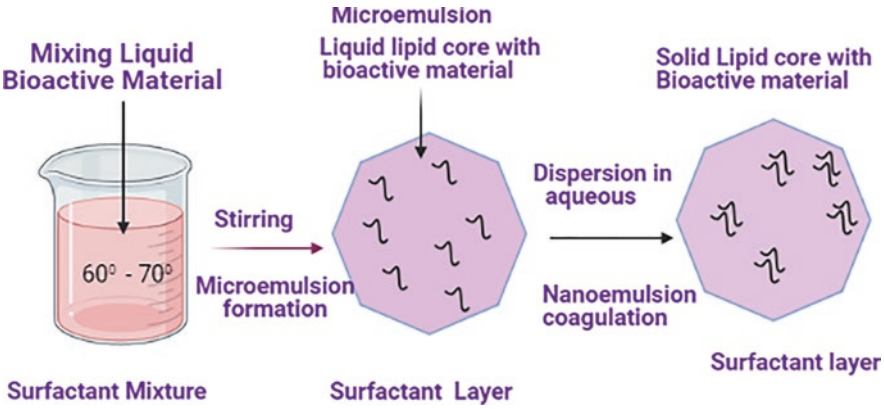

Fig. 2.28 Synthesis of SLN by microemulsion method

related to that of hot homogenization procedure, but further steps are altered. The drug containing melted lipid is cooled quickly (by applying liquid nitrogen) to attain consistent drug distribution. Then, the drug-loaded solid lipid is pulverized to microparticles of size 50–100 microns by ball/mortar milling (Jahnke 1998). In drug enriched shell prototype, the drug is loaded inside the shell, and the lipid core is free of the drug. Phase separation takes place when the preparation is cooled and precipitates resulting in lipid core free of the drug. Simultaneously, the drug repartitions into liquid-lipid phase, thus steadily increasing drug concentration in the outermost shell of the lipid core. A drug enriched core prototype nano emulsion is formed which is accomplished by melting the drug in the lipid at its supersaturating concentration. When this supersaturated melted lipid is cooled, it precipitates the drug before lipid. Additional cooling will precipitate lipid around the drug precipitate, thus acting as a membrane to loaded drugs (Fig. 2.28) (Esposito et al. 2018).

2.6.2.3 Drug Loading to Nanogels

Nanogels are versatile drug delivery vehicles for various drugs from hydrophobic to hydrophilic ones. There are several methods for the encapsulation or attachment of drugs. The commonly used approaches are the covalent conjugation method, direct addition method, and soaking method.

Covalent conjugation method forms a covalent bond between suitable compounds of the drug and nanogel. The most widely used covalent bonds are stimuli-sensitive, thus enabling the liberation of the drug at the place of therapeutic function inside the body. A pH-responsive hydrazone bond between doxorubicin and the methacrylamide polymeric nanogel was used recently for solid tumor drug delivery and initiation of reaction (Chen et al. 2017). Furthermore, biomacromolecules can be also covalently bound to nanogels. For example, enzymes are attached through a two-step reaction. The initial step is the reaction of the enzyme with

N-hydroxysuccinimidoacrylate under mild conditions. This reaction generates double bonds on the surface of enzyme. The second step is in situ polymerization with acrylamide monomer, N,N′-methylenebisacrylamide, as the cross-linking agent and N,N,N′,N′-tetramethylethylenediamine as the initiator of reaction (Yan et al. 2006). Otherwise, polyacrylamide nanogels with incorporated modified α-chymotrypsin can be prepared by copolymerization in an inverse micro polymerization reaction (Khmelnitsky et al. 1992). Nanogels with proteins with covalent bond can enhance their stability at high temperature and plasma half-life.

In direct addition technique, the drug is mixed with the monomer in the water phase of the emulsion before the synthesis of the nanogel. The drug is therefore encapsulated in the nanogel structure during its formation by hydrophobic or electrostatic interaction. Using this procedure, aspirin-containing nanogels were prepared by photoisomerization using a solution of the aspirin salt dispersed in a solution of linear dextran containing N-(6-aminohexyl)-4-[4- hydroxyphenylazo]-benzamide substituent attached via an amide linkage. The primary step in the synthesis was preparation of the hydrophobic substituent, while the second step was the reaction of the substituent with dextran. The nanogel was then formed through non-covalent self-aggregation induced by photoisomerization (Patnaik et al. 2007).

Soaking method is useful in the case of amphiphilic nanogels containing hydrophobic moieties such as cholesterol. The drugs are introduced by dipping the nanogels in a supersaturated solution of the drug. For example, this method was used to synthesize indomethacin-carrying nanogels (Sahiner et al. 2007).

2.6.2.4 Drug Loading to Dendrimers

Dendrimers are synthetic, branched structures with core at the center. The dendrimers can be synthesized by divergent or by convergent methods. In the first method, dendrimers extend outward away from core compound. The components in the core act in response with monomer sharing one reactive group, and two inactive groups give rise to the formation of first-generation dendrimer. On other hand, in the second method, the dendrimers are built from the periphery toward the center. Once the chains are sufficiently large, they bind to the core compound. The second method is advantageous because of the minimal defects in the final dendrimer structure. The degree of branching depends on the synthesis processes. The sizes are controlled while in the process of synthesis of dendrimers. The structure of dendrimers in the solution is based on many factors, like generation, spacer size, ionic strength, surface adjustment, pH, and temperature. Factors influencing drug delivery process are charge effect and electrostatic forces (Ballauff and Likos 2004).

Drugs of low molecular weight are entrapped inside the dendrimers and the drugs are immobilised by hydrophobic interactions or hydrogen or covalent bonds or linked to the functional compounds present on the exterior of dendrimer for a short period. Dendrimers enhance the solubility and bioavailability of lipophilic drug molecules (Lombardo 2009). Dendrimer nanodevices are developed to carry both targeting ligands and imaging molecules. The drug moieties conjugated to the

dendrimers for delivery follow two ways: formulation and nano-construction methods. Drugs are physically entrapped into the cavities of dendrimer branches via non-covalent interactions (formulation approach) or by covalent interactions (nanoconstruct approach) (Chauhan 2018).

Poly(amidoamine) PAMAM dendrimers are the most frequently used drug delivery systems. The dendrimer construction has three regions for entrapping the drug by using different binding forces: (i) void space entrapping, (ii) branching point bonding, and (iii) outside surface group interactions. The site where drug is entrapped and the type of binding force depend on the structure of both (dendrimers and drug). A dendrimer is a versatile nano drug delivery device that can perform many functions starting from enhancement of solubility to drug targeting as described below.

Solubility enhancers: PAMAM dendrimers enhance the solubility of entrapped hydrophobic molecules (Svenson and Chauhan 2008). The drug indomethacin was entrapped into G4-NH2 dendrimers by ionic interactions between negatively charged carboxylate groups of indomethacin and positively charged amine groups of dendrimers. These interactions are pH dependent (Chauhan et al. 2004).

Stability Dendrimers enhance the stability of the drug, for example, entrapped resveratrol into dendrimer shows more stability and solubility.

Dissolution Dendrimer-drug composite confirms faster drug dissolution than hydrophobic drug alone (Chauhan et al. 2018).

Drug release Controlled drug release from dendrimers depends on two factors.

(a) Chemical modification of dendrimer: For example, the drug indomethacin loaded on G4-NH2 dendrimer showed slow and controlled drug release when compared to the more rapid discharge noticed with G4-COOH dendrimer. Thus, chemical modification of functional groups determines the strength of interaction of drugs with dendrimers which in turn determines the kinetics of drug release by dendrimers (Chauhan 2018).
(b) Physical loading: The second parameter which plays an important role in the rate of drug release from dendrimers is physical loading which means dendrimer-to-drug molar ratio. For example, the rate of release of cisplatin from dendrimer was directly related to the cisplatin by dendrimer molar ratio (Kulhari et al. 2015).

2.6.2.5 Drug Loading to CNTs

Drug loading efficiency of carbon nanotubes is remarkably high. The higher drug packing efficiency is due to more surface area which offers sufficient room by loading more drugs and imaging molecules, both inside (cavity) and on the surface. CNTs provide easiness in cell uptake and thermal ablation, and these properties make it a unique drug delivery system.

Carbon nanotubes are capped or end-closed structures. So, in order to load the drug into the inner cavity, two approaches are used to fill carbon nanotubes in situ. They are either filling of drug during synthesis of CNTs or post-synthesis of CNTs. Filling in situ while producing CNTs is less efficient than post-synthesis of CNTs. The appropriate method depends on the melting point, surface tension, reactivity, and sensitivity of the drug to be incorporated (Monthioux 2002). Filling of CNTs by post-synthesis requires the ends must be opened by passing electricity, attacking the CNTs with acid or oxidizing by using CO_2 (Tsang et al. 1994; Ajayanet al. 1993). After opening the ends, drug molecules can be filled by two methods: decoration or capillarity. In the less efficient decoration method, functional groups are bonded to the inner wall or outer wall of CNTs (Ebbesen 1996). The most frequent mechanism followed for loading CNTs is capillarity. The drug loading by capillarity is based on two factors, such as the width of the CNT and the surface tension which is around 200mN/m. After filling, they are rinsed using a solution with partial solubility to the impregnating fluid so that the deposits left outside the CNT alone are removed. Then, the CNTs are closed by passing an electricity which closes the ends (Fu et al. 2008). Heister et al. (2012) studied drug filling, dispersion stability, and site directed drug release of cancer drugs with oxidized SWCNTs (oxSWCNTs) and reported that pH of 8 for doxorubicin and pH 9 for mitoxantrone are optimum for binding to oxSWCNTs by non-covalent bond at 4 °C in the dark.

2.6.2.6 Drug Loading to Fullerenes

Fullerenes can be produced when gaseous carbon is condensed in the presence helium gas. First, the vaporized carbon is produced when a strong beam of laser light is irradiated on the carbon surface. The liberated vaporized carbon is admixed with stream of helium gas, and the carbon atoms are joined to form clusters which are composed of few atoms to hundreds of atoms. When this condensed carbon is passed into a vacuum chamber, it expands and encountered a low temperature treatment just above absolute zero degrees. Also, by this technique, some drug molecules can be entrapped inside fullerenes (Szoka 1980).

2.6.2.7 Drug Loading to Gold Nanoparticles (AuNPs)

The surface modification of gold NPs can be carried out very easily, and this feature makes its use as versatile drug delivery system. After synthesis, the gold NPs are subjected to surface modification by using stabilizing agents; this imparts a net surface charge on gold NPs. The negative charge on gold core nanoparticles is utilized to conjugate a variety of small or large drug agents (antibiotics, proteins, nucleic acids targeting ligands) easily on gold NPs through physical absorption and ionic or covalent interactions.

Ligands binding to gold NPs through covalent bond enhance the drug stability and protect the drug from extreme conditions (e.g., elevated ionic strength, high

serum concentrations); otherwise, it would lead to undesirable clumping and insolubility. Generally covalent binding allows for easy binding to a range of ligands like biomolecules and biopolymeric compounds through thiol, amine, and carboxylate groups to gold NPs.

The widely used covalent bond and attaching group is a thiol linker. The gold-thiol bond is strong (45 kcal/mol). Generally gold NPs are synthesized by colloidal synthesis method. In this method, $AuCL_4$ salts are reduced by treating with sodium tetrahydroborate, in the presence of thiol group donating compounds which form a layer around the core gold atom and depend on gold to thiol ratio (Kong et al. 2017). A maximum drug load (up to 60%) of doxorubicin to gold NPs was attained since the drug forms a thin layer both on the internal and the external surfaces of the gold NPs through electrostatic interaction (Dreaden et al. 2012). Modified polymers and biomolecules contain a-sulfhydryl group which improves their conjugation on the surface of the AuNp.

Poly(ethylene glycol) (PEG) conjugated to 30 nm AuNPs via sulfhydryl group was found to impart improved stability of NPs inside the body and allows further conjugation of a NLS peptide (importins) with thiol groups of cysteine on the peptide (Kang et al. 2010). In addition, linking molecules are modified to possess a thiol group at one end, by which it can attach itself to gold surface and either amino or carboxylic group on the other end. Thus, the amino or carboxylic group allows drug to bind to the gold NPs.

McIntosh et al. (2001) prepared gold NPs coated with a cationic stabilizing agent, which binds with anionic phosphate groups of DNAs to the surface of the nanoparticle through non-covalent interactions, for gene therapy purpose. Anionic, citrate-stabilized Au nanospheres were prepared and conjugated efficiently with antibodies for prostate-specific antigen via electrostatic interactions. A 20 nm increase in size of Au nanosphere was observed after joining with antibody. Thus, the binding of nanosphere with antibodies was proven by measuring the size of hydrodynamic diameter of the Au nanosphere. This Au-antibody nanocomposite is used for the diagnosis of prostate cancer (Liu et al. 2008).

2.6.2.8 Drug Loading to Quantum Dots

The QDs are minute luminescent crystals of dimension lesser than 10 nm and emit fluoresce light of diverse colors when irradiated with visible light. They are prepared with exceptional optical properties, thus functioning as probes or tracers and drug carrier for theragnostic uses. QDs are designed for active targeting to specified cells or tissues by attaching with targeting ligands.

QDs with colloidal core-shell are used for medical treatments. They are synthesized by hot colloidal method. For example, core CdSe QDs are produced by treating CdO in oleic acid and Se in trioctylphosphine at very high temperature (up to 300 °C). By this process, monodispersed QDs are synthesized. For biomedical applications, the core of QDs must be passivated with a thin coating of nontoxic bandgap material like ZnS or ZnSe, which forms the shell (Peng and

Peng 2002). ZnS shell of CdSe QDs leads to red shifts (~10 nm) in the absorption and photoluminescence peaks (Akerman et al. 2002). Two techniques are in vogue for the formulation of drug-loaded QDs: (a) directly binding drug moieties to QD surface and upon reaching the target tissues and releasing the drug from drug-QD conjugate in response to internal biological stimulus like enzymes or pH and (b) loading the drug in a polymeric nano-delivery system that has either lipophilic or hydrophilic QDs, which depends on the kind of polymer used for its encapsulation (Bagalkot et al. 2007). Generally, hydrophilic QDs are made by terminating their surface with groups like COOH, NH_2, and SH to which targeting ligands are attached by traditional conjugation methods. Avidin-biotin cross-linking is an additional well-known system for binding biocompounds on the surface of QDs (Medintz et al. 2005).

2.6.2.9 Drug Loading to MSNs

MSNs are efficient drug carrier system utilized for the targeted delivery of different varieties of medicinal compounds from micro- to macromolecules. Since there is no chemical change during drug loading, the structure of drugs is not altered after loading and following its release. These systems are more suitable for hydrophobic drugs like proteins, since they resolve the troubles related to these drugs. The volume and pore diameter of MSNs are features which determine the drug loading efficiency. MSNs have inner cylindrical mesopores (internal surface) and an outer polymeric surface (external particle surface). Inner and outer surface can be selectively functionalized with diverse conjugation molecules. Drugs are loaded to either inner inorganic core or outer organic polymer shell (Lodha et al. 2012).

Zhang et al. (2010) synthesized and functionalized a new MSN-based drug carrier nanodevice to deliver the hydrophobic, antihypertensive medicine telmisartan (TEL) to the target tissues. In brief, MSNs were developed by an organic template approach using tetraethyl orthosilicate (TEOS) and cetyltrimethyl ammonium bromide (CTAB) as surface-acting agents. The functionalization was done by treating with aminopropyl groups by a post-synthesis process. MSNs were soaked in acetic acid solution of telmisartan. Thus, the drug was absorbed into MSN. During this process, MSN nanocarrier/drug ratio was kept at 2:3 (w:w). By applying ultrasonic waves, the mixture was vibrated for some time followed by vortexing for 10 hours which enhances the drug incorporation into the mesopores of MSNs. The final traces of acetic acid were removed completely by drying the mixture at 55 °C for a day. The dried drug-loaded MSN composite can be used as therapeutic agent. Similarly, Lodha et al. (2012) synthesized cyclosporine A-loaded mesoporous silica nanoparticles. In brief, they prepared MSN using TEOS and CTAB. The MSN nanocarrier/drug ratio was kept at 1:1 (w:w). Then, the sample and MSN mixture was stirred at 300 rpm for 24 hours. Thus, by stirring and centrifugation, the drug was loaded into pores of MSN.

2.6.3 Drug Loading Efficiency

The drug loading (entrapment/encapsulation) efficiency of synthesized nanoparticles is identified by finding the amount of free drug in the dispersion solution. The percentage of entrapment/encapsulation efficiency of the nanoparticle is defined as the ratio of mass of drug loaded into nanoparticle to the mass of initial drug. The entrapment/encapsulation efficiency is calculated using the following formula:

$$\text{Entrapment / encapsulation efficiency}\,(\%) = \frac{\text{Wt of initial drug} - \text{Wt of free drug}}{\text{Wt of initial drug}} \times 100$$

where "Wt of initial drug" = mass of initial drug and "Wt of free drug" = mass of free drug measured in dispersion medium.

2.6.4 Stability and Storage of Nanoparticles

Synthesized NPs must be stored in the active form till administered. Many factors can influence the stability of these NPs. Commonly, the colloidal suspension of nanoparticles is very stable and will not deposit because of continuous mixing by diffusion and convection. But sometimes, clumping may result in deposition and precipitation of nanoparticle in suspension. To overcome this, some additives are added. Chemical integrity of drug is another factor which is very important for the stability assessments. Other factors to maintain the stability of the loaded drug are the (i) length of contact period with aqueous phase (e.g., if the drug is hydrophilic, then the length contact period in water must be long), (ii) pH (for pH-sensitive drugs), and (iii) light exposure (for light-sensitive drugs). Hence, the pH of the medium and exposure to light must be taken care while in storage. Stability studies are more crucial and must be carried out in accordance to the characteristics of drugs and polymers. Few techniques are used to maintain the stability of the NPs. Lyophilization is the chief and economical stabilizing process. After lyophilization process, the desiccated powder form of NPs is obtained and packed in vials. The powder form is advantageous than colloidal suspension form since it is easy to handle, easy for transportation, and easy for storage. NP vials can be stored in vacuum-packed containers at appropriate temperatures, particularly for temperature-liable drugs. Before use, the freeze-dried powder can readily be converted to suspension form by simply dispersing in

aqueous solutions, or sometimes ultrasonication is needed for redispersion (Esquisabel et al. 1997).

2.6.5 Conclusion

Over the past few decades, proactive and continuous research has been performed in the area of nanomedicine for theranostic purpose. Site-specific or targeted drug delivery is the primary aim in any therapeutic investigations to enhance the therapeutic effects of drugs while lowering drug toxicity. Conservative drug carrier systems forever suffer from the unpredicted drug discharge in circulation and the slow discharge of drug at the target tissues. But recently developed nanoscale drug delivery systems provide novel opportunities for precisely targeted and controlled drug delivery. However, several problems remain to be solved and need further intense research. This chapter provides insight into various types of nanocarriers, mechanism of drug targeting, stimulus-responsive drug delivery systems, and drug loading techniques to nanostructures.

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Chapter 3
Recent Advances in Nanomaterials-Based Drug Delivery System for Cancer Treatment

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Abbreviations

BCS	Biopharmaceutical Classification System
CNTs	Carbon nanotubes
CS	Chitosan
DOX	Doxorubicin
DTX	Docetaxel
EPR	Enhanced permeation and retention effect
FA	Folic acid
FDA	Food and Drug Administration
GEM	Gemcitabine
GNPs	Gold nanoparticles
HA	Hyaluronic acid
MNPs	Magnetic nanoparticles
MPS	Mononuclear phagocytic system
MRI	Magnetic resonance imaging
MSNs	Mesoporous silica nanoparticles
Nano DDS	Nano drug delivery system
PAMAM	Polyamidoamine
PCL	Poly (ε-caprolactone)
PDCs	Polymer-drug conjugates
PET	Positron emission tomography
PEG	Polyethylene (glycol)
PLA	Polylactic acid
PLGA	Poly (D, L-lactide-*co*-glycolide)
PLL	Poly-l-lysine
PPI	Poly (propylamine)
PTT	Photothermal therapy
PTX	Paclitaxel
QDs	Quantum dots
RES	Reticuloendothelial system

SLNs	Solid lipid nanoparticles
TPGS	D-Tocopherol polyethylene glycol1000 succinate
WHO	World Health Organization

3.1 Introduction

Cancer is the second most severe lethal disease in the current world and spreading further with continuance and growing incidence in the twenty-first century. According to the estimates from the GLOBOCAN cancer statistics 2018 (International Agency for Research on Cancer, WHO), there are 9.6 million cancer cases deaths in 2018. More than 18.1 million cancer cases are diagnosed, and this rate has been estimated to rise to 29.5 million by the year 2040 (Faisca Phillips 2019; Bray et al. 2018). The condition is so alarming that every fourth person is having a lifetime cancer risk. Is cancer treatable? The short reply to this question is "yes." Cancer mortality rates can be decreased if cancer cases are detected and treated early with better treatment strategies (Siegel et al. 2019; Wild 2019). Cancer begins from transforming healthy normal tissues into tumor tissues in a multistage development that usually progresses from a precancerous to a malignant tumor. Many types of cancers affect the people, and the cancer cells show no symptoms at an initial stage of development (Papaccio et al. 2017; Kulikov et al. 2017). Cancer cells proliferate and continue to increase unless one of three things occur: (i) The tumor tissues are removed surgically, (ii) using radiation therapy, or (iii) using chemotherapy.

There are different methods of cancer treatment. Current cancer treatment options can be surgical intervention, radiation therapy, chemotherapy, immunotherapy and hormone therapy, or a combination of these options (Miller et al. 2019; Chowdhury et al. 2016). The types of cancer treatment that patients receive depend on the type of cancer patients have and what stage advanced it is. The treatment of cancer by surgery works best for small size solid tumors that are localized in one area (Tyson II et al. 2018; Derks et al. 2017). The surgery to remove the entire tumorous mass should not harm the surrounding normal healthy cells or tissues. Nonsurgical cancer treatment commonly followed is radiation therapy or chemotherapy medication. Radiation therapy practices with high ionizing radiation dose to eradicate cancer cells and slow tumor growth by damaging the DNA (Liu et al. 2016a; Baskar and Itahana 2017). The radiation therapy is commonly used in combination with the surgery to reduce the tumor size, so the tumor can be easily removed by surgical treatment (Bishop et al. 2018a, b). The body can safely receive a limited amount of radiation over the course of the treatment. The radiation dose to be delivered to the cancer site depends upon various factors such as the cancer type, tumor size and location in the body, age of the person, general health and medical history, and possible side effects on the nearby normal tissues (Ghahremani et al. 2018; Cabrera et al. 2016). Immunotherapy is a biological cancer therapy that supports the immune system battle against cancer, and it is not yet as extensively used

as surgery, radiation therapy, and chemotherapy (Zaidi and Jaffee 2019; Ishihara et al. 2017). Hormone therapy uses hormones to stop the growth of cancers (Axelrad et al. 2020; Eeles et al. 2016).

Chemotherapy or combined chemotherapy, a very common cancer treatment, uses anticancer drugs to kill or destroy the uncontrolled proliferation of cancerous cells. Conventional chemotherapy works principally by interfering with the synthesis of DNA and mitosis, leading to the death of rapidly proliferating and dividing cancer cells (Senapati et al. 2018; Wang et al. 2016). Unfortunately, due to nonspecific drug targeting by anticancer medicines, conventional chemotherapy fails to target the tumor specifically without interacting with the normal healthy cells (Kumari et al. 2016; Wakaskar 2017; Raza et al. 2019).

This chapter aims to present the limitations of conventional cancer treatment and principal concepts of nanomaterials for cancer treatment, to emphasize the distinguished advantage of nanomaterials-based drug delivery systems (nano DDS) and the mechanism of action underlying their selective targeted drug delivery effects, and to introduce successful recent nano drug delivery system for cancer treatment and diagnosis.

3.2 Limitations of Conventional Cancer Treatment

The conventional cancer treatments effectively destroy the cancer cells, but they are also harmful to the normal healthy cells and tissues (Johnson et al. 2018; Kalyanaraman 2017). Cancer cells cannot be entirely removed by the surgery, and even the existence of a single cancer cell that is unseen can redevelop into a new tumor and metastasize to other parts of the body. The cancer treatment by the surgical procedure is not used for hematological cancers or cancers that have metastasized to other tissues or parts of the body. The radiation therapy administered both internally or externally can also destroy the normal healthy cells and induce the side effects due to the ionizing radiation. The radiation therapy is not used if the tumor is located at extremely vulnerable locations or if the cancer is at the advanced stages. Immunotherapy and hormone therapy cause side effects in the body, and hormone therapy blocks the ability to produce hormones in the body system.

Chemotherapy is considered as an effective type of cancer treatment for all types of cancers, but it damages either normal healthy tissues or cells that divide rapidly, such as cells in the macrophages, digestive tract, bone marrow, and hair follicles. The notable drawback of conventional chemotherapy is that it cannot provide specific target action only to the cancer cells. The nonspecific delivery of chemotherapeutic drugs causes severe side effects such as mucositis, myelosuppression, organ dysfunction, alopecia, and thrombocytopenia, and these side effects impose treatment delay, dose reduction, and therapy discontinuation. Furthermore, most of the available chemotherapeutic drugs often cannot penetrate the outer membranes of solid tumors and reach the inside core of solid tumors, failing to destroy the cancer

cells. Also, the repeated administration of nonselective chemotherapeutic drugs can influence drug resistance.

Chemotherapeutic drugs are often eliminated from the plasma circulation engulfed by macrophages and P-glycoprotein, acting as the efflux pump, which is overexpressed on the cancer cells surface and prevents the accumulation of drugs inside the tumor. Thus, chemotherapeutic drugs stay in the plasma circulation for a very short and limited time and cannot interact with the cancer cells resulting in the chemotherapy entirely unsuccessful. The low drug solubility, large particle size, low specificity, and high toxicity of chemotherapeutic drugs are also important issues in conventional chemotherapy, making them unable to improve the bioavailability and reach the chemotherapeutic drugs at the tumor sites.

To circumvent the pitfalls as mentioned above and the limitations of conventional cancer treatments, chemotherapeutic drugs need to reformulate with various types of nanomaterials and drug delivery systems.

3.3 Nanomaterials as Drug Delivery System for Cancer Treatment

Since innovative researches and understanding of biological mechanisms of cancer tissues are emerging regularly, novel cancer treatment procedures are being developed to have improved effectiveness of the treatment, thereby enabling the patient's survivability and improving their quality of life. With the recent technological advances in medical sciences, different types of cancer treatment have been practiced in the past, and many new therapies, such as targeted therapy, are currently being practiced. There have been significant successes in the nanotechnology medical applications (nanomedicine) in recent years, particularly in the drug delivery system (Wolfram and Ferrari 2019; Salvioni et al. 2019; van der Meel et al. 2019; Tran et al. 2017; Prasad et al. 2017).

Treating cancer cells using a nanoparticulate drug delivery system (nano DDS) approach plays a pivotal role in circumventing the limitations of conventional cancer treatment methods by providing simultaneous diagnosis and treatment. The application of nano DDS to cancer treatment could extend beyond the drug delivery system into the making of new therapeutics capable of killing the cancer cells with negligible damage to normal healthy cells and tissues. Various types of organic and inorganic nanomaterials are used to formulate chemotherapeutic drug-loaded nano DDS for cancer diagnosis and treatment. Most of the organic nanomaterials (liposomes, solid lipid nanoparticles, dendrimers, polymeric micelles, polymeric (natural or synthetic) nanoparticles, and polymer-drug conjugates) and inorganic nanomaterials (mesoporous silica nanoparticles, gold nanoparticles, magnetic nanoparticles, carbon nanotubes, and quantum dots) were developed as a vehicle in nano DDS for cancer treatment.

3.4 Unique Advantages of Nano DDS

3.4.1 Particle Size (Kumar et al. 2017; Arms et al. 2018; Ghasemiyeh and Mohammadi-Samani 2018; Tiruwa 2016; Ghasemiyeh and Mohammadi-Samani 2020; Sarcan et al. 2018)

Particle size distribution and small size with high surface area characteristics of nanoparticles are the most important key factors for drug delivery applications. The great advantage of nano DDS is that the particle size and size distributions are tunable. Several types of research have reported that nanoparticulate systems have plenty of advantages over other microparticulate systems. Nanoparticles can improve drug loading, stability, controlled drug release, high cellular uptake, in vivo pharmacokinetics, plasma circulation half-life, biodistribution, targeted drug delivery, tumor accumulation, and ability to cross the blood-brain barrier and transport the drugs to the brain due to their smaller size and flexibility (Prasad et al. 2019). Nanoparticles can also be coated with different types of polymers or surface-functionalized with targeting moieties, peptides, and nucleic acids that bind to specific cancer target sites. The nanoparticles used in a nano DDS should be small size enough to escape or avoid capture by macrophages in the circulation system. Systemically administered nano DDS should have a particle size ranging from 10 to 200 nm, particle size less than 200 nm to avoid sequestration by the liver and spleen, and particle size larger than 10 nm to avoid first-pass metabolism or elimination through the kidneys, benefiting accumulation/clearance and biodistribution behavior. The particle size of nano DDS has been shown to influence the surface functionalization and targeted drug delivery applications for cancer treatment.

3.4.2 High Drug Payload (Ghasemiyeh and Mohammadi-Samani 2018; Meunier et al. 2017; Liu et al. 2020; Qu et al. 2016; Huang et al. 2016)

An effective nanoparticulate system should load and hold a higher amount of drugs, thereby decreasing the frequent dose of uptake and increasing drug plasma concentration after administration in the body. Drug loading in the nano DDS can be done by adsorption/absorption and incorporation techniques. A high drug loading capacity and encapsulation efficiency mainly depend on the classification of drugs (e.g., biopharmaceutical classification systems (BCS) Class I–IV) and drug solubility in the nano DDS, which is related to the drug-polymer interactions, compositions of excipients, and the presence of active functional groups from drug and excipients. For instance, the solid lipid core of solid lipid nanoparticles can accommodate a higher amount of hydrophobic chemotherapeutic drugs, and liposomes can load and

hold both hydrophobic and hydrophilic chemotherapeutic drugs due to their unique characteristics.

3.4.3 *Controlled Drug Release (Li et al. 2016a; Kamaly et al. 2016; Deodhar et al. 2017; Liu et al. 2019a; Paris et al. 2018)*

It is crucial to take consideration of both polymer biodegradation and drug release kinetics in simulated body conditions when formulating a nano DDS. The drug release behavior from nano DDS mainly depends on (i) solubility of active pharmaceutical ingredient, (ii) nano DDS degradation or erosion, (iii) desorption from the surface-attached drug or incorporated drug from the inside polymer core, (iv) drug diffusion through the nano DDS, and (v) the combination of diffusion and erosion processes. For example, the drug release of uniformly drug distributed nanospheres occurs by diffusion or matric erosion. If the active drug diffusion is more rapid than matrix erosion, then the drug release mechanism is mostly maintained by diffusion. The burst drug release from nanoparticles at the early stage is primarily attributed to surface-attached drug molecules to the large surface of nano DDS. It is indicated that the method of drug loading has a pivotal role in the drug release profile from nanoparticles. If the active pharmaceutical ingredient is entrapped in the nano DDS by the incorporation technique, then the nano DDS has a negligible amount of burst drug release and controlled drug release profile. If the nano DDS is surface-modified or coated by other synthetic or natural polymers, the drug release profile is then controlled by drug diffusion from the surface polymeric membrane.

3.4.4 *Surface Modification (Ahmad et al. 2018a; Choi and Meghani 2016; Ahmad et al. 2018b; Ganesan et al. 2018; Ramalingam and Ko 2016; Ramalingam and Ko 2015; Ramalingam et al. 2016)*

Surface modification or coating on the nano DDS can improve drug biodistribution, pharmacokinetics, and oral and brain drug delivery. To enhance drug targeting, it is crucial to prolong the nanoparticle circulation and minimize the opsonization in vivo, and it can be accomplished by coating or surface modification of nano DDS with biodegradable hydrophilic polymers, e.g., natural polymers such as chitosan and their derivatives, PEG, polysorbate 80, poloxamer, and polyethylene oxide. Several researches publish that PEG surface modification on nano DDS avoids opsonization and reduces phagocytosis.

3.5 Physiology of Tumor and Tumor Targeting Using Nano DDS

3.5.1 Angiogenesis and Tumor Vasculatures

A well understanding and knowledge of the angiogenesis and tumor vasculature characteristics have facilitated effective cancer treatment against various types of cancers. To develop the nano DDS, it is essential to find the biomarkers of the tumor microenvironment and the important differences in normal healthy cells (Liu et al. 2021). The process of angiogenesis in tumor sites promotes new blood vessels with discontinuous epithelium from preexisting vascular systems. The irregular blood vessels present in tumor regions have unusual morphological and physiological conditions dissimilar from normal vasculatures. The discontinuities between epithelial cells or vascular gap openings of tumors are remarkably 10 and 100 times larger in tumor models than in normal tissues. Lack of lymphatic drainage with leakiness favors the passive accumulation of long-circulating macromolecules and into the tumor (Li et al. 2016b; Park et al. 2016; Yang and Gao 2017; Wong et al. 2016). These findings suggest that the nano DDS of certain sizes can penetrate leaky tumor vasculatures and selectively carry the chemotherapeutic drugs to the tumor regions.

3.5.2 Mechanisms of Tumor Targeting by Nano DDS

Tumor-targeted drug delivery can be attained by inherent passive targeting and adopted active targeting strategies. Active drug targeting of chemotherapeutic drugs can be accomplished by conjugating the targeting moiety on the nano DDS. Passive drug targeting is achieved by loading chemotherapeutic drugs into a nano DDS that passively reaches the cancer target site or tissue through the EPR effect. For example, several studies reported that liposomes surface-modified with targeting moiety influenced the drug targeting and it can work as a drug reservoir exhibiting controlled drug release profile and drug accumulation at the tumor site (Kanamala et al. 2016; Masood 2016; Anarjan 2019; Derakhshandeh and Azandaryani 2016; Dai et al. 2016).

3.5.2.1 Passive Tumor Targeting

The EPR effect-mediated chemotherapeutic drug deliveries of nano DDS have been considered one of the strategies to accumulate the drug at the tumor sites. Compared to blood vessels in normal tissues, angiogenic blood vessels at the tumor sites have bigger size openings between nearby vascular endothelial cells. This can help the nano DDS to accumulate at the tumor tissues and then release a higher concentration of the drugs specifically into the tumor cells, thus permitting effective cancer

treatment with least systemic side effects. Various studies have demonstrated that EPR plays a pivotal part in passive drug targeting. The EPR effect mainly depends on many factors, such as the nano DDS surface properties, tumor types, and immunogenicity. Passive drug targeting is due to the faulty leaky tumor vasculature with irregular epithelium, reduced level of lymphatic drainage, and lowered uptake of the interstitial fluid, supporting passive targeting of nano DDS in tumors (Kumari et al. 2016; Wakaskar 2017; Masood 2016; Mahato 2017).

3.5.2.2 Active Tumor Targeting

Passive tumor targeting can help the localization of nano DDS at the tumor sites, but it is not able to encourage cellular uptake by tumor cells. This can be accomplished by active tumor targeting. Compared to passive tumor targeting, active tumor targeting strategy relies on a biological communication between targeting ligand on the surface of nano DDS and the receptor on the target tumor cell surface. Active tumor targeting strategy can easily differentiate the normal healthy cells and tumor cells. A large number of targeting ligands and targets have been identified and evaluated for facilitating active drug targeting of nano DDS for various types of cancers (Table 3.1). Such ligands on the surface of nano DDS often actively attach to specific receptors on the tumor cell surface, increasing the drug-containing nano DDS internalization by receptor-mediated endocytosis, improving the therapeutic efficacy, controlling the delivery of chemotherapeutic drugs to healthy tissues, and also decreasing the systemic adverse effects. Hence, active tumor targeting has displayed promising outcomes in circumventing different pitfalls, such as multidrug resistance in tumors and bypassing the blood-brain barrier (Anarjan 2019; He et al. 2020; Lin et al. 2016; Nag and Delehanty 2019).

Table 3.1 Targeting moiety and targets for active targeting of nano DDS

Targets	Targeting moiety	Type of cancer treatment
CD44 receptor	Hyaluronic acid	Human hepatocellular carcinoma, human lung adenocarcinoma, breast cancer (Yang et al. 2018a; Liu et al. 2016b; Song et al. 2017)
CD13	NGR motif peptide	Liver cancer, non-small cell lung cancer (Zheng et al. 2017; Schmidt et al. 2017; Corti et al. 2017)
FA receptor	Folic acid	Breast cancer, liver cancer (Vinothini et al. 2019; Zhang et al. 2018a)
Integrin $\alpha_v\beta_3$	RGD peptide	Prostate tumor, breast cancer (Kim et al. 2017; Wu et al. 2017a)
Prostate-specific membrane antigen	Aptamer	Prostate cancer (Ptacek et al. 2020; Pan et al. 2017)
Transferrin receptor	Transferrin	Breast cancer, lung cancer (Li et al. 2019a; Zhang et al. 2017; Xu et al. 2018)

3.6 Nano DDS for Cancer Treatment

3.6.1 Organic Nanomaterials for Cancer Treatment

Most of the organic nanomaterials (liposomes, solid lipid nanoparticles, polymeric micelles, dendrimers, polymeric nanoparticles, and polymer-drug conjugates) are used as a carrier and targeting system for cancer treatment (Fig. 3.1).

3.6.1.1 Liposomes

Liposomes are described as phospholipid vesicles comprising of one or more concentric bilayer vesicles surrounding the discrete aqueous phase. Because liposome composition is identical to that of cellular membranes, liposomes are safer and biocompatible than other synthetic polymers. Because of the unique structure of liposomes, both hydrophobic and hydrophilic drugs can be incorporated in liposomes. Liposomes can load and hold hydrophobic drugs in the lipid bilayers and hydrophilic drugs in the aqueous core. Liposomes have several advantages than other drug delivery systems, and it is administrated as a potential nanocarrier for drug delivery of chemotherapeutic drugs (Mishra et al. 2018; Ahmed et al. 2019). Currently, there are many liposomal products in the market (Table 3.2) and clinical development (Table 3.3) for cancer treatment.

The types of phospholipids, targeting ligand, PEGylation, and stimuli-sensitive materials determined the charge of the surface of the liposomes. In addition, liposomes with surface modification protect the incorporated drug from degradation, increase the targeting, improve the pharmacokinetic and pharmacodynamics properties, and reduce the toxic side effect of the chemotherapeutic drugs (Patel 2020; Mohamed et al. 2019). PEG conjugation has been identified as a unique strategy for the evasion of RES uptake. The targeting ligands, peptides, and nucleic acid-functionalized liposomes can specifically deliver the chemotherapeutic drugs to the tumor sites. The use of liposome targeted delivery systems in combination therapies of chemotherapy and phototherapy to transport anticancer drugs and photosensitizer can reduce the side effects, significantly enhance the drug accumulation at the target site, and improve the effectiveness of chemotherapy and photodynamic therapy (Cao et al. 2018). Different types of liposomes for targeted anticancer drug delivery are summarized in Table 3.4.

3.6.1.2 Solid Lipid Nanoparticles

Solid lipid nanoparticles (SLNs) are made from biological and safe grade lipids, and it is biocompatible and less toxic compared to polymeric or inorganic nanomaterials. SLNs promote the high drug upload of multiple hydrophobic and hydrophilic drugs. SLNs are a versatile drug delivery system that has been applied to enhance

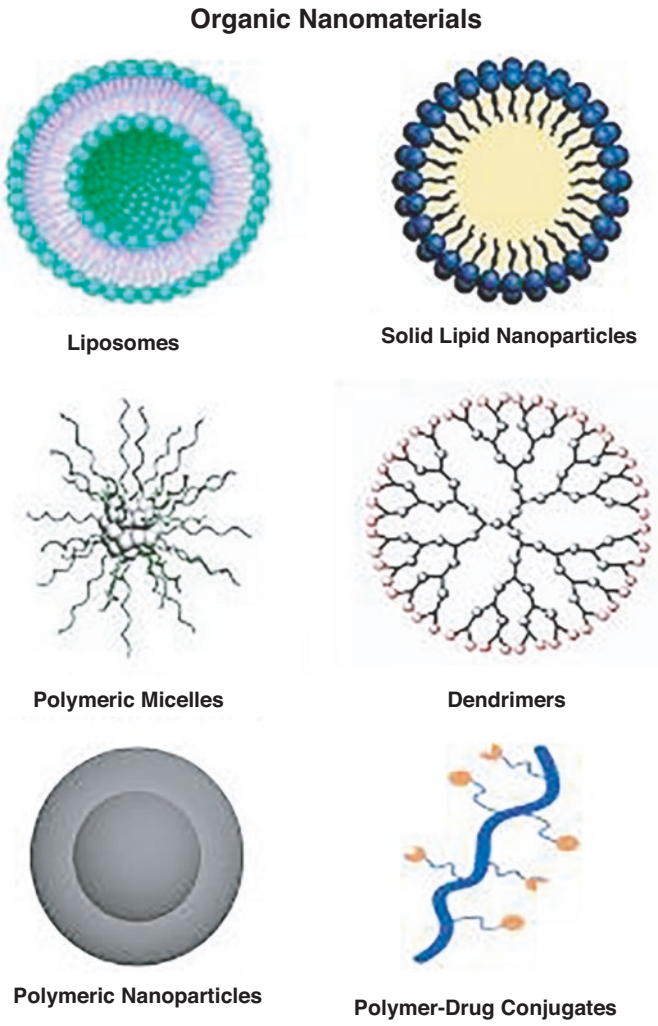

Fig. 3.1 Different types of organic nanomaterials for cancer treatment

the therapeutic effect of chemotherapeutic drugs. Targeted delivery of chemotherapeutic drugs from SLNs reduces the systemic side effects and improves the therapeutic action. SLNs can enhance the chemotherapeutic drug delivery applications for cancer treatment by tumor targeting mechanisms of actions such as passive, active, and codelivery mechanisms (Ganesan et al. 2018; Ramalingam and Ko 2016; Lingayat et al. 2017; Patel et al. 2018). Several studies have reported that SLNs are used as a targeted drug delivery vehicle for different types of tumors. The outcomes of SLNs as carriers of chemotherapeutic drugs are summarized in Table 3.5.

Table 3.2 Approved and marketed liposome-based drugs for cancer treatment

Product name	Drug name	Type of cancer treatment
Abraxane	PTX PTX + gemcitabine	Various cancers (Bobo et al. 2016) Metastatic pancreatic cancer (Saif 2013)
DaunoXome®	Daunorubicin	AIDS-related Kaposi's sarcoma (Dawidczyk et al. 2014)
Doxil®/ Caelyx®	DOX	Ovarian cancer, AIDS-related Kaposi's sarcoma and multiple myeloma (Barenholz 2012, 2016)
DepoCyt	Cytarabine	Lymphomatous meningitis (Bobo et al. 2016)
Lipusu®	PTX	Solid tumors (Barkat et al. 2019)
Lipo-dox®	DOX	Kaposi's sarcoma, breast and ovarian cancer (Chou et al. 2015)
Marqibo®	Vincristine	Acute lymphoblastic leukemia (Silverman and Deitcher 2013)
Myocet®	DOX	Metastatic breast cancer (Anselmo and Mitragotri 2016)
Oncaspar	PEGasparaginase	Acute lymphocytic leukemia (Alconcel et al. 2011)

Table 3.3 Liposome-based drugs in clinical development for cancer treatment

Product name	Drug name	Type of cancer treatment
Atragen™	Tretinoin	Acute promyelocytic leukemia, prostate cancer (Nayak et al. 2019)
CPX-1	Irinotecan HCI	Colorectal cancer (Pandey et al. 2016)
EndoTAG®-1	Paclitaxel	Breast cancer, pancreatic cancer (Sofias et al. 2017)
INX-0125	Vinorelbine	Advanced solid tumors (Rahman et al. 2017)
Lipoplatin™	Cisplatin	Pancreatic cancer, lung cancer, breast cancer (Serinan et al. 2018)
L-Annamycin	Annamycin	Acute lymphocytic leukemia (Eryılmaz and Canpolat 2017)
SPI-077	Cisplatin	Head and neck cancer, lung cancer (Zahednezhad et al. 2020)
ThermoDox®	Doxorubicin	Primary hepatocellular carcinoma, breast cancer (Lyon et al. 2017)

3.6.1.3 Polymeric Micelles

Polymeric micelles composed of amphiphilic block copolymers with a hydrophilic corona and hydrophobic core are colloidal nanoparticulate drug delivery systems for chemotherapeutic drugs. Polymeric micelles form a self-assembled structure spontaneously in an aqueous environment. The hydrophobic core of the polymeric micelles possesses a high drug loading of water insoluble chemotherapeutic drugs, and hydrophilic corona provides steric stability to avoid rapid uptake by the RES, resulting in extended drug circulation in the body. In addition to passive drug targeting, polymeric micelles can be surface-modified with targeting ligands for active tumor targeting to enhance the selectivity for cancer cells and improve intracellular delivery of anticancer drugs by receptor-mediated endocytosis while reducing systemic toxicity and severe side effects compared to systemic chemotherapy (Marzbali

Table 3.4 Liposome-based targeted drug delivery systems for cancer treatment

Liposome type	Drug	Ligand	Type of cancer treatment
Plain liposomes	PTX	Aspartic acid	Bone metastasis (Zhao et al. 2020)
	Resveratrol	Transferrin	Glioblastoma (Jhaveri et al. 2018)
	5-Fluorouracil	Transferrin	Colon cancer (Moghimipour et al. 2018)
Cationic liposomes	Daunorubicin and Honokiol	Hyaluronic acid	Breast cancer (Ju et al. 2018)
	Sorafenib	Hyaluronic acid	Cancer (Mo et al. 2018)
	DOX	Asparagine glycine Arginine (NGR) peptide	Breast adenocarcinoma (Yang et al. 2015)
pH-sensitive liposomes	Losartan	TH peptides	Cancer (Jain and Jain 2018)
	DTX	Eph A10	Cancer (Zhang et al. 2018b)
Photothermal therapy	Rapamycin and polypyrrole	Trastuzumab	Breast cancer (Nguyen et al. 2017)
Thermosensitive liposomes	DOX	iRGD	Cancer (Deng et al. 2016)
Thermoresponsive magnetic liposomes	DOX	Magnetic targeting	Cancer (Dai et al. 2017)
Magnetic liposomes	Curcumin	Magnetic targeting	Cancer (Hardiansyah et al. 2017)

and Khosroushahi 2017; Gothwal et al. 2016; Biswas et al. 2016). Currently, many chemotherapeutic drug-loaded polymeric micelles are evaluated for effective cancer treatment (Table 3.6).

3.6.1.4 Dendrimers

Dendrimers are highly branched globular macromolecules with their 3D nonpolymeric architectures: a central core, a corona with functional groups, and a hyperbranched mantle. Dendrimers' unique properties like polyvalency, well-defined molecular weight, nanosize, the high degree of branching, water solubility, and simple synthesis procedure make them promising drug carrier systems for anticancer drugs. The dendrimers' biological effect is initiated by terminal moieties, and the dendrimers seem to be excellent candidates for carriers of anticancer drugs. A variety of dendrimers, including PAMAM, PEG, PPI, and PLL, have been successfully developed for drug delivery applications, and the PAMAM is most widely employed for targeted cancer therapy. Surface modification or conjugation of

Table 3.5 Application of SLNs against different types of cancers

Drug/formulations	Ligand	Type of cancer treatment
PTX/SLNs	Tyr-3-octreotide	Antiangiogenic and anti-glioma (Banerjee et al. 2016)
	Folate-grafted chitosan	Lung cancer (Rosiere et al. 2018)
	TAT	Cervical cancer (Liu et al. 2017a)
Methotrexate/SLNs	Protein functionalization	Brain cancer (Muntoni et al. 2019)
	Fucose	Brain cancer (Garg et al. 2016)
Curcumin/SLNs		Breast cancer (Wang et al. 2018a)
Resveratrol/SLNs		Breast cancer (Wang et al. 2017a)
Erlotinib/SLNs		Non-small lung cancer (Bakhtiary et al. 2017)
Omega-3 PUFA/ SLNs		Colorectal cancer (Serini et al. 2018)
Linalool/SLNs		Liver cancer (Rodenak-Kladniew et al. 2017)
DOX/SLNs	cRGD	Breast cancer (Zheng et al. 2019)
IR-780 dye/SLNs	cRGD	Photothermal therapy (Kuang et al. 2017)

Table 3.6 Application of polymeric micelles against different types of cancers

Drug	Polymeric micelles	Ligand	Type of cancer treatment
DOX	Poloxamer 407 and vitamin TPGS	pH-responsive FA	Ovarian carcinoma (Butt et al. 2015)
	PLA-PEG	Aptamer	Prostate cancer (Xu et al. 2013)
	Cholic acid – PE	–	Colorectal cancer (Amjad et al. 2012)
	Succinylated gelatin micelles	Folic acid	Breast cancer (Wang et al. 2018b)
	PLGA-PEG	–	Cancer (Ma et al. 2016)
PTX	Redox-responsive micelles	Albumin	Breast cancer (Zhang et al. 2018c)
	Pluronic F87-PLA/TPGS	Folate	Cancer (Xiong et al. 2017)
	Pluronic F127-PEG	–	Ovarian cancer (Zhai et al. 2018)

dendrimers with PEG and other ligands can help reduce the cytotoxicity of dendrimers and enhance plasma circulation time and accumulation of tumor through the EPR effect (Kaur et al. 2016; Augustus et al. 2017; Munir et al. 2016; Parajapati et al. 2016; Abedi-Gaballu et al. 2018; Sherje et al. 2018). Numerous researches that have been conducted to study the application of dendrimers in cancer treatment are presented in Table 3.7.

3.6.1.5 Polymeric Nanoparticles

The polymeric nanoparticulate system from natural and synthetic biodegradable polymers has earned more attention due to their biodegradability, biocompatibility, tailorability and stability, ease of coating or surface modification, and low cost. Polymeric nanoparticles, in general, can be used to improve solubility, controlled

Table 3.7 Dendrimer-based nano DDS for cancer treatment

Polymer	Drug	Modification	Type of cancer treatment
PAMAM	DOX	–	Breast cancer (Khodadust et al. 2014)
	DTX	Trastuzumab	Breast cancer (Kulhari et al. 2016)
	Camptothecin	N-acetyl-D-glucosamine	Lung cancer (Pooja et al. 2020)
	pDNA/siRNA	–	Cancer (Li et al. 2018a)
PLL	DOX	PEG	Cancer (Mehta et al. 2018)

release, and bioavailability for systemic delivery of anticancer drugs. Drug-loaded polymeric nanoparticles can be developed to actively or passively accumulate in sites of the tumor by controlling their particle size or surface functionalizing with targeting moieties. Polymers like hyaluronic acid and pullulan are used to activate nanoparticles for active targeted drug delivery. These polymers degrade in physiological body conditions, and by-products of the polymers are not harmful to the body. Various natural and synthetic polymers-based nanoparticles were developed and reported for cancer treatment and diagnosis (Masood 2016; Prasad et al. 2017; Conte et al. 2016; Wong et al. 2020; Espinosa-Cano et al. 2018; Taghipour-Sabzevar et al. 2019). Natural and synthetic polymers-based nano DDS for cancer treatment are summarized in Tables 3.8 and 3.9.

3.6.1.6 Polymer-Drug Conjugates

Polymer-drug conjugates (PDCs) can be prepared as nano DDS by covalently conjugating one or more drugs to a polymer backbone before the synthesis of nanoparticles. PDCs are identified as the most examined type of nano DDS, and currently, many PDs in clinical trials and several polymer-drug conjugates are successfully transformed into clinical practice. For example, N-(2-hydroxypropyl) methacrylamide-DOX was the first chemotherapeutic PDC to reach clinical trial studies about 22 years ago. The conjugation of therapeutic drugs to polymers provides many benefits, including improved drug solubilization, stability, controlled drug delivery, enhanced efficacy and improved pharmacokinetics, biodistribution, as well as reduced toxicity and immunogenicity. The main advantage of using PDCs is that the physical and chemical characteristics of polymers can be modified to reduce the toxicity and improve the therapeutic efficacy of the loaded chemotherapeutics. In addition, PDCs have displayed increased accumulation of tumors, improved therapeutic index, prolonged circulation, controlled release of the anticancer drugs, and active tumor uptake by active targeting (Ekladious et al. 2019; Thanou and Duncan 2003; Vicent and Duncan 2006; Li and Wallace 2008) (Table 3.10).

Table 3.8 Natural polymers-based nano DDS for cancer treatment

Polymer	Conjugation	Drug	Type of cancer treatment
Chitosan	*N*-acetyl histidine and arginine	DOX	Breast (Raja et al. 2017)
	Trimethyl and folic acid	PTX	Hepatoma and colon (He and Yin 2017)
	TPGS and transferrin	DTX	Brain (Agrawal et al. 2017)
Alginate	PEI and FA	Curcumin	Cervical (Anirudhan et al. 2017)
	Glycyrrhetinic acid	Tetravalent platinum	Liver and lung (Wang et al. 2019)
	Chitosan	DOX	Breast (Katuwavila et al. 2016)
Pullulan	Arabinogalactan	DOX	Liver (Pranatharthiharan et al. 2017)
	PEI and MSA	DOX	Glioma (Priya and Rekha 2017)
	Folic acid	PTX	Liver (Huang et al. 2018)
Dextran	Folic acid	DOX	Breast and lymphoma (Tang et al. 2018a)
	Albumin	PTX	Colorectal (Zhang et al. 2019)
	Folic acid	Resveratrol	Lung (Zhao et al. 2017)
HA	Chitosan	5-Fluorouracil	Lung and liver (Wang et al. 2017b)
	PLGA	PTX	Breast (Cerqueira et al. 2017)
	PLGA	DTX	Lung (Wu et al. 2017b)

Table 3.9 Synthetic polymers-based nano DDS for cancer treatment

Polymer	Conjugation	Drug	Type of cancer treatment
PLGA	Folate-PEG	GEM and DTX	Ovarian (Li et al. 2019b)
	Transferrin	PTX	Breast and brain (Cui et al. 2017)
	Chondroitin sulfate	DOX	Glioma (Liu et al. 2019b)
PLA	Hydroxyethyl starch	DOX	Liver (Yu et al. 2017)
	PEG	DTX	Ovarian (Qi et al. 2017)
	FA-PEG	PTX	Ovarian (Yao et al. 2018)
PCL	PEG	Curcumin	Liver (Guo et al. 2017)
	PEG	Artemisinin	Breast (Manjili et al. 2018)
	TPGS	Sorafenib	Liver (Tang et al. 2018b)
PEG	Glycyrrhetinic acid-PCL	Curcumin	Liver (Feng et al. 2017)
	Lactoferrin-PLGA	Shikonin	Glioma (Li et al. 2018b)

3.6.2 Inorganic Nanomaterials for Cancer Treatment

Inorganic nanomaterials have been intensively studied for cancer therapy and diagnostic imaging due to their great advantages, such as high drug loading, large surface area, improved bioavailability, reduced toxic side effects and controlled release of anticancer drugs, and their tolerance to most organic solvents. Mesoporous silica nanoparticles, gold nanoparticles, magnetic nanoparticles, carbon nanotubes, and

Table 3.10 Polymer-drug conjugates for cancer treatment

Drug	Polymer	Conjugates	Type of cancer treatment
Dihydroartemisinin	HA	HA-dihydroartemisinin	Lung cancer (Kumar et al. 2019)
DOX	N-(2-hydroxypropyl) methacrylamide	N-(2-hydroxypropyl) methacrylamide-DOX	Breast cancer (Bobde et al. 2020)
	PEG	PEG-DOX	Breast cancer (Gu et al. 2018)
	Poly-l-glutamic acid	Poly-l-glutamic acid-DOX	Non-small cell lung cancer (Li et al. 2013)
DOX and GEM	HA	HA-DOX-GEM	Breast and lung cancer (Alven et al. 2020)
FA and trastuzumab	PEG	PEG-FA-trastuzumab	Breast and lung cancer (Alven et al. 2020)
PTX	N-(2-hydroxypropyl methyl) acrylamide	N-(2-hydroxypropyl methyl) acrylamide copolymer-gadolinium-PTX	Breast and lung cancer (Alven et al. 2020)
	HA	HA-PTX	Cancer (Wang et al. 2017c)
	PEG	PEG-PTX	Lung cancer (Luo et al. 2016)
GEM	Poly (l-glutamic acid)-g-methoxy PEG	Poly (l-glutamic acid)-g-methoxy PEG-GEM	Cancer (Yang et al. 2018b)

quantum dots are commonly used in cancer treatment and diagnosis in various ways (Fig. 3.2) (Khafaji et al. 2019; Veeranarayanan and Maekawa 2019; Liu et al. 2017b).

3.6.2.1 Mesoporous Silica Nanoparticles (Senapati et al. 2018; Ahmadi Nasab et al. 2018; Moreira et al. 2016; de Oliveira Freitas et al. 2017; Yang and Yu 2016; Saini and Bandyopadhyaya 2019)

Silica nanoparticles are extensively used nanoparticle systems in cancer treatment due to its various benefits such as easy synthesis, well-controlled diameter, adjustable pore volume, and potential surface modification. There are two types of silica nanoparticles (core or shell silica nanoparticles and mesoporous silica nanoparticles (MSNs)) established for cancer treatment. Of the two types, MSNs are mostly used as a nano DDS in cancer treatment. One study demonstrated that gemcitabine-loaded MSNs are used to treat pancreatic cancer. One research group developed the rod-shaped magnetic MSNs for suicide gene therapy. The shapes of the MSNs also

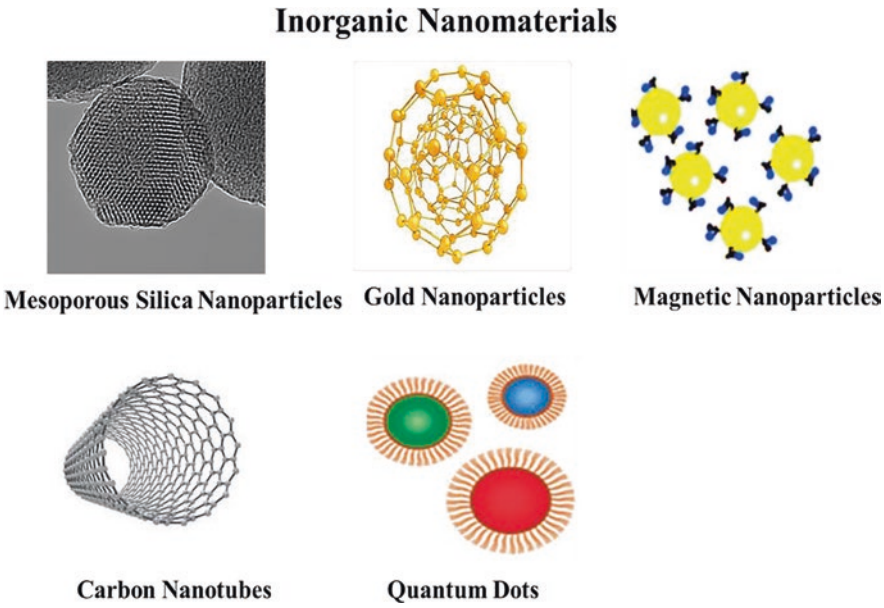

Fig. 3.2 Different types of inorganic nanomaterials for cancer treatment

play a vital role in drug delivery applications. Compared to spherical MSNs, rod shape-like MSNs displayed higher drug loading, better drug release, and gene delivery.

The research carried out by Lee et al. showed how MSNs decorated with doxorubicin-loaded multiple magnetite nanocrystals promoted effective cell death in a melanoma model, confirming passive targeting and nanoparticle accumulation in the tumor site. Huan et al. used MSNs modified with polyethyleneimine/PEG to deliver doxorubicin jointly with P-glycoprotein siRNA. This research explained that nanoparticles were efficiently biodistributed, resulting in 8% of the EPR effect at the tumor site. MSNs can also be surface-functionalized with various types of ligand molecules such as aptamers, growth factors, peptides, and vitamins to actively target tumors via receptor-mediated endocytosis. In the study carried out by Kayuan et al., DOX-loaded HB5 aptamer-functionalized MSNs were used for combined chemo-photothermal therapies. This study verified that combination therapies promote cancer cell killing compared to chemo-photothermal therapy alone. MSNs achieve a satisfactory level of active targeting and reduce toxic side effects in the healthy normal cells.

3.6.2.2 Gold Nanoparticles (Sztandera et al. 2018; Peng and Liang 2019; Kumar et al. 2012; Singh et al. 2018)

Gold nanoparticles (GNPs) have been investigated for its potential application in cancer treatment, diagnostics, and targeted drug delivery. Current researches confirm numerous advantages of GNPs for cancer treatment, primarily due to enabling the control of preparation of GNPs with multiple sizes and shapes and the possibility of surface functionalization on GNPs with various functional and targeting agents. Many features of GNPs are related to their shape and size. The size of spherical GNPs influenced plasma concentration, circulation time, and cellular uptake. It was also reported that the smaller particles of GNPs permeated into the blood-brain barrier, deep layers of skin, and placental barrier. Surface functionalization of GNPs provides significant effects on plasma half-life, protection against aggregation, biocompatibility, preventing the removal by the MPS and RES, targeted transport and drug accumulation at the desired site. For the GNP-based drug delivery system, passive targeting, active targeting, or a combination of both strategies can improve tumor accumulation. A remarkable approach confirming the intracellular delivery of chemotherapeutic drugs involves their conjugation to the surface of GNPs through thiol functional groups. The examples of chemotherapeutic drugs conjugated with GNPs are listed in Table 3.11.

Due to their exceptional properties of absorption and scattering of electromagnetic radiation, GNPs are of specific interest for the PTT in cancer treatment. This PTT treatment procedure involves the utilization of electromagnetic radiation or laser radiation to generate local heating and hyperthermia for the thermal destruction of cancerous cells. The PTT efficacy may be additionally improved by the application of photothermal compounds such as transition metal oxide/sulfide nanomaterials and nanocarbons, enabling an improved transformation of light into heat.

Table 3.11 Gold nanoparticles for cancer treatment

Nanomaterials	Targeting agents	Drug
Gold nanoparticles	PEG	Tamoxifen
	PEG, tumor necrosis alpha	PTX
	3-Mercaptopropionic acid	Daunorubicin
	PEG, folate	DOX
	Poly(L-aspartate), PEG, folate	DOX
	–	Methotrexate
	–	Gemcitabine
	Photocleavable and zwitterionic thiol ligands	5-Fluorouracil

3.6.2.3 Magnetic Nanoparticles (Zhang et al. 2018d; Kolosnjaj-Tabi and Wilhelm 2017; Fathi Karkan et al. 2017; Fathi et al. 2020; Lungu et al. 2016)

Magnetic nanoparticles (MNPs) have been discovered as a potential carrier system to modify the pharmacokinetics of loaded drugs, decrease the cytotoxicity, improve the controlled release, and increase the half-life. Due to the unique properties of higher magnetic moments and surface to volume ratios, it can be used for hyperthermia therapy of cancer treatment and targeted delivery. MNPs are in magnetic resonance imaging to enhance the image contrast of targeted tumor tissues. MNPs can be functionalized with high affinity ligands such as peptides and antibodies to enhance the selectivity further and localize MNPs at the tumor sites. Recently, the MNP application in biosensors has been extensively studied for rapid cancer diagnosis and prevention of cancer metastasis. Various types of MNPs employed in cancer treatment and diagnosis are summarized in Table 3.12.

3.6.2.4 Carbon Nanotubes (Chen et al. 2017; Son et al. 2016; Pardo et al. 2018)

Carbon nanotubes (CNTs) are very popular systems for cancer treatment and diagnosis due to their many unique properties such as structure and high specific surface area to volume. CNTs are classified into single-walled carbon nanotubes and multi-walled carbon nanotubes based on the number of graphene sheets used for the preparation. CNTs have been investigated in all the cancer treatment modalities, including thermal, photodynamic, and gene therapy, drug delivery, lymphatic targeted chemotherapy, and diagnostic techniques. Recently developed single-walled carbon nanotube-based drug delivery systems for cancer treatment are summarized in Table 3.13. CNTs may help the attached chemotherapeutic drugs to penetrate through the target cell to treat cancer.

The CNTs are used as a photosensitizer for photodynamic therapy. CNTs are used as a contrast medium for diagnostic imaging techniques, and it can be used in

Table 3.12 Magnetic nanoparticles for cancer treatment

Drug	Magnetic nanoparticles	Type of cancer treatment
Methotrexate	Chitosan grafted pH and thermoresponsive	Ovarian cancer (Fathi et al. 2020)
Doxorubicin	FA conjugated Fe3O4	Cancer (Rana et al. 2016)
	PEG coated	Hyperthermia therapy (Dabbagh et al. 2019)
	Dual stimuli responsive polymer modified	MR imaging (Bhattacharya et al. 2016)
	pH-sensitive polymer coating	Cancer, pH-sensitive release (Lungu et al. 2016)

Table 3.13 Carbon nanotube-based systems for cancer treatment

Drug	Surface functionalization	Type of cancer treatment
DOX	FA	Chemo-photothermal (Wang et al. 2017d)
PTX	Riboflavin and thiamine	Cancer (Singh et al. 2016a)
DOX	Polyphosphazene coated	Redox responsive and photothermal (Wang et al. 2017e)
DOX	Polyampholyte	Cervical cancer (Phan et al. 2020)
Temozolomide	Vitamin B6 and PEG	Cancer (Saberinasab et al. 2019)
DOX	Hyaluronic acid coated	Breast cancer (Liu et al. 2019c)
DOX	pH-sensitive nanogels	Glioblastoma (Seyfoori et al. 2019)
DTX	Vitamin E TPGS	Lung cancer (Singh et al. 2016b)

ultrasonography, photoacoustic imaging, PET, and MRM for cancer diagnostic applications.

3.6.2.5 Quantum Dots (Zhao et al. 2016; Fang et al. 2017; Lee et al. 2017)

Quantum dots (QDs) are nanosized crystals comprised of a semiconductor core within a shell composed of second semiconductor material. QDs have outstanding optical properties, such as high brightness, tunable emission spectra, and resistance to photo-bleaching. Quantum dots have been used in targeting and localizing tumors and sentinel lymph node mapping in vivo. New imaging techniques like quantum dots resolve the limitations of sensitivity and specificity from current imaging techniques like X-ray, ultrasound, radionuclide imaging, computed tomography, and MRI. Recent studies in surface functionalization of QDs improve their potential application in imaging of cancer. Bioconjugation of QDs with peptides and antibodies can be used for tumor-targeted drug delivery, nanodiagnostics, imaging, and photodynamic therapy. The application of quantum dot conjugates is listed in Table 3.14.

3.7 Challenges and Future Perspectives

Despite numerous advanced technologies in the production of safe biopolymers and nanomaterials, there remain controversies regarding the safety of nanoformulations. Although the benefits of some biopolymers, dendrimers, and metal-based inorganic nanomaterials are remarkable, toxicity remains a serious problem. It has been proven, for example, that PEI and excessive positive charges of dendrimers destabilize the cell membrane. Thus, advancements in biopolymer synthesis and purification techniques promise to reduce side effects and enhance treatment efficacy. The instability, immune response, potential toxicity, and chronic inflammation

Table 3.14 Quantum dots for cancer treatment and diagnosis

Conjugates	Application
DOX-D-glucosamine-folate-QD conjugates	Cancer cell imaging and treatment (Ranjbar-Navazi et al. 2018)
Antibody-QD conjugates	In vitro and in vivo molecular imaging (Tsuboi et al. 2017)
Titanium nitride MXene QDs	Phototheranostics in both NIR-I/II bio windows (Shao et al. 2020)
Polydopamine-black phosphorus QDs	Cancer theranostics (Li et al. 2019c)
pH-responsive fluorescent graphene QDs	Fluorescence-guided cancer surgery and diagnosis (Fan et al. 2017)
Aptamer conjugated graphene QDs	Photothermal therapy and photodynamic therapy (Cao et al. 2017)
Graphitic-C3N4 QDs	Photodynamic therapy (Chu et al. 2017)

challenges for micelles and inorganic nanomaterials need to be focused so that more effective cancer treatment strategies can be developed. Combination therapy with nanomaterials for different types of cancers remains a challenge because of the distinct cancer development mechanisms. For targeted drug therapy, inorganic nanomaterials and micelles can be surface-functionalized with target agents such as magnetic, light, and pH imaging contrast agents; the major limitation of these clinical treatment methods is the poor tissue penetration. All the nanomaterials are not biodegradable so that it can be retained and circulated in the body system for a more extended period after administration. Various research and strategies aimed at overcoming all these challenges will facilitate nanomaterial usage as a drug delivery system and eventually enhance patient survival.

The future perspective of stimuli-responsive nanomaterials can be obtained by various strategies, including enzymatic activation, pH variants, magnetic fields, ultrasound, light, redox potential, and thermal gradients for efficient cancer treatment and diagnosis. Further advancements in the nanomaterials system can improve their application in localizing metastasis, quantitative measurement of molecular targets, and monitoring the efficacy and tracking of drug delivery.

3.8 Conclusion

This chapter has summarized a variety of nanomaterials that are either being used or have the potential to be used as nano drug delivery systems for cancer treatment. Nanomaterials-based cancer treatment has shown significant advantages and new strategies over conventional cancer treatment. Passive or active targeting can significantly remove the systemic side effects of conventional chemotherapies. Targeted drug delivery has made a considerable impact on selective recognizing of the tumor tissues, controlled drug delivery, and overcoming limitations of the conventional

chemotherapies. Numerous nanomedicines have been approved by the FDA and indicated satisfactory performance in clinical practice. Although some nanomaterials have not been approved upon their clinical translation, new strategies and promising nanomaterials that are under progress show great assurance, thus providing hope for innovative cancer treatment choices in the near future.

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Chapter 4
Novel Organic and Inorganic Nanoparticles as a Targeted Drug Delivery Vehicle in Cancer Treatment

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Abbreviations

5FU	5-Fluorouracil
AITC-SiQDs	Allyl isothiocyanate-silicon QDs
AKT/mTOR	Serine/threonine-specific protein kinase/mechanistic target of rapamycin kinase
APAF1	Apoptotic protease activating factor 1
AuNPs	Gold nanoparticle
Bcl-2	B-cell lymphoma 2
CNTs	Carbon nanotubes
DSC	Differential scanning calorimetry
EGF	Epidermal growth factor
FA-NGO-PVP	Folic acid-graphene oxide-polyvinylpyrrolidone
FDA	Food and Drug Administration
GA-CdTe	Gambogic acid-cadmium-tellurium
GO-PVCL	Graphene oxide-poly N-vinyl caprolactam
HA	Hyaluronic acid
HA-DOX-GQD@MSN	Hyaluronic acid-doxorubicin-N-graphene quantum dots-mesoporous silica nanoparticles
HCC	Hepatocellular carcinoma
HER2 genes	Human epidermal growth factor receptor-2 genes
HPMA	N-2-hydroxypropyl methacrylamide
IGF1R	Type I insulin-like growth factor receptor
MALDI-MS	Matrix-assisted laser desorption ionization-mass spectrometry
MMP	Matrix Metallo Proteinases
NF-kB	Nuclear factor-κB
NGO-HA	Nanographene oxide-hyaluronic acid
NIPAAM	N-isopropylacrylamide
NMR	Nuclear magnetic resonance
PAMAM	Polyamidoamine
PEDOT:PSS	Poly 3,4-ethylenedioxythiophene-poly styrenesulfonate
PEG	Polyethylene glycol
PEG-A	Polyethylene glycol monoacrylate

PEG-PE	Polyethylene glycol-phosphatidyl ethanolamine
PEO-PCL	Polyethylene oxide-poly epsilon-caprolactone
PLA-PEG-PLL- DTPA	Poly lactic acid-polyethylene glycol-poly L-lysine-diethylene Triamine pentaacetic acid
PLGA	Poly D,L-lactic acid-co-glycolic acid
PLGA	Polylactide-co-glycolide
PLH-PEG-biotin	Poly L-histidine-polyethylene glycol-biotin
PPI	Polypropylene imine
PTT	Photothermal therapy
QDs	Quantum dots
ROS	Reactive oxygen species
SEM	Scanning electron microscope
TEM	Transmission electron microscopy
TPTN	Theranostic polymeric nanoparticle
TRC-NPs	Thermo-responsive chitosan-*g*-poly (*N*-vinylcaprolactam) nanoparticles
VP	N-vinyl-2-pyrrolidone
γ-PGA	Polyvinyl pyrrolidone and poly-γ-glutamic acid

4.1 Introduction

Free radicals are the toxic substances produced in our body due to our modern lifestyle patterns like food habits, lack of exercise, stress, and work pressure. Free radicals can multiply through a chain reaction mechanism resulting in the release of thousands of cellular oxidants which cause DNA damage and mutation, alter DNA codes, and compromise immunity, resulting in disease like cancer (Lobo et al. 2010). Cancer is medically known as neoplasm. It arises when the homeostatic balance between cell growth and death is disturbed. Current standard treatments for cancer like chemotherapy and radiation and with synthetic compounds affect not only the cancer cells but also normal cells causing organ dysfunction, reduced production of white blood cells, hair loss, inflammation of the mucous membranes lining the digestive tract, etc. (Labi and Erlacher 2015). But the nanoparticles or nanocarriers have diversiform structures, multiple targets, diversified pharmacological potential, targeted drug releasing capacity, sustainability, and solubility which could act as a better choice to treat cancer. Another advantage is the high permeability of nanoparticles along with the anticancer agents at tumor site, compared with healthy cells (ud Din et al. 2017). Homeostatic imbalance in cancer cells can be readily reverted by nanocarriers or nanoparticles (organic or inorganic) by enhancing the immune response and suppressing the cancer activity in our body. Our aim is to couple the anticancer drugs like 5-FU, irinotecan, oxaliplatin, bevacizumab, and capecitabine with nano-based encapsulation technology, for treating primary or advanced metastatic tumors. Although anticancer drugs have potent anticancer activity, sometimes it causes poor water solubility, due to its smaller size easily excreted in urine, less availability, and

less target specificity (Ungari et al. 2017). Nanotechnology is the most advanced in the field of medicine to overcome the limitations of conventional low molecular weight drugs. And it acts as a better anticancer drug delivery vehicle by using both organic and inorganic nanoparticles like polymeric micelles, liposomes, dendrimers, silica, gold, silver, carbon nanotubes, quantum dots, nanographene, and magnetic nanoparticles (Fig. 4.1). This nanocarriers have different biophysicochemical properties like different shapes, size, surface area, and material which may be hard (organic) or soft (inorganic) (Chenthamara et al. 2019). Smaller-size nanoparticles can easily pass through the circulation and release anticancer drugs at the specific tumor tissues. The lifespan of nanoparticles was particularly determined by the hydrophilic surfaces; this surfaces help to evade the nanoparticles from the macrophages when passing through the circulatory mechanisms (Patra et al. 2018). Coating the nanoparticles with a hydrophilic polymer (PEG) will provide the hydrophilic surface. Green synthesis of nanoparticles can be achieved by using the plant extracts or bioactive compounds of anticancer medicinal plants which are environment friendly with no toxic side effects and are the better choice to fight against cancer (Wei et al. 2019; Roy et al. 2021). Nanoparticles are regarded to be an ideal vehicle for antitumor drugs because of their hydrophobic inner core and hydrophilic outer shell, which enhanced the permeation and retention effect in tumor tissue (Bae et al. 2011). This review paper aims to cover the advantages of organic and inorganic nanoparticles as a novel drug carrier vehicle in cancer treatment in order to overcome the limitations of conventional drugs.

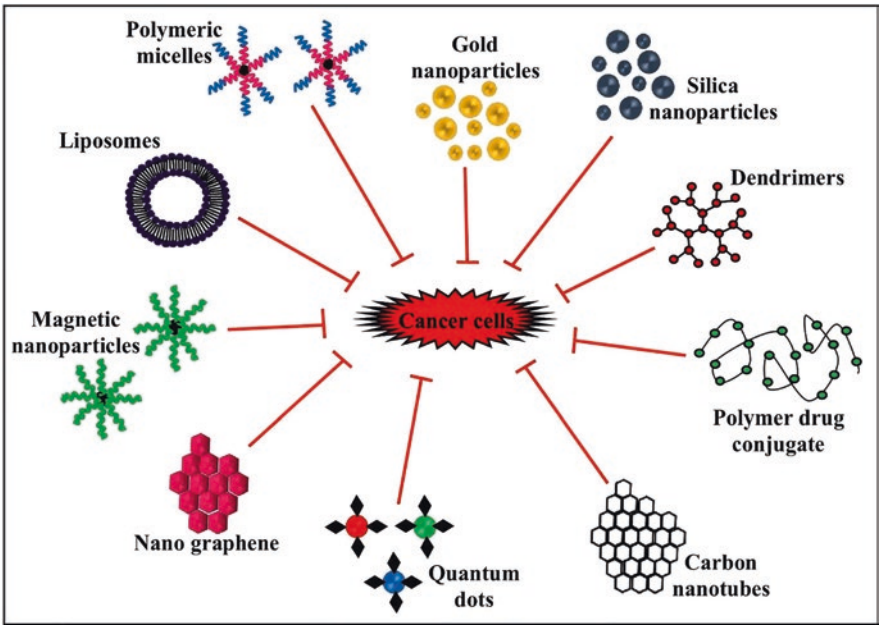

Fig. 4.1 Organic and inorganic nanoparticles as an anticancer drug delivery vehicle

4.2 Polymeric Micelles

A number of anticancer delivery vehicles are there, but polymeric micelles gained importance due its small sizes (10–100 nm) and its efficacy to solubilize the insoluble drugs and because they are more efficient in slow release of drug in the tumor tissue. Polymeric micelles consist of core shell with inner hydrophobic domains suitable for water-insoluble drugs and hydrophilic outer shell (Zhang et al. 2014a, Zhang et al. 2014b). Polymeric micelles act as an efficient drug carrier due to its prolonged and stable drug release at the specific site of cancer tissue (Rijcken et al. 2007) (Table 4.1). The core shell structure of polymeric micelles makes it more efficient to load the hydrophobic drugs and protect the drugs from protein degradation (Gaucher et al. 2004). Polymeric micelle-conjugated Genexol proves to be more efficient against breast cancer approved by the US FDA (Oerlemans et al. 2010). Polymeric micelles of naringin with a better anticancer and anti-ulcer activity by decreasing the level of mucosal damage, gastric expression of malondialdehyde, tumor necrosis factor-alpha, caspase-3, nuclear factor kappa-light-chain enhancer of activated B cells, and interleukin-6 with the elevation of gastric reduced glutathione and superoxide dismutase (Mohamed et al. 2018). 7-Ethyl-10-hydroxy-camptothecin (SN-38)-incorporating polymeric micelles have a better anticancer activity by inhibiting vascular endothelial growth factor in human colorectal cancer (Koizumi et al. 2006). Combinational anticancer effect of polymeric micelles along with the 5-fluorouracil showed the cell cycle arrest at S phase in colorectal cancer (Nakajima et al. 2008). Polymeric micelles incorporating cisplatin show complete cancer inhibition in solid tumor and reduced the nephrotoxic and neurotoxic effects (Nishiyama et al. 2003; Uchino et al. 2005). Non-covalent interactions of polymeric micelles with doxorubicin showed a potent anticancer activity and kinetic stability against human liver carcinoma cells (Yang et al. 2012a, Yang et al. 2012b, Yang et al. 2012c). Adriamycin as physically entrapped in the inner core of polymeric micelles showed antitumor activity against solid tumor (Yokoyama et al. 1998). Cisplatin-conjugated polymeric micelles (NC-6004) showed more efficient cytotoxic effect in solid tumor patients and contribute to low toxicity of NC-6004 (Plummer et al. 2011). Polyethylene glycol (5 K)-embelin nanomicellar delivered the paclitaxel in the tumor tissues of breast and prostate cancer and acts as a best anticancer drug vehicle (Lu et al. 2013). Polyethylene glycol-phosphatidyl ethanolamine (PEG-PE) and vitamin E tumor-targeted immunomicelles act as best anticancer drug carriers to carry water-insoluble camptothecin which showed improved cytotoxic activity in various cancer cells (Sawant et al. 2008). Doxorubicin-loaded polylactide-poly(ethylene glycol) aptamer micelles act as a best nanocarrier to treat prostate cancer (Xu et al. 2013a, Xu et al. 2013b). Polymeric micelles co-conjugated with gemcitabine and miR-205 inhibited tumor growth and increase apoptosis in pancreatic cancer (Mondal et al. 2017). Charge reversed polymer micelles conjugated with paclitaxel/disulfiram overcome multidrug resistance in breast cancer cell (Huo et al. 2017). Overexpression of glucose transporter-1 and glutathione in cancer cells was exploited to assemble aminoglucose-conjugated, redox-responsive

Table 4.1 Polymeric micelles as a drug delivery system

Sl. no.	Polymeric micelles	Cancer	References
1.	Polymeric micelle-conjugated Genexol	Brest cancer	Oerlemans et al. (2010)
2.	7-Ethyl-10-hydroxy-camptothecin (SN-38)-incorporating polymeric micelles	Colorectal cancer	Koizumi et al. (2006)
3.	Polymeric micelle with 5-fluorouracil	Colorectal cancer	Nakajima et al. (2008)
4.	Polymeric micelles incorporating cisplatin	Reduced solid tumors, nephrotoxic, neurotoxic effects	Nishiyama et al. (2003) and Uchino et al. (2005)
5.	Polymeric micelles with doxorubicin	Liver cancer	Yang et al. (2012a), Yang et al. (2012b), Yang et al. (2012c)
6.	Adriamycin with polymeric micelles	Solid tumor	Yokoyama et al. (1998)
7.	Cisplatin-conjugated polymeric micelles	Solid tumor	Plummer et al. (2011)
8.	Polyethylene glycol (5 K)-embelin nanomicellar with paclitaxel	Breast cancer, prostate cancer	Lu et al. (2013)
9.	Polyethylene glycol-phosphatidyl ethanolamine (PEG-PE) and vitamin E tumor-targeted immune micelles with camptothecin	Various cancer	Sawant et al. (2008)
10.	Doxorubicin-loaded polylactide-poly(ethylene glycol) aptamer micelles	Prostate cancer	Xu et al. (2013a), Xu et al. (2013b)
11.	Polymeric micelles co-conjugated with gemcitabine and miR-205	Pancreatic cancer	Mondal et al. (2017)
12.	Polymer micelles conjugated with paclitaxel/disulfiram	Breast cancer	Huo et al. (2017)
13.	Aminoglucose-conjugated nanomicelles with polyethylene glycol and polylactic acid	Lung cancer	Zhou et al. (2017)
14.	Polymeric micelles with mitoxantrone	Breast cancer	Li et al. (2017)
15.	Cyclic-Arg-Gly-Asp (cRGD) peptide-conjugated polymeric micelles with epirubicin	Brain tumor	Quader et al. (2017)
16.	Polymeric micelles with paclitaxel and tariquidar	Ovarian carcinoma	Zou et al. (2017)
17.	Polymeric micelles with paclitaxel and honokiol	Breast cancer	Wang et al. (2017)
18.	Polymer nanomicelles with doxorubicin and P-gp siRNA	Breast cancer	Babu et al. (2017)

(continued)

Table 4.1 (continued)

Sl. no.	Polymeric micelles	Cancer	References
19.	PEGylated cholesterol/α-tocopheryl succinate conjugated to polymer with curcumin	Murine melanoma, breast cancer	Muddineti et al. (2017)
20.	Blood-stable polymeric micelles with curcumin	Erythroleukemia	Gong et al. (2017)

nanomicelles, polyethylene glycol, and polylactic acid to overcome chemoresistance in lung cancer cells (Zhou et al. 2017). Polymeric micelles loaded with mitoxantrone have reversed multidrug resistance in breast cancer cells via photodynamic therapy (Li et al. 2017). Cyclic-Arg-Gly-Asp (cRGD) peptide-conjugated polymeric micelles loaded with epirubicin inhibit the growth of an orthotopic glioblastoma multiforme in brain tumor tissue (Quader et al. 2017). Transferrin-modified polymeric micelles loaded with paclitaxel and tariquidar reverse the multidrug resistance in ovarian carcinoma cells (Zou et al. 2017). pH-responsive polymeric micelles loaded with paclitaxel and honokiol inhibited multidrug resistance and metastasis in breast cancer (Wang et al. 2017). Penta block polymeric micelles grafted with folic acid loaded with doxorubicin are pronounced for targeting anticancer drug delivery and control release (Chen et al. 2018). Polymer nanomicelles co-conjugated with doxorubicin and P-gp siRNA showed cytotoxic effect in breast cancer cells (Babu et al. 2017).

Curcumin is the most important anticancer agent in many cancer cells against multidrug resistance. But curcumin alone has some disadvantages with lower bioavailability in the tumor sites due to the properties of water insolubility and more excretion through the kidneys. In order to overcome its disadvantages, it should be conjugated to some nanoparticles to increase its bioavailability and efficacy against cancer. A self-assembled PEGylated cholesterol/α-tocopheryl succinate conjugated to polymer loaded with curcumin to form a micellar system inhibits the cell proliferation and cancer progression in murine melanoma cell line and human breast cancer, MDA-MB-231 cell lines (Muddineti et al. 2017). Blood-stable polymeric micelles loaded with curcumin increases higher uptake and slower elimination of curcumin into the erythroleukemia with better cytotoxic activity (Gong et al. 2017).

4.3 Polymeric Nanoparticles

Polymeric nanoparticles are widely used as carriers in the pharmaceutical sector for targeted drug delivery mechanism (Prasad et al. 2017). Top-down and bottom-up approaches are used for the preparation of polymeric nanoparticles (Krishnaswamy and Orsat 2017). They are solid in nature and colloidal particles of size range 10 nm to 1 μm with two possible structures: nanosphere and nanocapsule (Sharma 2019). Polymeric nanoparticles can be made from synthetic polymers that are biodegradable and nonbiodegradable in nature (Zhang et al. 2013). The potent applications of

polymeric nanoparticles are the biocompatibility in nature which assists in drug release at specific target sites (Rana and Sharma 2019) (Table 4.2).

4.3.1 Role of Polymeric Nanoparticles in Cancer Treatments

van Vlerken et al. (2007) investigated the therapeutic efficiency of a combinational chemotherapeutic agent of ceramide with paclitaxel, which is encapsulated by poly (ethylene oxide)-modified poly (epsilon-caprolactone) (PEO-PCL) nanoparticles used as a drug-delivering vehicle to regain apoptotic signaling in ovarian cancer cell line SKOV3. The nanoparticle drug delivery method shows 100-fold increase in chemosensitization due to restoration of apoptotic signaling. Rejinold et al. (2011) studied the curcumin nanoparticle formulation for cancer drug delivery combined with biodegradable thermo-responsive chitosan-*g*-poly (*N*-vinylcaprolactam) nanoparticles (TRC-NPs). Curcumin-loaded TRC-NP treatment increased mitochondrial-mediated apoptosis on PC3. Bisht et al. (2007) developed a polymeric nanoparticle, N-isopropylacrylamide (NIPAAM), with N-vinyl-2-pyrrolidone (VP) and poly (ethylene glycol)monoacrylate (PEG-A) encapsulated nanocurcumin. The treatment enhances cellular apoptosis, downregulates pro-inflammatory cytokines (IL-6, IL-8, and TNFα), and inhibits nuclear factor kappa B (NFκB) activation. Katiyar et al. (2016) studied the formulation of nanoparticles of rapamycin combined with a chemosensitizer piperine, and they are loaded in poly (D,L-lactide-co-glycolide) nanoparticles against breast cancer. The uptake of rapamycin and its efficacy are increased by the presence of chemosensitizer piperine in killing breast cancer cells. The combined drug formulation along with poly (D,L-lactide-co-glycolide) nanoparticles results in improved bioavailability and long-term therapeutic action with less dosing frequency. Gong et al. (2013) investigated the NIR-absorbing conjugated polymer PEDOT:PSS with PEGylation surface coating to serve as a drug loading platform in cancer therapy for various types of aromatic therapeutic molecules . They found that PEDOT:PSS-PEG nanoparticles can act as a multifunctional drug carrier that has great applications in combined chemo-photodynamic and photothermal therapy of cancer. Aryal et al. (2011) examined the combination chemotherapy by loading doxorubicin and camptothecin into a single polymeric nanoparticle to obtain a drug-polymer conjugate, which is then encapsulated into the lipid-coated polymeric nanoparticles. This study points out that the dual drug approach offers a solution to overcome the challenge in ratiometric control over the loading of different types of drugs onto the same drug delivery vehicle. Jain et al. (2011) studied the therapeutic effects of tamoxifen-loaded PLGA nanoparticles (Tmx-NPs) against breast cancer. The results showed that when compared to untreated groups, oral Tmx-NP-treated group tumor size was reduced up to 41.56% along with reduced hepatotoxicity. Xiao et al. (2015) developed hyaluronic acid (HA)-functionalized polymeric nanoparticle (HA-CPT/CUR-NPs) to act as carriers to co-deliver camptothecin (CPT)/curcumin (CUR) in various weight ratios for colon cancer-targeted combination chemotherapy. HA-CPT/CUR-NPs have high

Table 4.2 Polymeric nanoparticle for the targeted drug delivery system

Sl. no.	Polymeric nanoparticle	Biological applications	Authors
1.	PEO-PCL nanoparticles	It shows 100-fold increase in chemosensitization due to restoration in apoptotic signaling	van Vlerken et al. (2007)
2.	TRC-NP nanoparticles	The treatment increased mitochondrial-mediated apoptosis on PC3	Rejinold et al. (2011)
3.	N-isopropylacrylamide (NIPAAM), with N-vinyl-2-pyrrolidone (VP) and poly (ethylene glycol) monoacrylate (PEG-A) nanoparticle	Enhanced cellular apoptosis, downregulates pro-inflammatory cytokines (IL-6, IL-8, and TNFα) and inhibits nuclear factor kappa B (NFκB) activation	Bisht et al. (2007)
4.	Poly (D,L-lactide-co-glycolide) nanoparticles	Improved bioavailability and long-term therapeutic action with less dosing frequency	Katiyar et al. (2016)
5.	PEDOT:PSS-PEG nanoparticles	Acts as a multifunctional drug carrier	Gong et al. (2013)
6.	Lipid-coated polymeric nanoparticles	It can load different types of drugs onto the same drug delivery vehicle	Aryal et al. (2011)
7.	Tmx-NP nanoparticles	Tumor size was reduced up to 41.56% along with reduced hepatotoxicity	Jain et al. (2011)
8.	HA-CPT/CUR-NP nanoparticles	High colon cancer cell-targeting ability	Xiao et al. (2015)
9.	Lactic-co-glycolic acid nanoparticles	Improved cellular uptake and highest cytotoxicity against CD44+ cells	Muntimadugu et al. (2016)
10.	Hypoxia-responsive nanoparticles	Drug showed higher toxicity toward hypoxic cells, and it has the ability to deliver doxorubicin into tumor cells under hypoxic conditions	Thambi et al. (2014)
11.	Temozolomide-loaded nanoparticles	Nanoparticle vector can act as an image-guided treatment of malignant glioma	Bernal et al. (2014)
12.	TPTN nanoparticle	Higher antitumor effect in H22 and HepG2 tumor cells Higher resolution and longer imaging time (>90 min) in the MRI diagnosis	Liu et al. (2014)
13.	PEO-PCL nanoparticles	Improved antitumor efficacy without any acute toxicity	Devalapally et al. (2008)
14.	HER-DMPNP nanoparticles	Great cancer cell affinity and ultrasensitivity via magnetic resonance imaging	Yang et al. (2007)

colon cancer cell-targeting ability. The extremely low 1:1 weight ratio shows highest antitumor efficiency against Colon-26 cells. Muntimadugu et al. (2016) formulated an efficient drug delivery system for the co-delivery of salinomycin and paclitaxel in the form of poly (lactic-co-glycolic acid) nanoparticles for targeting both cancer cells and cancer stem cells. In vitro cytotoxicity studies show that the combination therapy has great specificity toward the targeted cells, improved cellular uptake, and highest cytotoxicity against CD44+ cells. Thambi et al. (2014) examined the efficiency of self-assembled hypoxia-responsive nanoparticles loaded with doxorubicin as a potent drug carrier against hypoxic tumor tissues. The conjugated drug showed higher toxicity toward hypoxic cells, and it has the ability to deliver doxorubicin into tumor cells under hypoxic conditions. Bernal et al. (2014) reported a polymeric nanoparticle vector which has the ability to deliver viable therapeutic drugs and also be tracked in vivo using MRI. Convection-enhanced delivery of temozolomide-loaded nanoparticles improved the survival ratio of animals. And the nanoparticle vector can act as an image-guided treatment of malignant glioma. Liu et al. (2014) formulated a self-assembled target pH-sensitive theranostic polymeric nanoparticle (TPTN) concerning the cancer cell examination and also treatment. They loaded sorafenib, an anti-hepatocellular carcinoma drug, inside the multi-block polymer, poly (lactic acid)-poly (ethylene glycol)-poly (L-lysine)-diethylenetriamine pentaacetic acid and poly(L-histidine)-poly(ethylene glycol)-biotin. The TPTN nanoparticle showed antitumor effect against HepG2 cells, higher antitumor effect in H22 tumor cells, and higher resolution and longer imaging time (>90 min) in the MRI diagnosis. Overall it has the capacity for drug loading, imaging agents, precise targeting, pH-triggered drug-delivering qualities, and also exceptional biocompatibility. Devalapally et al. (2008) studied the potency and preceding protection of tamoxifen with paclitaxel in the biodegradable polymeric nanoparticle. Nanoparticle consists of poly (ethylene oxide) revised poly (epsilon-caprolactone), (PEO-PCL) nanoparticles, toward ovarian adenocarcinoma. The results showed improved antitumor efficacy without any acute toxicity. Yang et al. (2007) developed antibody-conjugated doxorubicin magnetic poly (D,L-lactide-co-glycolide) (PLGA) nanoparticles (HER-DMPNP) for diagnostic and treatment of cancer. The nanoparticle has high cancer cell affinity and ultrasensitivity via magnetic resonance imaging.

4.4 Liposomes

Liposomes are small spherical shape drug distributing vesicles created from nontoxic substances like phospholipids and cholesterol with varying sizes ranging from 0.025 μm to 2.5 μm. There are different types of liposomes like multilamellar vesicles; small unilamellar vesicle and large unilamellar vesicle were used for drug encapsulation to treat different types of cancers. It is widely used as an auxiliary in vaccination, signal carriers, or inducers in disease diagnosis and also in encapsulation technology for the targeted drug delivery against different types of cancer cells

Table 4.3 Liposomal-based drug delivery system

Sl. no.	Type of the liposomal encapsulates	Biological applications	References
1.	Doxorubicin-loaded anti-HER2 immunoliposomes	Suppressed the activity of overexpressing HER2 genes	Park et al. (2002)
2.	Liposome conjugated paclitaxel and gemcitabine	Induce endothelial apoptotic activity, inhibit the vasculature system	Eichhorn et al. (2010)
3.	Liposome-coloaded paclitaxel/epigallocatechin gallate	Arrest the MMP-2 and MMP-9 expression	Ramadass et al. (2015)
4.	Liposomal encapsulate curcumin and resveratrol	Enhance the apoptotic activity, cyclin D1 activity, and androgen receptor proteins and arrest AKT/mTOR signaling pathways	Narayanan et al. (2009)
5.	Paclitaxel- and curcumin-loaded liposomes	Arrest the NF-κB and Akt pathways, G2/M cell cycle phase	Ruttala and Ko (2015)
6.	Vincristine-/quercetin-loaded liposomes	Upregulate the activity of trastuzumab and arrest JIMT-1 cell-insensitive activity	Wong and Chiu (2011)
7.	PEGylated liposomal doxorubicin	Arrests the activity of HER2 genes and decreases the cardiac toxicity	O'Shaughnessy (2003)
8.	Magnetic liposomes with doxorubicin	Enhance cytotoxic effects	Hardiansyah et al. (2014)
9.	Liposomal encapsulated curcumin nanoparticles	Induce apoptotic activity	Saengkrit et al. (2014)

(Daraee et al. 2016) (Table 4.3). These liposomal drug formulations were used in several disease treatments based on their capacity of self-assembly, to carry large drug payloads, and biocompatibility (Sercombe et al. 2015). The liposomal encapsulating drugs offer a safe platform which have potent cytotoxic effect toward cancer cells with no toxic side effects in normal cells (Akbarzadeh et al. 2013).

4.4.1 Liposome-Encapsulated Drugs in Cancer Treatment

Park et al. (2002) developed doxorubicin-loaded anti-HER2immunoliposomes that suppressed the activity of overexpressing HER2 genes and decrease the cardiotoxicity in breast cancer tumor-induced xenograft models, compared to the doxorubicin treated group alone. Eichhorn et al. (2010) demonstrate that liposome conjugated paclitaxel and gemcitabine were targeted against specific tumor sites to induce endothelial apoptotic activity and inhibit the vasculature (reduce blood circulation in tumor area) system in lung and pancreatic cancer. Ramadass et al. (2015) investigated paclitaxel-/epigallocatechin gallate-coloaded liposomes induced apoptotic activity via caspase enzymes and arrests the MMP-2 (Matrix Metallo Proteinases are zinc-dependent family proteases) and MMP-9 expressions in breast cancer cells.

Narayanan et al. (2009) investigated the liposomal encapsulated curcumin and resveratrol drug to enhance the apoptotic activity, cyclin D1 activity, androgen receptor proteins and arrest AKT/mTOR signaling pathways for decreasing the tumor progression in prostate cancer cells. Ruttala and Ko (2015) studied paclitaxel- and curcumin-loaded liposomes to inhibit NF-κB and Akt pathways and G2/M cell cycle phase via increasing the apoptotic activity and subG1 cell population in skin and breast cancer cells. Wong and Chiu (2011) demonstrated vincristine-/quercetin-loaded liposomes inhibit drug-resistant activity and downregulate cell proliferation in breast cancer cells. O'Shaughnessy (2003) investigated PEGylated liposomal (liposomes enclosed with in polyethylene glycol (PEG) layer) doxorubicin drug shows an efficient progress compared with the different dosage/other combination of drugs in breast cancer cells against HER2 gene expression. These PLD drugs decrease the tumor progression as well as cardiac toxicity, myelosuppression, and alopecia. Hardiansyah et al. (2014) developed magnetic liposome (citric acid-coated magnetic nanoparticles encapsulated by liposomes) encapsulated with doxorubicin that is a best antineoplastic agent to arrest the colorectal cancer cell progression. Saengkrit et al. (2014) developed liposomal encapsulated curcumin nanoparticles that caused cell membrane damage by inducing the apoptotic activity in cervical cancer cells.

4.5 Dendrimers

Dendrimers are a molecule consisting of a central core and branches. It is a polymer classified as hyperbranched polymers or brush polymers (Morikawa 2016). It acts as a best antitumor vehicle by conjugating with anticancer drugs, monoclonal antibodies, and plant-based bioactive compounds through by its branches. Interactions between the branches of dendrimers and drugs are hydrophobic/hydrogen-bond and electrostatic. It also has encapsulating ability by encapsulating the drug using the central cavity or between the multiple channels of dendrons (Mignani and Majoral 2013) (Table 4.4). It has attracted much attention of the researchers due to its highly branched symmetrical architecture and its center core to encapsulate the molecular drugs. The dendrimer molecular structure was characterized using nuclear magnetic resonance (NMR) of proton (1 H) and carbon (13C), differential scanning calorimetry (DSC), matrix-assisted laser-desorption ionization-mass spectrometry (MALDI-MS), transmission electron microscopy (TEM), scanning electron microscope (SEM), rheology, and scattering techniques (Valdés Lizama et al. 2016).

PAMAM-doxorubicin conjugate is a best anticancer drug-delivering vehicle, which shows cytotoxic effect by inhibiting GLUT1 transporter in human breast adenocarcinoma cell lines (Sztandera et al. 2019). Polyamidoamine-docetaxel-trastuzumab and polyamidoamine-paclitaxel-trastuzumab conjugates exhibit antiproliferative impact on HER-2-positive breast cancer cells (Marcinkowska et al. 2019). Polyamidoamine, astramol dendrimers, and maltose-modified PPI dendrimers exhibit cytotoxic effect toward human ovarian carcinoma cell lines and

Table 4.4 Dendrimers as drug delivery agents

Sl. no.	Dendrimers	Cancer	References
1.	PAMAM-doxorubicin	Breast cancer	Sztandera et al. (2019)
2.	PAMAM-doc-trastuzumab and PAMAM-ptx-trastuzumab	Breast cancer	Marcinkowska et al. (2019)
3.	PPI dendrimers	Ovarian cancer	Janaszewska et al. (2012)
4.	Trastuzumab-grafted PAMAM	Breast cancer	Kulhari et al. (2016)
5.	Dendrimer-doxorubicin conjugates	Hepatocellular carcinoma	Kuruvilla et al. (2017)
6.	DOX conjugated with EGF receptor-binding peptide	Colon cancer	Ai et al. (2013)
7.	Lactobionic acid dendrimers with polyethylene glycol	Liver cancer	Fu et al. (2014)
8.	Dendrimer-curcumin	Breast cancer	Debnath et al. (2013)
9.	Cationic chlorambucil-dendrimer	Colon cancer	Seixas et al. (2019)
10.	G3 PAMAM-NH_2 dendrimer-chlorambucil	Breast cancer	Bielawski et al. (2011)
11.	Methotrexate-loaded polyether-copolyester dendrimers	Gliomas	Dhanikula et al. (2008)
12.	PAMAM-paclitaxel-conjugated omega-3 fatty acid	Gastrointestinal cancer	Dichwalkar et al. (2017)
13.	Doxorubicin-conjugated dendrimer	Lung cancer	Kaminskas et al. (2014)
14.	Polyamidoamine dendrimers with hyaluronic acid	Pancreatic cancer	Kesharwani et al. (2015)
15.	Dendrimer-camptothecins	Breast cancer	Morgan et al. (2006)
16.	Cisplatin-dendrimer	Lung cancer	Nguyen et al. (2015)
17.	J591 antibody-dendrimer	Prostate cancer	Patri et al. (2004)

Chinese hamster ovary cell lines (Janaszewska et al. 2012). PAMAM dendrimers stimulate the mitochondria of dermal cell line to synthesize reactive oxygen production, apoptosis, and DNA damage that shows a better cytotoxic and antiproliferative effect (Mukherjee et al. 2010). Trastuzumab-grafted PAMAM dendrimers have better intra-tumoral delivery and apoptosis stimulation in HER2-positive breast cancer cells; thus, it acts as a better candidate to deliver anticancer drugs (Kulhari et al. 2016). Dendrimer-doxorubicin conjugates showed efficient anticancer activity in murine hepatocellular carcinoma cells and the conjugation of dendrimer to doxorubicin which reduce the cardiotoxicity induced by doxorubicin (Kuruvilla et al. 2017). DOX conjugated with an EGF receptor-binding peptide shows targeted drug delivery and decreases the drug resistance and anticancer activity in human colon cancer cells (Ai et al. 2013). Lactobionic acid-modified dendrimers conjugated with polyethylene glycol spacer showed the better cytotoxic effect in liver cancer cells (Fu et al. 2014). Dendrimer-surcumin conjugate shows cytotoxic activity in breast cancer cell lines by inducing apoptosis via caspase-3 activation (Debnath et al.

2013). Dendrimer-curcumin conjugate dissolves in water and thus is used as a potent cytotoxic factor against breast cancer cell lines. This conjugate is efficient in inducing cytotoxicity, as estimated by the MTT assay, and it also efficiently induced cellular apoptosis measured by caspase-3 activation. Cationic chlorambucil dendrimer will exhibit the cell cycle arrest at the G2 phase of mitosis and stimulate the caspase-independent apoptosis activity in prostate and colon cancer cell lines (Seixas et al. 2019). G3 PAMAM-NH_2 dendrimer-chlorambucil conjugate induces apoptotic effect and cytotoxic activity in human breast cancer cells (Bielawski et al. 2011). The anti-HER2 mAb conjugated to polyamidoamine dendrimer generation 5 was labeled with alexaFluor 488 and showed cytotoxic activity against HER2-expressing tumors (Shukla et al. 2006). Resorcinarene-PAMAM-dendrimer conjugates of flutamide have more apoptotic and anticancer activity than flutamide derivatives (Pedro-Hernández et al. 2018).

Methotrexate-loaded polyether-copolyester dendrimers act as a potential delivery system in the treatment of gliomas with enhanced permeability across the blood-brain barrier (Dhanikula et al. 2008). DHATX is significantly more potent than PTX or PAX at inhibiting cellular proliferation, suppressing long-term survival, and inducing cell death in UGC cells. PAMAM-paclitaxel-conjugated omega-3 fatty acid inhibits the cellular proliferation and induced cell death in upper gastrointestinal cancer cells (Dichwalkar et al. 2017). Doxorubicin-conjugated dendrimer inhibits the drug-resistant activity in lung cancer and improves the anticancer activity (Kaminskas et al. 2014). Polyamidoamine dendrimers conjugated with hyaluronic acid were an efficient drug delivery vehicle of curcumin to target and inhibit CD44 in pancreatic cancer cells (Kesharwani et al. 2015). Dendrimer-encapsulated camptothecins increased cellular uptake, increased intracellular drug retention, and afford enhanced anticancer activity in human breast adenocarcinoma (Morgan et al. 2006). Cisplatin-dendrimer nanocomplex has sufficient antiproliferative activity against lung cancer (Nguyen et al. 2015). J591 antibody-dendrimer conjugate is used as a targeted drug delivery vehicle in prostate cancer (Patri et al. 2004).

4.6 Polymer Drug Conjugates

Polymer is a chemical compound which is essentially combined together to form repeating subunits. Polymers are classified in to two types: natural polymers (naturally found in plants and animals) or synthetic polymers (synthetically prepared). There is an increased use of polymers in several fields like aerospace, sports, 3D printing, holography, water purification, molecular recognition, and drug distribution. Naturally polymers had a unique property like being hard, lightweight, and strong and having thermal and electrical stability, low cost, high specificity, and adaptability. Based on these qualities, polymers are used in biological-related researches, treatments, and drug distributions. Polymers were conjugated with drugs to form polymer drug conjugates to treat different types of diseases including cancer (Table 4.5).

Table 4.5 Polymeric conjugates for drug delivery

Sl. no.	Polymer drug conjugate	Cancer	References
1.	Poly L-glutamic acid with paclitaxel	Breast cancer, ovarian cancer, non-small cell lung cancer	Oldham et al. (2000), Li et al. (1999), Auzenne et al. (2002), and Zou et al. (2004)
2.	Poly1,2-glycerol carbonate with paclitaxel	Peritoneal cancer, lung cancer	Ekladious et al. (2017)
3.	N-2-hydroxypropylmethacrylamide copolymer with paclitaxel and gemcitabine	Ovarian cancer	Zhang et al. (2014 a), Zhang et al. (2014b)
4.	Polyl-γ-glutamyl glutamine-conjugated docetaxel	Breast cancer	Tavassolian et al. (2014)
5.	γ-Polyglutamic acid with docetaxel	Colon cancer, gastric cancer	Maya et al. (2014) and Sreeranganathan et al. (2017)
6.	N-2-Hydroxypropylmethacrylamide copolymer/docetaxel	Prostate cancer	Liu et al. (2012a), Liu et al. (2012b)
7.	Poly D,L-lactide-co-glycolide/ hyaluronic acid with docetaxel	Breast cancer	Huang et al. (2014)
8.	Poly-γ-glutamic acid-coated doxorubicin	Liver cancer, non-small cell lung cancer	Qi et al. (2017) and Li et al. (2013)
9.	Polyethylene glycol-conjugated doxorubicin and paclitaxel	Non-small cell lung cancer	Lv et al. (2014)
10.	N-2-hydroxypropylmethacrylamide copolymer-doxorubicin	Ovarian cancer	Shiah et al. (2001)
11.	Poly-l-glutamic acid-gemcitabine	Breast cancer	Kiew et al. (2010) and Voon et al. (2012)
12.	Poly N-2-hydroxypropylmethacrylamide gemcitabine and paclitaxel	Ovarian cancer	Larson et al. (2013)
13.	Gemcitabine-polyethylene glycol	Lung cancer	Garg et al. (2012)
14.	Gemcitabine-loaded polylactide-*co*-glycolide	Pancreatic cancer	Jaidev et al. (2015)
15.	Irinotecan with poly 2-ethyl 2-oxazoline-*b*-poly L-glutamic acid	Colorectal carcinoma	Salmanpour et al. (2019)
16.	Poly-L-glutamic acid-camptothecin	Melanoma, lung cancer	Singer et al. (2001), Bhatt et al. (2003), and Zou et al. (2001)
17.	Camptothecin-polyethylene glycol	Ovarian cancer	Minko et al. (2002)

Polymer drug conjugates (PDCs) are nano medicines that conjugated with specific drugs to act as a carrier molecule. The polymer drug-conjugated technology enhances the solubility of anticancerous drugs and controls the target site-specific drug distributions in cancer cells by enhanced permeability and retention (Girase et al. 2019). Different types of polymers like poly (L-glutamic acid), polyethylene

glycol (PEG), N-(2-hydroxypropyl) methacrylamide (HPMA), polylactide-co-glycolide (PLGA), polyvinyl pyrrolidone, and poly-γ-glutamic acid (γ-PGA) were used for drug conjugation to treat different types of cancers. Familiar cancer drugs like paclitaxel, docetaxel, doxorubicin, gemcitabine, irinotecan, and camptothecin were commonly used in polymer drug conjugation process in cancer treatment (Duncan et al. 2005).

4.6.1 Polymer Drug Conjugates Against Cancer

Poly L-glutamic acid with paclitaxel conjugate induces apoptotic, tumor suppressor p53 activity and G2/M cell cycle arrest, downregulated HER2/neu expression in breast cancer cells (Oldham et al. 2000; Li et al. 1999), and decreases the tumor progression in ovarian cancer (Auzenne et al. 2002) and non-small cell lung cancer (Zou et al. 2004). Ekladious et al. (2017) reported that high dose of poly 1,2-glycerol carbonate with paclitaxel conjugates is exhibiting greater efficiency to inhibit cell proliferation of cancer cells when compared to normal multi-dosage of paclitaxel drug in mesothelioma cancer cells, lung cancer cells, and pancreatic cancer cells. N-2-hydroxypropylmethacrylamide copolymer with paclitaxel and gemcitabine induces apoptotic activity and replication arrest in ovarian cancer. Paclitaxel and gemcitabine inhibit the micro tubulin formation and decrease the tumor cell proliferation in ovarian cancer cell (Zhang et al. 2014a, Zhang et al. 2014b). Tavassolian et al. (2014) investigated the anticancer efficacy of poly l-γ-glutamyl glutamine-conjugated docetaxel in mice model and MCF7 cancer cells; compared to chemotherapeutic drub Taxotere, the poly l-γ-glutamyl glutamine-conjugated docetaxel has better efficacy to inhibit tumor growth in breast cancer. γ-Poly glutamic acid-docetaxel inhibits the cell cycle progression of G2/M phase by inducing apoptotic function in colon cancer cells and downregulating EGFR, in gastric cancer cells (Maya et al. 2014; Sreeranganathan et al. 2017). N-2-Hydroxypropylmethacrylamide copolymer/docetaxel conjugate increases the enhanced permeability and retention effect to downregulate the tumor progression in prostate cancer cells (Liu et al. 2012a, Liu et al. 2012b). Poly D,L-lactide-co-glycolide/hyaluronic acid copolymers with docetaxel conjugate target the overexpressing CD44 and inhibit cell proliferation in breast cancer (Huang et al. 2014). Poly-γ-glutamic acid-coated doxorubicin arrests the cell cycle at S phase and enhances apoptotic activity in liver cancer and non-small cell lung cancer (Qi et al. 2017; Li et al. 2013).

Lv et al. (2014) developed poly-ethylene glycol-conjugated doxorubicin and paclitaxel co-drug delivery inducing apoptotic activity was monitored and visualized by fluorescence images in A549 xenograft models. The co-drug delivery exhibits high level of antitumor activity and reduces the tumor size compared to single drug-loaded polymers and free drug combinations. N-2-hydroxypropylmethacrylamide copolymer with doxorubicin conjugates cleaved the oligopeptides of cancer cells and incorporated antibodies into specific antigens to induce antitumor efficacy in ovarian cancer cells (Shiah et al. 2001). Poly-l-glutamic

acid-gemcitabine conjugate enhances the plasma stability and decreases the tumor growth in breast cancer cells (Kiew et al. 2010; Voon et al. 2012). Poly N-2-hydroxypropylmethacrylamide gemcitabine and paclitaxel conjugates are found to be with potent anticancer activity to inhibit cell proliferation in ovarian cancer cells (Larson et al. 2013). Garg et al. (2012) developed gemcitabine with polyethylene glycol conjugate tightly bound to sigma receptors of cancer cells to effectively transport the drug inside the cancer cells and to bring high level of cytotoxic response in lung cancer cells. Jaidev et al. (2015) demonstrate that gemcitabine-loaded polylactide-*co*-glycolide was to increase the antiproliferative and apoptotic activity in pancreatic cancer. The polymer polylactide-*co*-glycolide is an efficient drug carrier to release the drugs within 3 hours in pancreatic cancer cells. Irinotecan with poly 2-ethyl 2-oxazoline and *b*-poly L-glutamic acid double copolymers decreases tumor proliferation rate in colorectal cancer (Salmanpour et al. 2019). Poly-L-glutamic acid-camptothecin conjugates decrease the tumor progression in melanoma and lung cancer cells (Singer et al. 2001; Bhatt et al. 2003; Zou et al. 2001). Camptothecin-polyethylene glycol conjugates to induce apoptotic genes APAF-1 and caspases 3 and 9 by downregulating the BCL-2 gene in ovarian cancer cells (Minko et al. 2002).

4.7 Silica Nanoparticles

Silica nanoparticle also termed as silicon dioxide nanoparticles or nano silica is the promising tool in biomedical research and also widely used in various applications due to their excellent thermal stability, biocompatibility, low toxicity, and large-scale synthetic availability. The particle with its high surface area has the chances for the possibility of chemical modification which could help in drug delivery, gene therapy, and site-specific target therapy (Slowing et al. 2007) (Table 4.6). Stober method is one of the most widely used and accepted methods in the synthesis of silica nanoparticle. It has the property of uniform synthesis and the particle size ranges from 5 to 2000 nm. Based on the structure and particle size, it could be divided into P-type and S-types. The synthesized particle can be characterized by SEM, TEM, X-ray diffraction, absorption spectroscopy, and EPR spectroscopy studies (Tan et al. 2004).

4.7.1 Silica Nanoparticles toward Cancer Therapy

Nano medicine against cancer as an upcoming field has major impact in the field of health and medicine. Previous studies have claimed that silica nanoparticle has the potent anticancer activity to induce apoptosis in cancer cells. Conjugated mesoporous silica nanoparticles with anticancer drug of paclitaxel have significant effect to arrest cell cycle and inhibit cell proliferation in human pancreatic cancer cell lines

Table 4.6 Silica-based nanoparticles as drug delivery systems

Sl. no.	Compound	Type of cancer	Action	References
1.	Paclitaxel-conjugated mesoporous silica nanoparticles	Pancreatic cancer	Inhibit cell proliferation	Lu et al. (2007)
2.	Doxorubicin-loaded silica nanoparticles	Various types of cancer	Inhibit oncogenes	Chen et al. (2009)
3.	Hyaluronic acid-loaded mesoporous silica nanoparticles	Colon cancer	Downregulate CD44 expression	Yu et al. (2013)
4.	Doxorubicin-loaded silica nanoparticles	Cervical cancer	Decrease cancer cell viability	Qiu et al. (2013)
5.	Curcumin-loaded silica nanoparticles	Breast Cancer	Induce cytotoxic effect	Ma'mani et al. (2014)
6.	Quercetin-loaded mesoporous silica nanoparticles	Breast cancer	Reduce overexpressed signaling pathway	Sarkar et al. (2016)
7.	Lectin-conjugated silica nanoparticles	Bone cancer	Reduce cancer cell viability	Martínez-Carmona et al. (2018)
8.	Chemo drug-loaded silica nanoparticles	Lung cancer	Induce apoptosis	Liu et al. (2012a), Liu et al. (2012b)
9.	Epirubicin-loaded silica nanoparticles	Colon cancer	Arrest targeted tumor cells growth	Xiong et al. (2015)
10.	Snake venom (*Walterinnesia aegyptia*)-conjugated silica nanoparticles	Breast and prostate cancer	Alter mitochondrial function	Badr et al. (2013)
11.	Glycosylated cytochrome C-conjugated silica nanoparticles	Cervical cancer	Induce apoptosis	Méndez et al. (2014)
12.	Cisplatin- and nitric oxide-loaded mesoporous silica nanoparticles	Lung cancer	Induce C toxicity effect	Munaweera et al. (2015)
13.	Curcumin-loaded silver nanoparticles	Head and neck cancer	Inhibits NF-κB pathway	Singh et al. (2014)

(Lu et al. 2007). Loading of doxorubicin drug to silica nanoparticles enhances the anticancer activity by suppressing the tumor gene and induces apoptosis in multi-drug-resistant cancer cell lines (Chen et al. 2009). Modified hyaluronic acid capped with mesoporous silica nanoparticles acts as an efficient drug delivery vehicle and induces cellular uptake to react against CD44 overexpressed human colon cancer cells (Yu et al. 2013). Doxorubicin-loaded silica nanoparticles successfully act toward cancer cells and reduced the tumor volume in cervical cancer (Qiu et al. 2013). Conjugation of cetuximab with silica nanoparticle was an efficient drug delivery vehicle to target tumor cell function in human colon cancer cells (Cho et al. 2010). Curcumin-loaded silica nanoparticle efficiently defeats cancer cell propagation and generates apoptosis in breast cancer cell lines (Ma'mani et al. 2014).

Quercetin-loaded mesoporous silica nanoparticles strongly inhibit cell cycle progression and stimulate cancer cell death by inhibiting Akt/Bax pathway. The developed compound also increases the expression of caspase protein and decreases cancer cell viability in breast cancer cells (Sarkar et al. 2016). Lectin-conjugated silica nanoparticle reduces the cancer cell viability and inhibits the cancer inducing proteins in bone cancer (Martínez-Carmona et al. 2018). Combinational loading of both hydrophilic and hydrophobic types of chemo drugs with silica nanoparticle was efficiently internalized into cancer cells to induce apoptosis effect in human pulmonary adenocarcinoma cell lines (Liu et al. 2012a, Liu et al. 2012b). Dual targeting ligands such as folic acid and dexamethasone are modified with mesoporous silica nanoparticle which significantly inhibit only the cancer growth and prevent the non-cancer cell from the toxic side effects by means of receptor-mediated cellular uptake in cervical cancer cell line (Xiong et al. 2015). Epirubicin-loaded silica nanoparticle shows the anticancer activity in C-26 colon cancer-induced mice (Hanafi-Bojd et al. 2015). Loading of silica nanoparticle with snake venom (*Walterinnesia aegyptia*) raises the reactive oxygen species level and modifies the mitochondrial membrane potential and then subsequently arrests tumor cell spread and provokes apoptosis in breast and prostate cancer cell lines (Badr et al. 2013). Administration of glycosylated cytochrome C-conjugated silica nanoparticle induces cytotoxic and apoptotic effect toward cervical cancer cell lines (Méndez et al. 2014). Cisplatin- and nitric oxide-loaded mesoporous silica nanoparticles exhibit toxicity effect and induce tumor cell death in lung cancer (Munaweera et al. 2015). Curcumin-loaded silver nanoparticles suppress NF-κB proteins and induce necrotic cell death in human squamous cell carcinoma cell line (Singh et al. 2014).

4.8 Gold Nanoparticles

Gold nanoparticles (AuNPs) have the smallest nanoparticle size ranging from 1 to 100 nm in diameter. It could effectively act as a carrier vehicle for gene and drug delivery in therapeutic applications. It was differentiated into various subtypes based on their shape, size, and morphological characters with greater potential in fighting against various diseases including cancer. It also extends its applications in molecular diagnosis, molecular therapy, and molecular profiling (Arvizo et al. 2010). Synthesis of gold nanoparticles by way of chemical reduction method by using gold salts of citrate and hydrogen tetrachloroaurate (HAuCl4) as reducing agents is one of the novel methods (Salcedo and Sevilla III 2013). Synthesized nanoparticles hold novel chemical and physical traits to deliver antibiotics and drugs to the aspired targeted molecules accurately (Wilczewska et al. 2012). Covalent attachments and supramolecular assembly are the two primary strategies accomplished to incorporate the gold nanoparticles in gene therapy. The nanoparticle appears in different colors like blue, red, etc., based on the morphology, assemblage, and their local environment (Vigderman and Zubarev 2013).

4.8.1 Applications of Gold Nanoparticles

Gold nanoparticles exhibit a wide range of application in the field of medicine, bioimaging, biological research, gene therapy, photothermal therapy, etc. and as catalyst, drug delivery vehicle, and biosensors (Ghosh et al. 2008) (Table 4.7). As a biosensor device, gold nanoparticles are extensively used for the purpose of detecting the enzyme. The major advantages of using gold nanomaterial include easy scaling up, increased bioavailability, and enhanced time-resistant and targeted drug delivery at the specific target (Sperling et al. 2008). Gold nanoparticles have been utilized to increase the sensitivity of magnetic resonance imaging (MRI). One of the newly developed technologies of DNA labeled gold nanoparticle has gained much attention in the field of bio-nanotechnology research (Cai et al. 2008). Gold nanoparticle has numerous biomedical applications in the development of potential therapies for serious human diseases like HIV, cancer, etc. (Dykman and Khlebtsov 2012).

4.8.2 Gold Nanoparticle Toward Cancer Therapy

Administration of gold nanoparticles into cancer cell selectively damages the DNA double strand and inhibits the mitotic division of binucleate formation, leading to the complete arrest of cancer cell division which induces cell death (Kang et al. 2010). Conjugation of anticancer drug doxorubicin with gold nanoparticles provides the efficient drug releasing capacity with greater solubility and stability in cancer cells. This developed compound significantly reduces the cancer cell proliferation and provides efficient cytotoxic effect at the metastatic levels of cancer cells (Aryal et al. 2009). Dendrimer encapsulated gold nanoparticle loaded with thiol-containing anticancer drug shows efficient cytotoxic effect and induces mitochondrial enzyme function to activate apoptosis in cervical cancer cell lines (Wang et al. 2013). Chloroquine-loaded gold nanoparticle alters oncogenes and inhibits cancer cell proliferation in breast cancer cells (Joshi et al. 2012). Methotrexate conjugate gold nanoparticle shows rapid drug release and inhibits tumor development in syngeneic lung cancer model (Chen et al. 2007). Porphyran encapsulated gold nanoparticles stimulate the tumor suppressor gene to resist cancer cell initiation and arrest the cell cycle progression in human glioma cell lines (Venkatpurwar et al. 2011). Conjugation of gallic acid with gold nanoparticle significantly increases the caspase enzymes activity to induce apoptosis by both the extrinsic and intrinsic pathway in cervical cancer cell lines (Daduang et al. 2015). Fucoidan mimetic glycopolymer-coated gold nanoparticle increases the level of caspase enzyme through death receptor and mitochondrial apoptotic pathway. This decreases the cancer cell migration and invasion in human colon cancer cell lines (Tengdelius et al. 2015). Exposure to 1.4 nm range of gold nanoparticle increases oxygen consumption in cervical cancer cells to repair the mitochondrial dysfunction and to induce cell death (Pan et al. 2009). Conjugated gold nanoparticle with galactoxyloglucan decreases cancer cell

Table 4.7 Gold nanoparticles in targeted cancer drug delivery

Sl. no.	Compound name	Cancer type	Action of compound	Type of compound	References
1.	Doxorubicin-conjugated gold nanoparticle	Metastatic cancer	Inhibits cancer cell proliferation	Synthesized drug	Aryal et al. (2009)
2.	Thiol-containing anticancer drug-loaded gold nanoparticle	Cervical cancer	Apoptosis activity	Synthesized drug	Wang et al. (2013)
3.	Chloroquine-loaded gold nanoparticle	Breast cancer	Decreases oncogene expression	Synthesized drug	Joshi et al. (2012)
4.	Methotrexate-loaded gold nanoparticle	Lung cancer	Inhibits tumor growth	Synthesized drug	Chen et al. (2007)
5.	Porphyran-synthesized gold nanoparticle	Brain cancer	Induces tumor suppressor gene	Synthesized drug	Venkatpurwar et al. (2011)
6.	Gallic acid-synthesized gold nanoparticle	Cervical cancer	Increases apoptotic enzyme function	Synthesized drug	Daduang et al. (2015)
7.	Fucoidan mimetic glycopolymer-loaded gold nanoparticle	Colon cancer	Induces cell death	Synthesized drug	Tengdelius et al. (2015)
8.	1.4 nm gold nanoparticle	Cervical cancer	Increases ROS level	Synthesized drug	Pan et al. (2009)
9.	Galactoxyloglucan-loaded gold nanoparticle	Various types of cancer	Increases life span	Synthesized drug	Joseph et al. (2014)
10.	*C. guianensis*-loaded gold nanoparticle	Blood cancer	Decreases cell viability	Phytomedicine	Geetha et al. (2013)
11.	*Enterococcus* sp.-loaded gold nanoparticle	Lung cancer	Regulates signaling molecule	Phytomedicine	Rajeshkumar (2016)
12.	*Abelmoschus esculentus* (L.)-synthesized gold nanoparticle	Blood cancer	Increases ROS level	Phytomedicine	Mollick et al. (2014)
13.	*Indigofera tinctoria*-synthesized gold nanoparticle	Lung cancer	Cytotoxicity	Phytomedicine	Vijayan et al. (2018)
14.	*Gymnema sylvestre*-synthesized gold nanoparticle	Epithelial cancer	Increases ROS level	Phytomedicine	Nakkala et al. (2015)
15.	*Cassia tora*-synthesized gold nanoparticle	Colon cancer	Inhibits cell proliferation	Phytomedicine	Abel et al. (2016)
16.	*Nerium oleander*-synthesized gold nanoparticle	Breast cancer	Cell death	Phytomedicine	Barai et al. (2018)
17.	*Bauhinia purpurea*-synthesized gold nanoparticle	Various types of cancer	Reduces cancer cell volume	Phytomedicine	Vijayan et al. (2019)

(continued)

Table 4.7 (continued)

Sl. no.	Compound name	Cancer type	Action of compound	Type of compound	References
18.	*Mimosa pudica*-synthesized gold nanoparticle	Breast cancer	Cell cycle arrest	Phytomedicine	Uma Suganya et al. (2016)
19.	*Abies spectabilis*-synthesized gold nanoparticle	Bladder cancer	Alters apoptotic enzymes	Phytomedicine	Wu et al. (2019)
20.	*B. citriodora*-synthesized gold nanoparticle	Liver cancer	Induces cytotoxicity	Phytomedicine	Khandanlou et al. (2018)
21.	*Solanum xanthocarpum*-synthesized gold nanoparticle	Head and neck cancer	Induces autophagy	Phytomedicine	Zhang et al. (2018)
22.	*Sargassum swartzii*-synthesized gold nanoparticle	Cervical cancer	Alters mitochondrial function	Phytomedicine	Dhas et al. (2014)

viability and increased the life span of murine cancer-induced mouse model (Joseph et al. 2014).

4.8.3 Combinational Therapy of Phytochemicals with Gold Nanoparticle in Cancer Cells

Aqueous flower extract of *C. guianensis*-loaded gold nanoparticle efficiently acts against cancer cells and induces apoptotic activity in human leukemia cancer cells (Geetha et al. 2013). *Enterococcus* sp. marine bacteria-loaded gold nanoparticle downregulates overexpressed signaling molecule of Akt/Ras/m-TOR pathway in lung cancer cells (Rajeshkumar 2016). Synthesis of gold nanoparticles using *Abelmoschus esculentus* (L.) pulp extracts significantly increases apoptotic activity by regulating mitochondrial enzyme. This compound also elevates intracellular oxygen level to prevent cancer cell proliferation in human blood cancer cells (Mollick et al. 2014). *Indigofera tinctoria* leaf extract-synthesized gold nanoparticle exhibits more toxicity toward lung cancer cells (Vijayan et al. 2018). *Gymnema sylvestre* leaf extract-loaded gold nanoparticles increase intracellular oxygen concentration and induce antiproliferative effect in human epithelial cancer cell line (Nakkala et al. 2015). Gold nanoparticles capped with *Cassia tora* arrest cancer cell proliferation in colon cancer cells (Abel et al. 2016). Gold nanoparticle conjugates with *Nerium oleander* extract significantly increase cellular oxygen level and induce apoptosis in breast cancer cells (Barai et al. 2018). *Bauhinia purpurea* leaf extract-synthesized gold nanoparticle acts as an excellent anticancer agent on different types of cancer cells (Vijayan et al. 2019). Synthesized gold nanoparticles using *Mimosa pudica* extract on cancer cell reveals apoptotic effect and induced cell cycle

arrest at early G1/S phase in breast cancer cell lines (Uma Suganya et al. 2016). *Abies spectabilis* plant extract-synthesized gold nanoparticle upregulates the Beclin-1, Bax, and caspase-3 enzyme and downregulates Bcl-2 and BidT24 in bladder cancer cells (Wu et al. 2019). *Backhousia citriodora* leaf extract-synthesized Au-NPs induce cytotoxicity effect and apoptotic activity in breast and liver cancer cells (Khandanlou et al. 2018). *Solanum xanthocarpum*-synthesized AuNPs increase ROS level, autophagy, and apoptosis through activation of caspase-3 and caspase-9 and nuclear fragmentation in nasopharyngeal carcinoma cell lines (Zhang et al. 2018). Biosynthesis of AuNPs using *Sargassum swartzii* induces cytotoxic effect and reverts mitochondrial function in HeLa cell lines (Dhas et al. 2014).

4.9 Carbon Nanotubes

Carbon nanotubes (CNTs) are cylindrical molecules made up of hexagonal arrangements of hybridized carbon atoms. It appears in tubular shape that was coated with graphite carbon atoms in the form of layer. Carbon nanotubes are classified in two types: single-walled carbon nanotubes with diameter ranging from 1 to 10 nm and multiwalled carbon nanotubes with diameters ranging approximately 5 to 30 nm. The nanotubes consist of 1–100. There are two major methods to synthesize carbon nanotubes using chemical vapor deposition (CVD) method (fossil-based hydrocarbon method) and plant-based hydrocarbon method. It has unique properties such as high thermal conductivity, highly flexible property, and strong tensile strength. The inner and outer surfaces of carbon nanotubes are well modified with a variety of functional groups which helps in conjugating with targeting ligands and drug molecules. The strength and flexibility of carbon nanotubes are used to control the other nanoscale structures which play significant role in nano engineering field. Carbon nanotubes have a wide range of applications as tiny sensors, electronic devices, optical devices, catalyst process, batteries, fuel cells, solar cells, and drug delivery vehicles (Prasek et al. 2011) (Table 4.8).

4.9.1 Carbon Nanotubes in Cancer Therapy

Carbon nanotubes stand as a popular tool in cancer therapy due to their unique physiochemical properties. It is also considered as one of the most promising nanomaterials with capability of both detecting tumor cells and delivering drug therapy to cancer cells. Single-walled carbon nanotube selectively activates caspase-3 and cytochrome C enzyme to induce mitochondrial function which inhibits tumor growth in breast cancer cells (Zhou et al. 2011). Methotrexate-conjugated multiwalled carbon nanotube possesses rapid drug release and exhibits higher cytotoxicity effect toward breast cancer cells (Samorì et al. 2010). Single-walled carbon nanotube conjugate with anticancer drug of SN-38 carries good biocompatibility

Table 4.8 Carbon nanotubes in cancer therapy and drug delivery

Sl. no.	Compound name	Types of cancer	Mode of action	Reference
1.	Single-walled carbon nanotube	Breast cancer	Induces mitochondrial function	Zhou et al. (2011)
2.	Methotrexate-conjugated multiwalled carbon nanotube	Breast cancer	Cytotoxic effect	Samorì et al. (2010)
3.	SN-38-loaded single-walled carbon nanotube	Colon cancer	Induces apoptosis	Lee et al. (2013)
4.	Paclitaxel-loaded single-walled carbon nanotube	Breast cancer	Inhibits cancer cell proliferation	Liu et al. (2008a), Liu et al. (2008b)
5.	Curcumin-loaded carbon nanotubes	Prostate cancer	Downregulate Wnt signaling pathway	Li et al. (2014)
6.	Betulinic acid-conjugated multiwalled carbon nanotubes	Lung cancer	Inhibit Warburg pathway	Tan et al. (2014)
7.	Polyethylene glycol-coated carbon tubes	Lung cancer	Induce Bcl-2-mediated apoptosis	Kim et al. (2017)
8.	Doxorubicin-loaded multiwalled carbon nanotube	Breast cancer	Decreases cancer cell viability	Ali-Boucetta et al. (2008)
9.	Cisplatin-loaded carbon nanotubes	Solid tumor	Inhibit neuroblastoma cell growth	Vittorio et al. (2014)
10.	Doxorubicin-conjugated single-walled carbon nanotubes	Cervical cancer	Induce apoptotic activity	Meng et al. (2012)
11.	Cisplatin-loaded carbon nanotubes	Cervical cancer	Enhanced antiproliferative effect	Peng et al. (2010)
12.	Doxorubicin-loaded carbon nanotubes	Cervical cancer	Autophagy reaction	Zhang et al. (2009a), Zhang et al. (2009b)
13.	Oxaliplatin encapsulated single-walled carbon nanotubes	Various types of cancer	Inhibit tumor growth	Rezvani et al. (2016)
14.	Indole-3-carbinol cyclic-loaded single-walled carbon nanotube	Breast cancer cells	Promotes antiproliferative and cytopathic effect	De Santi et al. (2013)
15.	Polyethylene glycol-coated multiwalled carbon nanotubes	Pancreatic cancer cell line	Enhance mitochondrial function	Mocan et al. (2014)

and efficient cellular uptake and induces cancer cell death in colon carcinoma cell lines (Lee et al. 2013). Paclitaxel-loaded single-walled carbon nanotube inhibits cancer cell proliferation and induces apoptotic activity in murine breast cancer model (Liu et al. 2008a, Liu et al. 2008b). Curcumin-loaded carbon nanotubes downregulate Wnt signaling pathway in human prostate cancer (Li et al. 2014).

Oxidized multiwalled carbon nanotube conjugates with betulinic acid suppress Warburg pathway by inhibiting lactate dehydrogenase enzyme secretion and enhance anticancer activity in lung cancer cell line (Tan et al. 2014). Polyethylene glycol-coated carbon tubes generate intracellular oxygen level and induce Bcl-2-mediated apoptosis in lung cancer cells (Kim et al. 2017). Doxorubicin-loaded multiwalled carbon nanotube enhances cytotoxic effect and reduces cancer cell viability in breast cancer cell line (Ali-Boucetta et al. 2008). Cisplatin-loaded carbon nanotubes significantly inhibit neuroblastoma cell growth in nerve tissues and enhance cytotoxic effect against human neuroblastoma cell lines (Vittorio et al. 2014). Doxorubicin-conjugated single-walled carbon nanotubes increase ROS level and induce apoptotic activity in cervical cancer (Meng et al. 2012). Cisplatin-loaded carbon nanotubes promote extracellular drug release and enhance the antiproliferative effect in cervical cancer cell line (Peng et al. 2010). Doxorubicin-loaded carbon nanotubes accumulate inside the cancer cell lysosomes and inhibit transcription activity which ultimately leads to autophagy reaction in cervical cancer cell line (Zhang et al. 2009a, Zhang et al. 2009b). Oxaliplatin encapsulated single-walled carbon nanotubes provide efficient drug releasing ability and inhibit cancer cell growth in various types of cancer cells (Rezvani et al. 2016). Anticancer drug of indole-3-carbinol cyclic-loaded single-walled carbon nanotube induces cell death and promotes antiproliferative and cytotoxic effect in breast cancer cells (De Santi et al. 2013). Polyethylene glycol-coated multiwalled carbon nanotubes stimulate mitochondrial function which in turn activates free radicals in the cells and induces oxidative state in the pancreatic cancer cell lines (Mocan et al. 2014).

4.10 Quantum Dots

Quantum dots (QDs) are nanoparticles ranging from 2 to 10nm semiconductor crystals which have unique optical properties including intensive fluorescence and tunable wavelength (Zhang et al. 2008). QDs differ from natural biogenic nanoparticles by its crystalline metalloid structure and quantum confinement effect (Hardman 2006). These small probes can penetrate cells and organelles (Jovin 2003). QDs have a semiconductor core made up of CdS, CdSe, CdTe, ZnS, and PbS metals, and the core region is overcoated by a shell to enhance its optical activity and an outermost cap for increasing solubility in aqueous buffers (Ghasemi et al. 2009). QDs can be used for bio labeling and biosensing by conjugating them with the appropriate biomolecules (Chan and Nie 1998; Bruchez et al. 1998). Just like organic fluorophores, quantum dots can perform as photosensitizers because they have energy levels in the range of 1–5 eV (Bakalova et al. 2004; Samia et al. 2003). QDs can act as high-energy photons like gamma and X-rays, so they can be used as radiosensitizers for the targeted therapy of cancer cells (Carter et al. 2007) (Table 4.9).

Table 4.9 Quantum dot nanoparticles for drug delivery and diagnostic systems

Sl. no.	Quantum dots	Biological applications	Authors
1.	Cadmium and tellurium conjugated with gambogic acid	It promotes drug accumulation in HepG2 cells It repressed cancer cell propagation It influenced the G2 cell cycle phase arrest of cancer cell lines, raising cell apoptosis	Xu et al. (2013a), Xu et al. (2013b)
2.	Anti-GRP78 scFv	The antitumor activity is detected by the enhanced pyrophosphate-AKT-ser473 Inhibit the breast cancer growth	Xu et al. (2012)
3.	AVE-1642	Downregulates IGF1R levels in MCF-7 cells. Cell proliferation is inhibited	Zhang et al. (2009a), Zhang et al. (2009b)
4.	AITC-SiQDs	Lower and long-lasting activation of Nrf2 translocation into the nucleus is detected ROS production is triggered	Liu et al. (2018)
5.	QD-labeled monoclonal anti-HER2 antibody	Quantitatively analyzed the six processes of drug delivery Identified the rate-limiting constraints on QD-antibody delivery	Tada et al. (2007)
6.	HER2-RQDs	Target the gastric cancer MGC803 cells Inhibit the growth of gastric cancer tissues. Prevent protein synthesis and induce cell apoptosis	Ruan et al. (2012)
7.	ZnO QDs-conjugated gold nanoparticles	Nanocarriers have anticancer activity against HeLa cells	Chen et al. (2013)
8.	Mn-doped ZnS QDs	Great thermal stability (20–80 °C) Determined the glucose in real serum samples	Wu et al. (2010)
9.	CdS QDs	Anticancer activity by arresting the A549 cell growth at the S phase	Shivaji et al. (2018)
10.	Peptide-conjugated graphene Qds	Target and image tumor cells simultaneously	Su et al. (2015)
11.	Graphene QDs	Cytotoxic effect on cervical cancer cell lines and breast cancer cell lines	Thakur et al. (2016)
12.	Carbon QDs	Green fluorescent nature Possess imaging and phototherapy on cancer cell lines	Meena et al. (2019)
13.	Peptide-PEGylated lipid QDs	Inhibited the prostate cancer cell growth	Yeh et al. (2016)
14.	HA-DOX-GQD@MSN	Cytotoxicity effect against HeLa cell lines. Fluorescent monitoring ability	Gui et al. (2018)
15.	Cadmium telluride QDs	Inhibited the p53 inhibitor pifithrin-α Decrease cell viability	Choi et al. (2008)

(continued)

Table 4.9 (continued)

Sl. no.	Quantum dots	Biological applications	Authors
16.	Carbon QDs	Cytotoxic efficiency against MCF-7 and PC-3 cell lines by the activation of caspase-3 protein	Arkan et al. (2018)
17.	CdSe/ZnS QDs loaded with curcumin	Enhance apoptosis, cell death, ROS generation, and single/double DNA strand breaks in HL-60 cells	Belletti et al. (2017)
18.	Curcumin-coated QDs	Enhance the cellular internalization of curcumin. Tracked drug release and nanocarrier's destiny into cells	

4.10.1 Quantum Dot-Conjugated Inhibitors in Cancer Treatment

Various types of semiconductor QDs are nowadays studied for labeling, imaging, targeted drug delivery, and photodynamic therapy (Wang et al. 2009). Xu et al. (2013a) and Xu et al. (2013b) examined the fluorescent nanocomposites gambogic acid (GA) and cadmium tellurium QDs. They adjusted it with cysteamine for cancer cell labeling and merged treatment in HepG2 cell lines. GA-CdTe treatment promotes drug accumulation in HepG2 cell lines. GA-CdTe nanocomposites also inhibited cancer cell proliferation and enhance the drug action of GA molecules in HepG2 cells and induced the G2/M phase arrest of the cancer cell cycle, promoting cell apoptosis. Xu et al. (2012) described a conjugating QD-anti-GRP78 scFv, by conjugating QDs with tiny antibody components targeting membrane-bound proteins (GRP78). And its pattern is observed by visualization of multicolor fluorescence imaging in both in vitro and in vivo techniques. It can efficiently internalize cancer cells. The antitumor activity is evaluated from the elevated pyrophosphate-AKT-ser473 levels and shows hindrance of breast cancer growth in a xenograft model. Zhang et al. (2009a) and Zhang et al. (2009b) developed AVE-1642 (IGF1R antibody, AVE-1642) QDs to measure type I insulin-like growth factor (IGF) receptor (IGF1R) levels in breast cancer cells. AVE-1642 QDs can downregulate IGF1R levels in MCF-7 cells and rendered cells refractory to IGF-I stimulation; thus, cell proliferation is inhibited by AVE-1642 QDs. Liu et al. (2018) investigated the anticancer activities of allyl isothiocyanate, a dietary phytochemical, conjugated with silicon QDs (AITC-SiQDs). Lower and long-lasting activation of Nrf2 translocation into the nucleus is shown by AITC-SiQDs by the fluorescence detection of their cellular uptake. They concluded that ROS production may trigger the anticancer effect of AITC-SiQDs. Tada et al. (2007) studied the tracking of a quantum dot labeled monoclonal anti-HER2 antibody in mice with HER2-overexpressing breast cancer to analyze the molecular processes of its mechanistic delivery to the tumor. They used a dorsal skinfold chamber and a high-speed confocal microscope with a high-sensitivity camera for tracking process. They quantitatively analyzed the six processes of drug delivery and identified the rate-limiting constraints on QD-antibody

delivery. Ruan et al. (2012) developed HER2-RQDs (HER2 monoclonal antibody-conjugated RNase A-associated CdTe quantum dot cluster) for the evaluation of its cytotoxicity, bio-distribution, and therapeutic effects. HER2-RQD nanoprobes can effectively target the gastric cancer MGC803 cells and can inhibit the growth of gastric cancer tissues by destroying functional RNAs in the cytoplasm by RNase A released from HER2-RQDs nanoprobes, preventing protein synthesis and inducing cell apoptosis. Chen et al. (2013) developed core-shell structured nanocarriers for targeted anticancer drug delivery using ZnO quantum dot-conjugated gold nanoparticles and amphiphilic hyperbranched block copolymer as core and shell, respectively, against HeLa cells. Wu et al. (2010) examined the conjugation of glucose oxidase onto phosphorescent Mn-doped ZnS quantum dots for effective glucose biosensing. The conjugate showed greater thermal stability in the range of 20–80 °C and effectively determines the glucose in real serum samples. Shivaji et al. (2018) demonstrated a CdS QDs (2–5nm) from tea leaf extract. The Qds show anticancer activity by arresting the A549 cell growth at the S phase for inhibiting the growth of lung cancer cell. Su et al. (2015) demonstrated a peptide with trifunctional motifs and conjugated with graphene Qds. This nano hybrid has the capacity to target and image tumor cells simultaneously. Thakur et al. (2016) developed aqueous soluble graphene QDs for drug delivery and imaging in cancer, and it is synthesized from cow milk by microwave-assisted heating. The QDs were then loaded with cysteamine hydrochloride-berberine hydrochloride complex, which showed a potent cytotoxic effect on cervical cancer and breast cancer cell lines. Meena et al. (2019) reported a simple and cost-effective method for the synthesis of fluorescent carbon QDs from the leaves of *Azadirachta Indica*, *Ocimum tenuiflorum*, and *Tridax procumbens*. These QDs are green fluorescent in nature and have homogeneous size distribution (∼6–12 nm). They possess cancer cell imaging property and phototherapy against cancer cell lines. Yeh et al. (2016) developed conjugated QDs using peptide-PEGylated lipids for targeting prostate cancer cells. This peptide conjugate inhibited the tumor growth. Gui et al. (2018) illustrated a bifunctional mesoporous silica nanoparticle coated with blue fluorescent N-graphene quantum dots. This conjugate is bound with the drug doxorubicin and then covered with hyaluronic acid (HA-DOX-GQD@MSN). The conjugated drug has cytotoxicity effect against HeLa cell lines and also has fluorescent monitoring ability. Choi et al. (2008) investigated the epigenomic and genotoxic response of cadmium telluride QDs in breast cancer cell lines. QD treatment inhibited the p53 inhibitor pifithrin-α and it simultaneously decreases cell viability. Epigenetic changes have more effects on gene expression. Arkan et al. (2018) reported a simple hydrothermal method for the synthesis of carbon quantum dots from walnut oil, and also its cytotoxic and apoptogenic properties are analyzed. QDs possessed potent cytotoxic efficiency toward PC-3 and MCF-7 cell lines by the activation of the caspase-3 protein, which prompts apoptosis. Goo et al. (2013) reported a conjugated CdSe/ZnS QDs with curcumin to reduce QD-induced cytotoxicity on the cancer treatment using HL-60 cells and normal lymphocytes. The combined treatment enhances apoptosis, cell death, ROS generation, and single/double DNA strand breaks in HL-60 cells, and at the same time curcumin protects the normal lymphocyte cell viability, apoptosis, and ROS

generation. Belletti et al. (2017) described a single-emulsion procedure for pure curcumin-loaded nanoparticle coated with QDs against primary effusion lymphoma. The QD conjugate can enhance the cellular internalization of curcumin and also track drug release and nanocarrier's destiny into cells.

4.11 Nanographene

Nanographene, a class of two-dimensional carbon nanomaterial, is widely used for biosensing, drug/gene delivery, different types of cancer therapies, as well as tissue engineering and imaging in the area of biomedicine (Geim and Novoselov 2010; Yang et al. 2016a, Yang et al. 2016b). Nanographene and its derivatives could act as photothermal agents for efficient photothermal therapy (PTT) of cancer if it has an absorbance at near-infrared rays (Yang et al. 2012a, Yang et al. 2012b, Yang et al. 2012c). Various types of biomolecules can be loaded in nanographene due to its high specific surface area (Liu et al. 2008a, Liu et al. 2008b). Various inorganic nanoparticles and radionuclides such as 64Cu, 66Ga, 125I, and 131I can be loaded with nanographene to offer additional optical, magnetic properties and to find applications in nuclear imaging and radiotherapy of cancer, respectively (Yang et al. 2012a, Yang et al. 2012b, Yang et al. 2012c; Hu et al. 2012; Hong et al. 2012a, Hong et al. 2012b) (Table 4.10).

4.11.1 Nanographene-Conjugated Inhibitors in Cancer Treatment

Yang et al. (2016a) and Yang et al.(2016b) demonstrated the efficient targeting of breast cancer metastasis using conjugated nanographene oxide with a monoclonal antibody against follicle-stimulating hormone receptor. This method can be used as an early detector of metastasis in breast cancer. Jung et al. (2014) designed a nanographene oxide using hyaluronic acid conjugate. It can be used for the photothermal ablation treatment of melanoma skin cancer utilizing a near-infrared laser. It can be transdermally given to the tumor tissues in the skin of mice to enable the enhanced penetration and retention of nanoparticles. The near-infrared radiation produced a complete ablation of tumor tissues with no account of tumorigenesis. Kavitha et al. (2014) examined an efficient nano-cargo vehicle for the distribution of drugs into cells using graphene oxide. The nanocarrier has polyvinyl caprolactam conjugate and the drug camptothecin is loaded inside it. It can be used as an efficient drug delivery vector with high biocompatibility, solubility, and stability in physiological solutions. Camptothecin-loaded polyvinyl caprolactam conjugate exhibited immense potency in killing cancer cells. Zeng et al. (2017) developed multifunctional graphene, folic acid (FA)-conjugated polyethylenimine-modified PEGylated

Table 4.10 Nanographene conjugate for target-specific delivery of an anticancer drug

Sl. no.	Type of the nanographene conjugate	Biological applications	Authors
1.	Nanographene oxide with a monoclonal antibody (64Cu-NOTA-GO)	Used as an early detector of metastasis in breast cancer	Yang et al. (2016a), Yang et al. (2016b)
2.	Nanographene oxide- hyaluronic acid (NGO-HA)	Exhibits the total ablation of tumor tissues with no appearance of tumorigenesis	Jung et al. (2014)
3.	Graphene oxide-poly N-vinyl caprolactam (GO-PVCL) loaded with camptothecin	Used as an effective drug transportation vector Camptothecin-loaded polyvinyl caprolactam conjugate has high potency in killing cancer cell lines	Kavitha et al. (2014)
4.	Folic acid (FA)-conjugated polyethylenimine-modified PEGylated nanographene (PPG-FA/siRNA/Dox)	It has high drug and siRNA loading ability, gene silencing effect, and efficient intracellular delivery of doxorubicin	Zeng et al. (2017)
5.	Nanographene oxide conjugated with D-α-tocopheryl polyethylene glycol-1000 succinate	Reduced the cell viability of breast cancer cell lines Enhanced drug stability	de Melo-Diogo et al. (2017)
6.	Nano-conjugate of artesunate with PEGylated nanographene oxide (nGO-PEG-ARS)	It showed the complete tumor cure ability within 15 days without causing any apparent histological lesion	Pang et al. (2017)
7.	FA-NGO-PVP	Targeted chemo-photothermal therapy showed high anticancer efficiency	Qin et al. (2013)
8.	^{66}Ga-NOTA-GO-TRC105	It has excellent stability and tumor target specificity	Hong et al. (2012a), Hong et al. (2012b)

nanographene (PPG-FA/siRNA/Dox), for the delivery system for siRNA and doxorubicin. This nano-conjugate exhibited high drug/siRNA loading ability and satisfactory gene silencing effect as well as efficient intracellular delivery of doxorubicin. de Melo-Diogo et al. (2017) investigated the therapeutic efficiency of D-α-tocopheryl polyethylene glycol-1000 succinate conjugated with nanographene oxide in breast cancer cells. It enhanced the drug stability and also reduced the cell viability of breast cancer cell lines. Pang et al. (2017) developed a nano-conjugate of artesunate with PEGylated nanographene oxide (nGO-PEG-ARS) for obtaining photothermal effect. The nano-conjugate nGO-PEG-ARS with near-infrared irradiation resulted in complete tumor cure within 15 days without causing any apparent histological lesion. Qin et al. (2013) designed a nanographene oxide (NGO) conjugated drug using polyvinylpyrrolidone functionalized NGO with folic acid (FA-NGO-PVP), for testing the combination chemotherapy and near-infrared photothermal therapy. The drug conjugate targeted chemo-photothermal therapy

showed high anticancer efficiency. Hong et al. (2012a) and Hong et al. (2012b) designed a nanographene conjugate by covalently linking with polyethylene glycol, NOTA, and TRC105 (^{66}Ga-NOTA-GO-TRC105) for tumor targeting. The nanographene conjugate has excellent stability and tumor target specificity which was vasculature specific with little extravasation.

4.12 Magnetic Nanoparticles

Magnetic nanoparticles consist of magnetic elements, such as iron, nickel, cobalt, chromium, manganese, gadolinium, and their chemical compounds. Chemo- and radiotherapy are used for the treatment of cancer cells. However, none of them is cancer cell-specific. Nanotechnology can bring a useful alternative to current cancer therapies, which can target the cancer-specific cells from normal cells (Pautler and Brenner 2010). Superparamagnetic iron oxide nanoparticle size can vary within 10-100nm and used extensively in biomedical treatments. Magnetic hyperthermia is a nonintrusive strategy for tumor excision (Pankhurst et al. 2003). The magnetic nanoparticle consists of a magnetic core with a specific coating. Superparamagnetic nanoparticles have a single magnetic domain because of their small magnetic core and are magnetize under an externally applied magnetic field (Yigit et al. 2012) (Table 4.11).

4.12.1 Role of Magnetic Nanoparticles in Cancer Treatments

Yallapu et al. (2011) invented a water-soluble superparamagnetic iron oxide nanoparticle. It can be used for hyperthermia, magnetic resonance imaging, and drug distribution purposes. Drug-loaded formulation of F127250 has good stability, enhanced cellular uptake, and multilayer imaging contrast properties. Curcumin packed drug formulation (F127250-CUR) exhibited equal growth inhibition impacts on (A2780CP) ovarian cancer cell line (MDA-MB-231), breast cancer cell line, and (PC-3) prostate cancer cell lines. Li et al. (2015) examined a hollow magnetic nanoparticle (HMNPs) as an actively established drug delivery scheme which performs both infrared thermal imaging and magnetic resonance imaging characteristics. Under the presence of an alternating magnetic field, this system showed the potential for thermo-chemo combination to induce cancer cell apoptosis via the in vivo method. Chu et al. (2013) studied the photothermal impact of surface-functionalized Fe3O4 magnetic nanoparticles in both in vitro and in vivo approaches. Fe_3O_4 nanoparticles are taken up by esophageal cancer cells, and upon irradiation at 808 nm and incubation with near-infrared radiation, the cell viability and cellular organelles are damaged. Mouse esophageal tumor growth is reduced by the photothermal effect of Fe3O4 nanoparticles. Sadhukha et al. (2013) synthesized an epidermal growth factor receptor-targeted, inhalable superparamagnetic iron oxide

Table 4.11 Magnetic nanoparticles for drug delivery

Sl. no.	Type of magnetic nanoparticles	Biological applications	Authors
1.	Superparamagnetic iron oxide (F127250)	It has good stability, enhanced cellular uptake, and multilayer imaging contrast properties The curcumin-loaded formulation exhibited equal tumor repression influences on ovarian, breast, and prostate cancer cell lines	Yallapu et al. (2011)
2.	Hollow magnetic nanoparticles (HMNPs)	The system exhibits both infrared thermal imaging and magnetic resonance imaging characteristics Induce cancer cell apoptosis	Li et al. (2015)
3.	Fe3O4 magnetic nanoparticles	Cancer cell viability and cellular organelles are damaged Mouse esophageal tumor growth is reduced	Chu et al. (2013)
4.	Superparamagnetic iron oxide nanoparticles (SPIO)	Magnetic hyperthermia causes a greater reduction in lung tumor growth	Sadhukha et al. (2013)
5.	Magnetic nanoparticles embedded in polylactide-co-glycolide	It can deliver both hydrophobic and hydrophilic cancer therapeutic drugs	Singh et al. (2011)
6.	ODN-dendrimer-MNP-magnetic nanoparticle composites	Inhibit cancer cell growth in a dose- and time-dependent manner by downregulating the survivin gene and protein	Pan et al. (2007)
7.	Fe3O4-curcumin conjugate	It showed a high loading cellular uptake Antitumor efficiency of curcumin is delivered to the cells through macrophages	Dai Tran et al. (2010)

nanoparticles against magnetic hyperthermia of lung cancer cells. Magnetic hyperthermia treatment using the inhalable superparamagnetic iron oxide nanoparticles showed a greater reduction in lung tumor growth. Singh et al. (2011) developed and characterized the magnetic nanoparticles embedded in polylactide-co-glycolide (PLGA-MNPs) matrixes as dual drug delivery and imaging system capable of encapsulating both hydrophilic and hydrophobic drugs by examining the biocompatibility, cellular uptake, cytotoxicity, membrane potential, and apoptosis in MCF-7 and PANC-1 cell lines. Magnetic nanoparticles embedded in polylactide-co-glycolide matrixes showed an enhanced contrast effect due to higher T2 relaxivity with a blood circulation half-life ~47 min. Thus it can deliver both hydrophobic and hydrophilic cancer therapeutic drugs. Pan et al. (2007) developed a modified magnetic nanoparticle with a diameter of 8nm using different polyamidoamine dendrimers and mixed with antisense survivin oligodeoxynucleotide and incubated in (MCF-7) breast cancer cell line, (MDA-MB-435) melanoma cell line, and (HepG2) liver cancer cell lines. The modified magnetic nanoparticle (ODN-dendrimer-MNP composites) can enter into tumor cells within 15 min which appears in the hindrance of cancer cell growth in a shot- and the time-dependent manner by downregulating the survivin gene and protein. Dai Tran et al. (2010) investigated the magnetic drug

targeting using Fe_3O_4-curcumin conjugate, which has magnetic nano Fe3O4 core and chitosan as outer shell and entrapped curcumin, and also studied its efficiency to label, target, and treat tumor cells. It showed a high loading cellular uptake. Antitumor efficiency of curcumin is delivered to the cells through macrophages for enhanced phagocytosis process.

4.13 Conclusion

Conventional anticancer drugs against proliferating cells with high toxicity show diverse severe dilemmas upon the gastrointestinal tract, hematopoietic system, immune system, and nervous systems. This drawback can be reduced by using the organic and inorganic nanoparticles. These nanocarriers are the ideal candidate to carry anticancer drugs to the specific cancer sites. Due to its smaller size, it potentially reacts to solubilize the insoluble drugs and in sustainable release of drug in the tumor tissue. It acts as a best antitumor vehicle by conjugating with anticancer drugs, monoclonal antibodies, and plant-based bioactive compounds due to its inner hydrophobic domains and hydrophilic outer shell. Inorganic nanoparticles are due to the uniform size, shape, and optoelectronic properties used in the field of medicine. Particularly, the metal nanoparticles are highly utilized in imaging, optical, sensors, cancer therapy, and drug delivery. Poly(lactic-*co*-glycolic acid) (PLGA) acid is a biodegradable polymer which is extensively accepted as a matrix to fuse a broad range of therapeutic tools. That comprises hydrophobic and hydrophilic small particles, nucleic acids, and proteins. PLGA is licensed by the Food and Drug Administration (FDA) for aid in pharmaceutical commodities. Association of poorly soluble cytostatic agents and drugs into polymeric nanoparticles is presumably the most efficient and simplest way to enhance their therapeutic effectiveness. Nanoparticles including polymeric nanoparticles, polymeric micelles, gold, dendrimers, or quantum dots are effectively used in cancer treatments by enhancing apoptotic activity, cell death, ROS generation, and single/double DNA strand breaks and inhibit cell growth in cancer cells.

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Chapter 5
Potential of Metal Oxide Nanoparticles and Nanocomposites as Antibiofilm Agents: Leverages and Limitations

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5.1 Introduction

The transformation of atoms from one state to a smaller form was first proposed by Richard Feynman in 1959 who is termed as the "father of nanotechnology" (Feynman 1959) with the term "nanotechnology" coined later in 1974 by Norio Taniguchi (Taniguchii 1974). It was these findings which laid the foundations leading to the discovery that properties of materials changed drastically compared to conventional solids when their dimensions were reduced to less than 1–100 nm in one dimension leading to the concept of "nanoparticles." Metal oxide nanoparticles (MONs) find application as semiconductors, catalyst, sensors, and solid oxide fuel cells and as antifouling/antimicrobials, with metallic, insulator, and semiconductor properties.

Metal oxide NPs have been used to combat biofilms and biofouling ranging from *Ship Hulls to Bandages* (Kurtz and Schiffman 2018). The use of MONs was initiated as an alternate antimicrobial to the emergence of antibiotic and multidrug-resistant strains (MDR). MONs offered an alternate viable method to control these bacterial strains as resistance to metal ions seemed to be a nonviable proposition (Negi et al. 2012). Compared to their planktonic counterparts, bacterial biofilms are more resilient to the penetration of biocides and antibiotics. This was also an area of concern, where the use of MONs became prominent with the development of antimicrobial coatings for marine biofouling control, public hygiene, and water treatment. Mortality due to antibiotic resistance in the USA has been reported to be 23K and projected to be around 10 million/year worldwide by 2050 (O'Neill 2014; CDCP 2013) which also has been instrumental in developing alternate antimicrobial agents.

The science of nanotechnology advanced with the fruits of these small-sized particles, due to their low surface area/mass ratio and high reactivity making them efficient from their bulk counterparts (Nair et al. 2009). A reduction in particle size from 10 μm to 10 nm increases the surface contact area hypothetically by 10^9 which enhance the probability of surface contact toward a bacterial cell imparting toxicity (Hamouda 2012). Apart from surface area, novel physicochemical properties of nanoparticles also play a significant role in antimicrobial activity (Pal et al. 2007). An inverse relationship exists between nanoparticle size and antimicrobial activity, and it is understood that most nanoparticles in the size range of 1–10 nm elicit the highest antimicrobial activity (Morones et al. 2005). Several properties of MONs like size (Azam et al. 2012), shape (Gold et al. 2018), crystallinity (Espetia et al.

2012; Cha et al. 2015), solubility (Zhong et al. 2017), dispersion (Guan et al. 2019), agglomeration (Zhong et al. 2017), surface charge (Van et al. 2013), concentration (Jones et al. 2008; Pandiyarajan et al. 2013), chemical composition, and physicochemical characteristics (Lemire et al. 2013) have a say on antimicrobial activity. In this context, studies have tried to improvise on synthesis methods to yield nanoparticles of reduced sizes for superior antimicrobial activity.

Ideally, microbial cells require trace amounts of Cu, Zn, Ni, and the divalent cations Ca^{2+}, Mg^{2+} $Fe^{2+,3+}$ for their metabolic process, whereas excess quantities of the same are toxic (Lemire et al. 2013). Metal oxide nanoparticle surfaces are highly reactive due to the presence of increased number of unsaturated atoms/ions at the surface as a result of nano size features enabling easy release of metal ions from MONs. Surface charge of MONs is another important factor influencing antibacterial activity (AB) which is represented by the zeta potential. In general, metal oxide nanoparticles with zeta potential values between +30 and -30 mV are stable in suspension (Kadu et al. 2011). Stanic and Tanaskovic (2020) outlined the importance of "point of zero charge" (PZC) of MONs as a function of pH wherein the total number of positive and negative charges becomes zero or neutral which is vital for antimicrobial activity of MONs at a given pH. PZC of MONs is again dependent on impurities, crystallinity, and type of electrolyte. MONs with positive charge showed high antimicrobial activity followed by neutral and negative charge. Another significant factor involving MONs is with regard to their solubility, with particle size, pH of media, and temperature playing a major role during antimicrobial assays evaluating MON efficacy. Solubility was found to increase with decreasing particle size which was in turn affected by their aggregation property (Zhong et al. 2017).

Concentration of MONs is another vital factor involved in antimicrobial activity. This is usually represented by the minimum inhibitory concentration (MIC) which is the concentration which inhibits visible growth of microorganisms, and for biofilms, it is termed as biofilm inhibitory concentration (BIC) (Jones et al. 2008). Antimicrobial activity and environmental toxicity (to nontarget organisms by release from products) of nanoparticles are two sides of a coin. For assessing toxicity to aquatic organisms and human cell lines, the protocol of lethal concentration 50 (LC 50) is followed which is the concentration at which 50% mortality of an organism is observed. Interestingly, MONs were less toxic to bacteria than to higher-level organisms. MIC of Ag (7.1 mg/L), CuO (200 mg/L), and ZnO (500 mg/L) were recorded for bacteria, whereas LC50 values were around 0.01, 2.1, and 2.3 for aquatic organisms and 1.36, 100, and 3.0 for fish and 11.3, 25, and 43 mg/L for mammalian cells for the three nanoparticles, respectively (Bondarenko et al. 2013). Hence, environmental release of MONs is still an issue hindering their extensive application.

Several classes and combination of metallic nanoparticles have been synthesized and have been classified into (1) monometallic NP, viz., copper (Cu), copper oxide (CuO), cuprous oxide (Cu_2O), gold (Au), silver (Ag), iron oxide (FeO), lead oxide (PbO), aluminum oxide (Al_2O), calcium oxide (CaO), magnesium oxide (MgO), zinc oxide (ZnO), nickel (Ni), nickel oxide (NiO), platinum (Pt), palladium (Pd), selenium (Se), silver chloride ($AgCl_2$), silver sulfide (AgS), tellurium (Te), tin oxide

(SnO_2), and titanium dioxide (TiO_2); (2) bimetallic NP, viz., cobalt ferrites ($CoFe_2O_4$), lead and selenium (Pb/Se), copper and platinum (Cu/Pt), iron oxide and silver (Fe/Ag), zirconium oxide (ZrO_2), silver and gold (Ag/Au), silver and iron (Ag/Fe), silver and nickel (Ag/Ni), silver and palladium (Ag/Pd), and silver and ZnO (Ag/ZnO); and (3) trimetallic nanoparticles, viz., cerium oxide/copper oxide/zinc oxide (CeO/CuO/ZnO) and copper/chromium/nickel (Cu/Cr/Ni). Another significant development is the quantum dots (cadmium sulfide and cadmium selenide) which have also demonstrated antimicrobial properties (Ju-Nam and Lead 2008). Monometallic nanoparticles have been synthesized using a single metallic salt solution, whereas bimetallic nanoparticles have been synthesized with reduction of two metal salt solutions, with trimetallic nanoparticles being a recent development. The antibacterial activity of bimetallic nanoparticles has been observed to be higher than monometallic nanoparticles due to their higher reactivity and synergistic activity of both metallic NP (Sumbal et al. 2019). Bimetallic nanoparticles have been very effective against strong biofilm producers like *C. albicans*, *S. aureus*, and *P. aeruginosa* (Yallappa et al. 2015). Trimetallic nanoparticles have been shown to be more effective antibacterial agents compared to mono- and bimetallic nanoparticles (Yadav et al. 2018). Crystalline structure of MONs also influences antimicrobial activity, and different synthesis methods and precursors have yielded 0D (nanoparticles, nanocube), 1D (nanorods, nanotubes, nanowires and nanofibers), 2D (nanosheets, nanoplates), and 3D (nanoflowers, nanopillars) (Nikalova and Chavali 2019).

Several advancements of MONs with respect to their synthesis methods, physicochemical characteristics like shape, size, charge, solubility, dispersion, aggregation, binding with polymers, antibacterial activity against planktonic and biofilm forms, mechanism of action on different organisms viz: bacteria, fungi and virus, incorporation into polymer matrix to develop nanocomposites, role in medical implants, prosthesis, drug delivery agents, imaging and detection of pathogens have all been extensively reviewed. For detailed reviews on these aspects, refer to (Raghunath and Perumal 2017), (Negi et al. 2012), (Seabra and Duran 2015), (Abozeid and Williams 2019), (Kobayashi et al. 2019), (Malaekeh-Nikouei et al. 2020), (Peng et al. 2020), (Kawish et al. 2020), (Jeyaprakashvel et al. 2020), (Jandt et al. 2009), (Dhanalekshmi et al. 2020), and (Ahamadbadi et al. 2020).

5.2 Biofilms: The Way of Life of Microbial Cells

In general, bacterial cells were thought to be existent in a planktonic mode of life. It was revealed by Claude E. Zobell (1943) that bacterial cells adhered to surfaces. The concept of "biofilm theory" was proposed later on by Costerton et al. (1978). Biofilm formation is ubiquitous on all surfaces whether biotic or abiotic and is influenced by environmental conditions. The switching from a planktonic to a sessile (biofilm) mode involves environmental factors, species composition, signaling, and genetic factors. The developmental process of biofilms on surfaces does not follow a common cycle and varies depending on local environment conditions, viz.,

multispecies biofilms in the case of natural aquatic environments and unispecies biofilms growing on implant materials (Wille and Coenye 2020).

5.2.1 *Stages in Biofilm Development*

A general biofilm development/maturation cycle (Fig. 5.1) involves (1) changes to an immersed surface by formation of a conditioning film comprising of dissolved organics and biomolecules; (2) attraction of bacterial cells to the surfaces, held together by weak electrostatic forces of attraction; (3) sensing of substratum suitability resulting in secretion of exopolymeric substances (EPS) and firm adhesion of microbial cells resulting in biofilm maturation and microcolony formation with increase in density and diversity (O'Toole et al. 2000); and (4) dispersion of cells from mature biofilms again to a planktonic mode of life (Davies 2011; Flemming and Rumbaugh 2017). Adhesion of bacteria to surfaces is a complex phenomenon involving substratum properties as well as bacterial cell surface properties to influence the adhesion process. Initial adhesion is mediated by hydrophilic, hydrophobic cell surface interactions and hydrogen bonding to substratum. Bacterial cell surface charge plays a role with a predominantly net negative charge on their hydrophilic surfaces and coexistence of positively charged hydrophobic areas which are involved

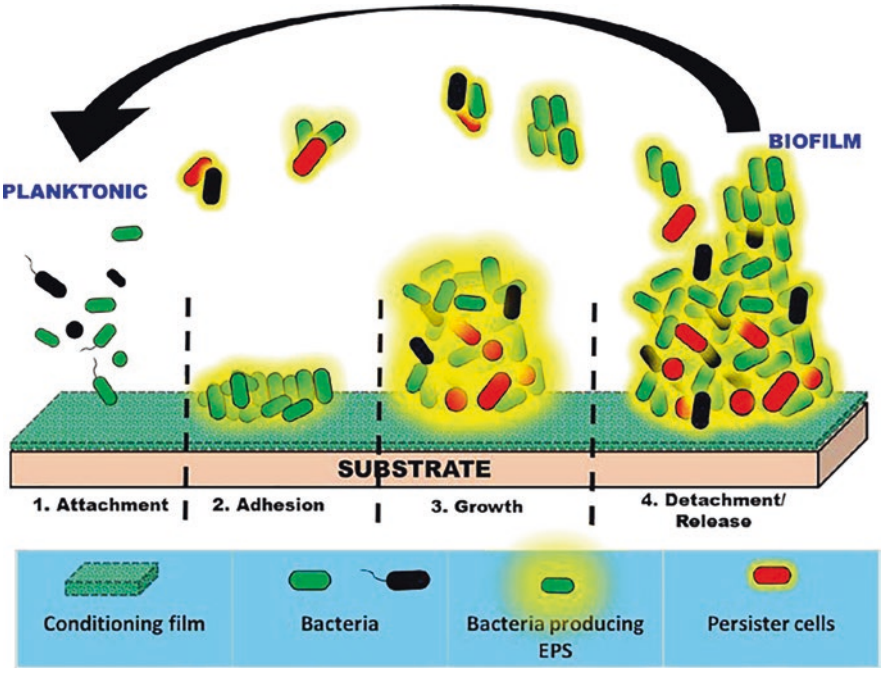

Fig. 5.1 Stages in biofilm development on biotic and abiotic surfaces

in the adhesion of cells to the substratum. The firm adhesion is brought about by secretion of EPS.

5.2.2 Detrimental Effects of Biofilms

Biofilms constitute 80% of the microbial infections as outlined by the National Institute of Health (Davies 2003). Biofilms have been shown to be physiologically heterogeneous (Stewart and Franklin 2008). Biofilms offer several advantages to resident microbes by providing increased nutrient availability and dissolved oxygen (Xu et al. 2000), quenching of antimicrobials and biocides, and gene transfer within communities and serve as a reservoir for microbes. Biofilm-induced infections have been revealed to be the cause of pathogenesis in several cases and are very difficult to eradicate (Costerton et al. 1999; Stewart 2015; Hall-Stoodley et al. 2004). Biofilm matrix/mode offers protection to microorganisms with a 1000-fold increase in concentration of antibiotics/biocides required to eliminate them compared to their planktonic counterparts (Hall and Mah 2017). Similarly, Nickel et al. (1985) also reported that biofilm cells of *P. aeruginosa* were ~1000-fold resistant to the antibiotic tobramycin compared to planktonic cells. Tetz et al. (2009) have reviewed and reported studies wherein antibiotics with 10^2 and 10^4 times their MIC concentration had no killing effect on bacteria in biofilms. Involvement of extracellular DNA in the tolerance process was observed, and when neutralized by DNase, the response/sensitivity to antibiotics increased.

Biofilm infections, development on medical devices, pathogenesis, and intervention strategies have been reviewed extensively (Donlan and Costerton 2002; Prasad et al. 2020). Donlan and Costerton (2002) also have reported that the common biofilm forming bacterial species *Streptococcus viridans*, *S. epidermidis*, *S. aureus*, *Enterococcus faecalis*, *E. coli*, *Moraxella catarrhalis*, *K. pneumoniae*, *Proteus mirabilis*, and *P. aeruginosa* are potential infection-causing agents. Common chronic biofilm infections caused by biofilm bacteria are cystic fibrosis, endocarditis, meningitis, periodontitis, dental caries, rhinosinusitis, otitis, osteomyelitis, chronic wounds, prosthesis and implantable devices. Biofilm infections in humans are resistant to the host immune defense systems and have to be systemically treated with antibiotics. In addition, implant devices like orthopedic prostheses, heart valves, venous and urinary catheters, surgical sutures, contact lens, and arteriovenous shunts are prone to biofilm development and need protective strategy.

5.2.3 Antibiotic and Biocide Tolerance/Resistance Mechanisms

Resistance or tolerance to antibiotics and biocides by microbes is dependent on several variables like bacterial strains, diffusion, or penetrating power of antimicrobials and adaptive phenotypic response of organisms in biofilm matrix. Hall and

Mah (2017) have reviewed several studies where different antibiotics were able to penetrate into biofilm matrix of different strains, without affecting the viability of cells inside the biofilm matrix (Tseng et al. 2013) which is attributed to the slow penetration of antibiotics resulting in adaptive tolerance of the cells to antimicrobial compounds. To a certain extent, this effect can be explained by the decreased diffusion limitation of biofilms, with their high cell densities and extracellular polymer matrix (EPS) resulting in throttling or impeding convective transport (Stewart 2003). Mechanism of antibiotic resistance in biofilms has been known to be mediated by diffusion barrier and quenching of antibiotics by components of the extracellular polymer matrix (EPS) and the existence of persister cells (Percival et al. 2011). Another aspect of action of antibiotics is that most of the antibiotics are active against growing cells and exhibit growth-dependent killing activity (Olsen 2015). Alteration of pH within the biofilm matrix and depletion of substrate result in reduced metabolic activity which influences the cells growing in biofilm. The switching of the toxin-antitoxin (TA) system by starvation and DNA damage is also known for the development of persister cells (Sharma et al. 2015). Stewart (2015) after reviewing several studies came up with the conclusion that the antibiotic resistance is mainly due to the physiological status of the cells in the biofilm. However, the factor responsible/involved in full biofilm developing tolerance/resistance mechanism is still elusive, and how physiologically different cells in a biofilm render this property on the entire biofilm is still a question mark.

Biofilms also have an altered chemical microenvironment which is due to the presence of aerobic species at the surface layers and anaerobic species deep down near the substratum as the biofilm matures (deBeer et al. 1994). The presence of both aerobic and anaerobic strains in biofilms is another matter of concern with conventional aminoglycoside antibiotics shown to be ineffective against anaerobes (Gupta et al. 2016). In addition, production of enzymes like the β-lactamase enzyme which cleaves/inactivates the β-lactam rings of antibiotics neutralizing it (Kawai et al. 2018) has necessitated the search for alternative antimicrobials. AmpC-type cephalosporinase enzyme isolated from cystic fibrosis patients infected with *P. aeruginosa* revealed degradation of the drug cephalosporin (Chalhoub et al. 2018) which is also indicative of the resistance mechanisms operating for the major known antibiotics in use. Other factors like local antibiotic sequestration by electrostatic interactions, negative charge of EPS matrix interacting with the positively charged regions of antibiotics, and gene transfer confer antibiotic resistance to the microbes are also responsible for the observed tolerance mechanisms (Molin and Nielsen 2003). Due to increased tolerance of biofilms, higher doses of antibiotics need to be administered which also leads to systemic toxicity. Similar to efflux of metal ions from cytosol of bacterial cells to overcome metal toxicity, antibiotic efflux from cells through multidrug efflux system of bacterial cells and transposons has also been involved in antibiotic tolerance/resistance (Levy 2002).

This has triggered the research into alternative biocidal agents wherein metal oxide nanoparticles (MONs) have filled the void as antibiofilm agents/coatings, assisted as carriers for antibiotics (clinical settings) in enhancing antibiofilm and antimicrobial activity. However, environmental biofilms constitute a heterogeneous

proposition with respect to coexistence of multiple phenotypes, differential gene expression, and metabolic status which all pose new challenges to the development of a biofilm-resistant surface/coating. Nano functionalized surfaces and polymer nanocomposites which can inhibit, kill, and prevent biofilm formation are at a nascent stage even though voluminous literature on their antimicrobial activity is available, and as a much sought after requirement, research efforts for the development of a broad-spectrum antibiofilm surface are a priority.

5.3 Routes of Synthesis on Physicochemical Characteristics of MONs Influencing Antibiofilm Efficacy

5.3.1 Chemical and Hydrothermal Synthesis of MONs

The chemical method involves reaction of salt solutions using precursors and surfactants at high temperature. Copper oxides, zinc oxide, and magnesium oxide NP have been synthesized using this method. This route of synthesis is used wherein aqueous salt solutions are difficult to dissolve at normal conditions. The process involves the use of high temperature and high pressure autoclaves with temperatures ranging from 120 to 200 °C and pressures ranging from 15 to 200 psi (Byrappa and Haber 2001).

5.3.2 Sol-Gel Synthesis of MONs

Sol-gel method involves condensation and hydroxylation reactions of reactants, and this method offers a scope for variation of pH and temperature of gels to regulate hydrolysis rates as well as condensation reactions (Ennas et al. 1998). Example novel MgO nanoparticles have been synthesized by this process which has demonstrated ~98% biofilm inhibition of *S. aureus*, *E. coli*, and *C. albicans* (Wong et al. 2020). A characteristic feature observed was that MgO particles synthesized by sol-gel process had minimum aggregation tendency.

5.3.3 Sonochemical Synthesis of MONs

Most of the metal oxide nanoparticles have been synthesized using this method wherein the metal salt solution is sonicated which relies on acceleration and collision of particles in solution which impart different particle size, composition, and morphologies. This method is usually applied for preparing polymer nanocomposites where NPs are incorporated into polymers (Malka et al. 2013).

5.3.4 Coprecipitation Synthesis of MONs

This is a simple facile method for large-scale production of MONs with the addition of either ammonium hydroxide or sodium hydroxide to a metal salt solution under constant stirring and temperature conditions. The process involves initial nucleation of the metals and then nuclei growth onto the crystal surface through diffusion of the solutes (Sugimoto 2003).

5.3.5 Wet Chemical Synthesis of MONs

This route of synthesis offers for large-scale production of nanoparticles and is a simple and inexpensive method. The process involves mixing of reactants by stirring and use of mild heating in some cases (Wu et al. 2005).

5.3.6 Electrochemical Synthesis of MONs

This involves the electrolysis process under inert conditions using a suitable electrolyte with the bulk material as the anode. In the process, the cations move toward the cathode, and the bulk material is oxidized at the anode resulting in release of small metal clusters which are stabilized by stabilizers. During the process, the residual oxygen present in the electrolyte oxidizes the metals into respective metal oxide nanoparticles (Reetz and Helbig 1994).

5.3.7 Biosynthesis of MONs

Physical and chemical methods of synthesis of nanoparticles involve the use of high temperature and vacuum conditions with a time- and energy-consuming process. However, in the last decade, the advent of green synthesis using biological agents like plants, bacteria, fungi, and different cell cultures has added advantages compared to physical and chemical methods in that the biological metabolites also act as capping agents which aid in better dispersion of nanoparticles (Zhang et al. 2016; Prasad et al. 2016, 2018; Srivastava et al. 2021) in solution and also offer large-scale synthesis and production of these NP. A major disadvantage of this approach is that the growth of biological organisms like bacteria, algae, and fungi is dependent to a great extent on different synthetic media, varying nutrient requirements, and wide range of environmental conditions which trigger production of different metabolites during their growth phase. These metabolites reduce metal ions resulting in synthesis of green nanoparticles. The active metabolic moiety involved in the process of

reduction of salt solution has however not been characterized in majority of studies using the bio-route for synthesis. The reproducibility of size, shape, and charge properties of such green synthesized nanoparticles is still a big question mark compared to those synthesized by physical and chemical methods where there is more control over the synthesis parameters.

5.3.8 Growth of Metal Oxide Nanomaterials

The advent of nanotechnology as an outstanding versatile technology has paved the way for superior functionality of products in various sectors (D'Souza and Richards 2007; Fernandez-Garcia et al. 2004; Jeevanandam et al. 2018; Pradeep 2007). The characteristic of nanomaterials such as large specific surface area with higher interfacial nature has given them unique fascinating features and functionalities. The synthesis of a material is a backbone for novel applications, and it is truly a challenging demand to synthesis nanomaterials for antifouling applications (Abioye et al. 2019; Wang and Chen 2019). Depending on the application of a material, the requirements need to be met. For instance, self-cleaning coatings should have efficacy in the specific environment against the relevant microbes with toxicity to the microbes. In this respect, the use of nanomaterials has yielded promising results for antimicrobial and antifouling coatings (Sathya et al. 2019; Salazar-Hernandez et al. 2019). Biofouling and biofilm formation are a major concern in the marine industry due to the impact it has on the maintenance of system for functioning and the cost for prevention (Scardino et al. 2009; Sankar et al. 2015). Methods such as mechanical and chemical processes related to the application of biocides currently used to control biofouling are not always effective and environment friendly. The need for alternative methods for the prevention of biofouling therefore exists. In this respect, nanomaterials have yielded promising results. There is widespread use of nanomaterials in the form of metal or metal compounds, mostly as oxides which are chemically stable even in ambient and moist environments (Scardino et al. 2009; Sathya et al. 2019; Ruiz-Sanchez et al. 2020).

In defining nanomaterials, it is usually described as control of matter at dimensions between approximately 1 nm and 100 nm. Importantly, these materials at the nanoscale reveal new physiochemical and biological properties compared to their bulk counterparts. Noble metals, like silver, gold, and copper nanoparticles, have, for example, shown higher antimicrobial activities against certain bacterial species (Yael et al. 2017; Bankier et al. 2019). Even pure carbons in the forms of nanotube and graphene do show antimicrobial activities (Wiaraja et al. 2018; Mohammed et al. 2020). Metal oxide nanomaterials are used for biological applications, and these oxides have to cope with the process-related demands and challenges. Thus, essential methods may have to be tuned wisely to fit the needs of an application. For instance, one-dimensional (1D) metal oxides are efficient for biomedical applications (Yah et al. 2011; Bonu et al. 2019), while the nanoparticles (0D) suit better for the antifouling treatment (D'Souza and Richards 2007; Sankar et al. 2015; Yael

et al. 2017; Pradeep 2007). Some well-known adopted approaches are classified such as "bottom-up" – starting from atoms or molecules to reach to the desired goal with shape, size, and morphology – and another approach is the "top-down" which deals with larger sizes to reach to smaller ones (Fig. 5.2). Considering the focus of applications on antifouling treatments, bottom-up approach allowing large-scale synthesis with ease processable methods is likely to be adopted. Top-down process such as ball milling can be of use for large-scale process; however, possible contamination-free uniformity nanoparticles are a formidable task (Basnet et al. 2019).

A few methods which are well utilized for synthesis of metal oxides, such as CuO, ZnO, TiO_2, SnO_2, etc., are precipitation, sol-gel, hydrothermal, solvothermal, and template-assisted techniques (Fernandez-Garcia et al. 2004; D'Souza and Richards 2007; Rao et al. 2007; Lee and Soltis 2014). In coprecipitation, a soluble metal salt in the form of chloride or nitrate is used in a solvent to form a precipitate mostly with the help of a base such as NaOH and NH_4OH. The simplicity of the technique attends attention for the preparation of coprecipitation of mixed-metal oxides. Furthermore, with control on precursor concentration and pH solvent medium along with the use of capping/surfactants, the method is able to provide uniform nanoparticles including quantum dots (Deshmukh and Niederberger 2017; Juine and Das 2020).

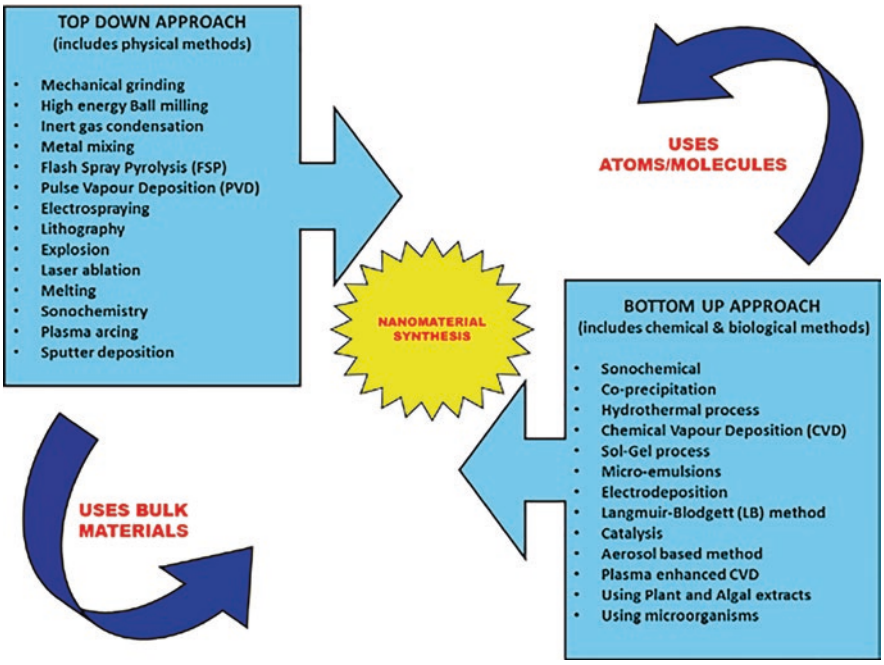

Fig. 5.2 Approaches toward synthesis of metal oxide nanoparticles

Similarly, sol-gel, a highly economic and simple method, is of high interest for the preparation of metal oxides (Li et al. 2015; Deshmukh and Niederberger 2017; Juine and Das 2020). In this process, hydrolysis of precursors results in the corresponding oxo-hydroxide, followed by the condensation of molecules to release water molecules to provide a gel-like formation, via polymerized hydroxides. Further drying process and sometime high temperature calcinations offer stable metal oxides. The process can be aquatic or non aquatic friendly environment. Highly porous metal oxides are obtained by the process. A popular method is solvothermal/hydrothermal process where a solvent (water) is raised to the boiling point in a closed vessel to impart pressure (Li et al. 2015, 2016). An appropriate chemical molecule is used as a capping agent for controlling the size and shape. There are several methods like template, light assisted and electrochemistry for creating varied sizes of nanoparticles (Rao et al. 2007; Li et al. 2016).

5.3.9 Influence of Growth of MONs on Morphology Vis-a-vis Synthesis Methods

In most of the above methods, the formation of crystal may not follow a traditional nucleation and growth mechanism. Undoubtedly, understanding of the growth process is helpful for the desired outcome and further improvement in a predictive way. In general, it includes pre-nucleation, nucleation and growth processes, assembly, and agglomeration of nanomaterials. However, unique mechanistic explanations with the predictive character are strongly limited. In fact, foreseeing the morphology and the composition of the crystal structure considering the influence of all chemical species remains a demanding challenge. There are several concepts on the growth, oriented attachment, cluster-mediated pre-nucleation, particle-based and mesocrystals which do not conform the classical view of crystallization (Ludi et al. 2012; Lee and Soltis 2014; Li et al. 2015; Li et al. 2016; Zhang et al. 2009; Liu et al. 2020; Weigiang et al. 2014). With the presence of further liquid/gas phase as seen, for instance, in solvothermal methods for final metal oxide crystals, steps like Ostwald ripening may also take part. Crystallization is an important phenomenon to define the size, shape, and crystalline orientation of the final nanoparticles. In a broad view, the basic crystallization process may be categorized into two types – (1) classical and (2) nonclassical crystallization – depending on whether an atom-/ion-mediated growth or a particle-mediated growth mechanism takes place. In classical crystallization model, small units arising from precursors, like atoms, ions, or molecules, undergo nucleation from a supersaturation point and thus its nucleation leads to a cluster. Total energy including the surface and crystal lattice energies of the system determine the growth or disintegration of it. In contrast, particles or clusters participate in nonclassical crystallization process such as oriented attachment growth (Lee and Soltis 2014). The smaller units have same orientation and get together to form crystal structures. TiO_2 nanoparticles can be synthesized

mechanically for self-supporting networks of macroscopic size, e.g., aerogels. Studies with HRTEM reveal the formation the anatase nanocrystals which leads to the oriented attachments (Dalmaschio and Leite 2012). Typical surface dominance of {101} faces is also reported. Such mechanism may proceed in various directions to result in 3D morphologies and provides various shapes, like spindle and flowers (Jianfeng et al. 2011). Precipitation methods are utilized for the growth of SnO_2 nanoparticles where a selective dopant is also incorporated (Das and Jayaraman 2014; Das and Panda 2019). In general, chloride salt of Sn is used to react with base, NaOH or NH_4OH. The precipitated gel is washed and calcinated for obtaining nanomaterials. Further, in gel with suitable surfactant, a hydrothermal method is used to produce improved quality of SnO_2 crystals. Similarly, oriented attachment is also reported, while $SnCl_4$ and benzyl alcohol are used with anisotropic growth along the <110> directions, a low energy facet of rutile SnO_2 phase (Daniel et al. 2011). Another important metal oxide is ZnO which is well utilized for the antimicrobial studies (Sathya et al. 2019).

The most commonly used semiconducting metal oxide, ZnO, has attracted large attention as a promising material for a wide range of technological applications mainly wastewater treatment via photocatalysis and antibacterial activity (Bhuyan et al. 2015; Enas et al. 2020). Various methods, such as precipitation; solvothermal approaches with metal salts like zinc acetate and zinc nitrate with base; and capping agents are well utilized. Various morphologies resulting from a sol-gel process with zinc acetylacetonate hydrate in benzyl alcohol are well documented (Li et al. 2015). Here, authors discuss the critical role of concentration for supersaturation to lead a nucleation and further growth through agglomeration into different shapes. Synthesis methods and precursors (Fig. 5.3) were found to influence morphology and also influence catalytic activity.

ZnO NPs obtained from zinc nitrate and oxalic acid via precipitation-decomposition method were found to have a heterogeneous morphology with some of the particles spherical in shape and that also appeared as nano-bundles (Fig. 5.1a, b) due to the formation of intermediate chemical moieties of zinc oxalate. The precursors zinc nitrate and oxalic acid aqueous solutions were brought to their boiling points separately. After reaching their boiling points, both were mixed rapidly and stirred for a time, and the obtained zinc oxalate precipitate was filtered and dried. In order to get the ZnO, the formed zinc oxalate was decomposed at 450 °C. In comparison with ZnO, NP obtained from zinc acetate and sodium hydroxide via simple physical grinding method using pestle and mortar offered a rodlike structure (Fig. 5.1c, d). The length of the nanorods ranged from 100 to 300 nm, and the width of the rods was approximately 20–40 nm (Krishnakumar and Imae 2014; Krishnakumar et al. 2014). In physical grinding method using zinc acetate and NaOH precursors, formation of zinc hydroxide intermediate was observed which was washed with water and ethanol, filtered and dried at room temperature. The dry crystals were calcined for 3 h at 200 °C in a muffle furnace to obtain rodlike ZnO. The method of preparation and precursors slightly influenced the bandgap energy of the materials. From DRS analysis, the bandgap energies of the prepared

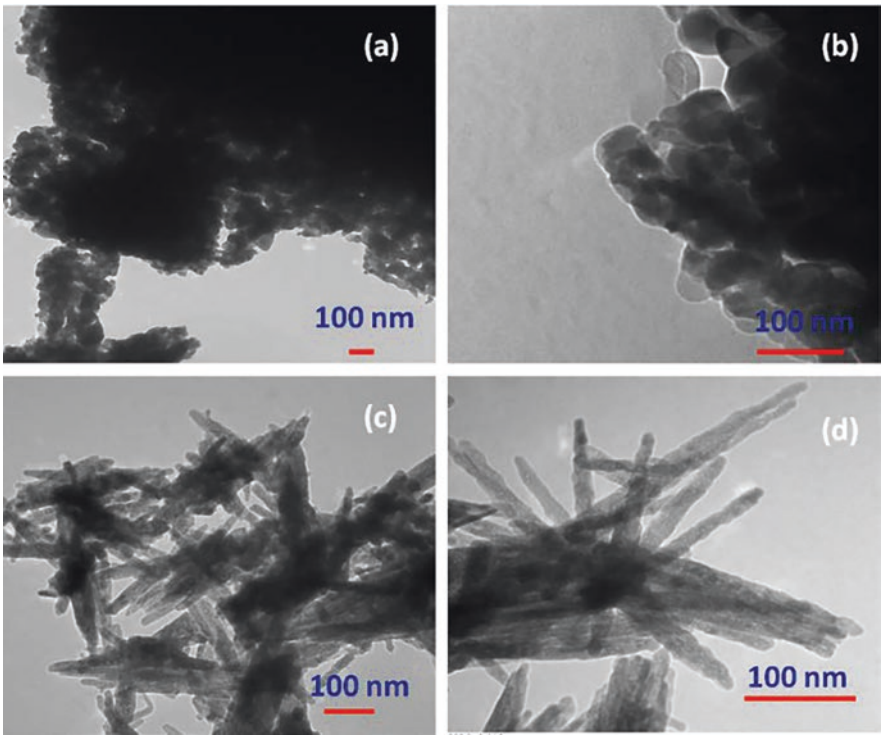

Fig. 5.3 TEM images indicating morphological variation of ZnO synthesized from precipitation-decomposition method (**a**, **b**) and physical grinding method (**c**, **d**) with different precursors

ZnOs were found to be 3.02 and 3.13, respectively, for ZnO obtained from precipitation-decomposition and physical grinding methods.

TiO_2 NP synthesized via sol-gel method and gelatin incorporation influenced the morphology as observed by corresponding FE-SEM images (Fig. 5.4a {sol-gel} and Fig. 5.4b {gelatin-assisted}). Morphology of TiO_2 was not much affected with addition of gelatin during synthesis. Both sol-gel-derived and gelatin-assisted TiO_2 yielded spherical-shaped particles. However, the variation in the BET surface area and pore size was observed (Krishnakumar et al. 2018).

SiO_2 prepared by a simple sol-gel method and gelatin-assisted Ni/SiO_2, ZnO-loaded SiO_2, and CdS-loaded SiO_2 were synthesized which revealed bare SiO_2 had spherical morphology from FESEM images (Fig. 5.5a–f) whose diameter was found to be between 400 and 500 nm. The particles were well separated and did not show aggregation (Fig. 5.5a) (Krishnakumar et al. 2017, 2019, 2020). Incorporation of Ni was carried out to the particles by the sol-gel method where the gelatin was dissolved in hot liquid and $Ni(NO_3)_2$. $6H_2O$ solutions were added resulting in the formation of the g-Ni/SiO_2 NP which was found to be aggregated (Fig. 5.5b). However, ZnO and CdS synthesized by similar route did not affect the shape of the SiO_2 particles, and the spherical-shaped were retained without aggregation (Figs. 5.5c–f).

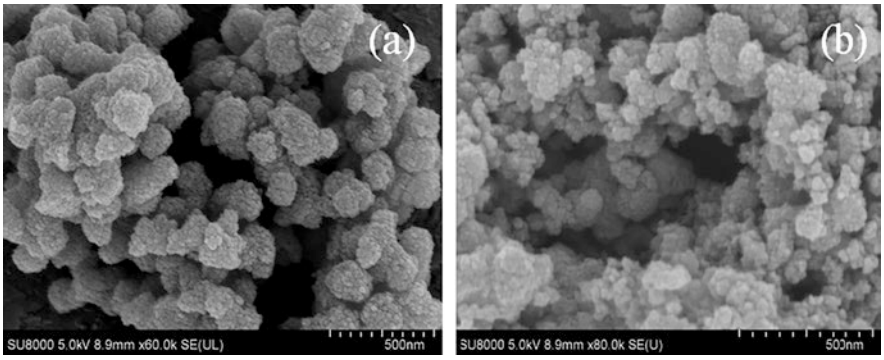

Fig. 5.4 FE-SEM images of (**a**) TiO_2 and (**b**) gelatin assisted TiO_2

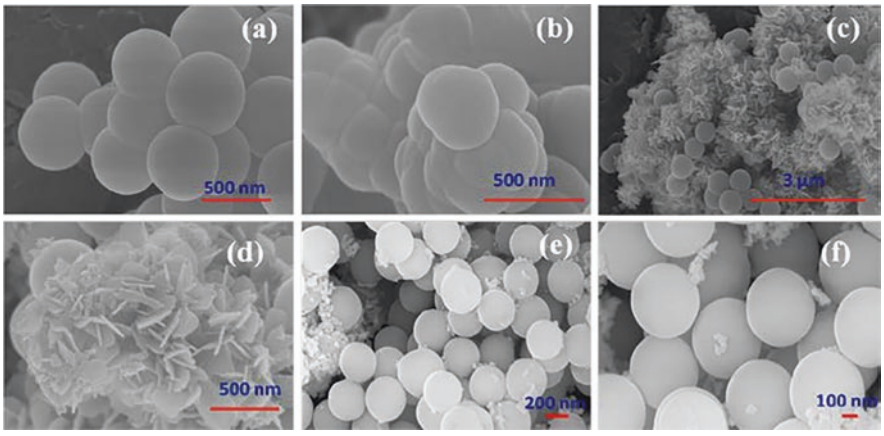

Fig. 5.5 FE-SEM images of (**a**) SiO_2, (**b**) g/Ni-SiO_2, (**c**, **d**) ZnO/SiO_2, and (**e**, **f**) CdS/SiO_2

Copper oxides (Fig. 5.6) are used as antimicrobial agents. The growth of CuO nanoparticles commencing from its salts, like nitrate and acetates, with ammoniacal solution via Cu-OH formation and decomposition is well described (Zhang et al. 2006). Different kinds of CuO structures, i.e., urchin-like and sheetlike, are obtained (Vaseem et al. 2008). The growth of urchin-like CuO structures is observed with the high alkaline solution of copper nitrate where the critical role of surfaces of the copper powder and a layer of copper hydroxide are correlated according to a chemical reaction $Cu(OH)_2 \rightarrow CuO + H_2O$.

Likewise, in the method of preparation as shown in Fig. 5.6, precursors and surfactant have tremendous influence on the morphology. Typical CuO nanomaterials grown with various precursors and surfactant are shown in Fig. 5.7. As precursor changes from $Cu(NO_3)_2$ in Fig. 5.7a to $Cu(CH_3COO)_2$ as in Fig. 5.7c, a visible change in the morphology was found. With the use of hexamine, an organic base, bitter gourd-type morphology with large small nanoparticles (Fig. 5.7b) develops

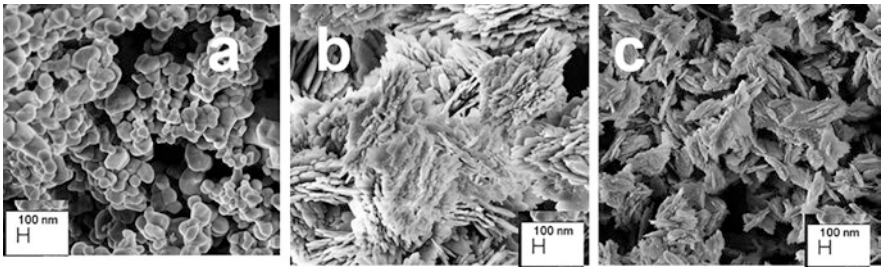

Fig. 5.6 FESEM of CuO nanomaterials. Clear demonstration of morphological variation from bulk (**a**) is found when a hydrothermal process at 100 °C (**b**) or a surfactant CTAB (**c**) is used

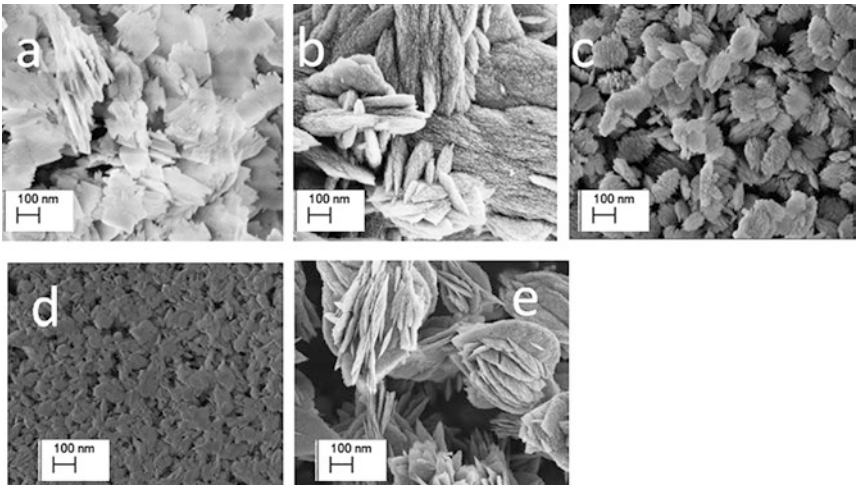

Fig. 5.7 FESEM images of CuO nanostructures arising due to change of precursor and surfactant

compared to the use of inorganic base, ammonia solution as shown in Fig. 5.7a where the morphology is more like snowflakes. In both cases, Cu $(NO_3)_2$ is used as starting material. Furthermore, the use of CTAB as a surfactant was found to impact morphology as seen in Fig. 5.7d, e where 1.0 M CTAB was added to starting materials for Fig. 5.7a, c, respectively. The above morphology links to growth of oriented attachments (Zhang et al. 2006; Vaseem et al. 2008).

In addition to size and shape, the growth processes influence crystal phase and can lead to different polymorphs. For instance, TiO_2 exhibits anatase and rutile crystal phases, and they differ strongly in physiochemical properties. Thus, controlled synthesis of particular phase is an important aspect to consider for an application. By using various solvents and surfactants, formation of crystals can be controlled. For instance, the lowest surface energy crystallographic facet {111} of Fe_2O_3 is predominantly obtained with no energy stabilizer, whereas surfactant-mediated growth provides other facets (Guo et al. 2015). Simple solvothermal reaction is found to yield $\alpha-Fe_2O_3$ rhombohedra with {104} facet by variation of water and 1−propanol solvent (Wang et al. 2010). Thus, it shows potential control on the

growth direction and crystallographic phase and hence the shape of the nanomaterials.

It is obvious to have large surfaces with decreasing size of nanoparticles which may facilitate improved applications. The physical and chemical properties are also drastically influenced when the size approaches below 10 nm. Such a quantum confinement size effect may take place as the particle size becomes equivalent to the Bohr's radius to cause a blue shift in the optical bandgap of the nanomaterials (Das and Jayaraman 2014; Deshmukh and Niederberger 2017). Moreover, large surfaces result in larger surface energy and surface defects rather than the counter bulk material. Prevalent defect states, such as oxygen or metal vacancies in SnO_2 or in CuO, offer new properties by influencing electronic structures (Das and Jayaraman 2014). Importantly, defects in SnO_2, TiO_2, or ZnO make them *n*-type semiconductors whereas CuO becomes a p-type semiconductor. At nanoscale, large defects inflict strongly a non-stoichiometric layer and influence the surface chemistry including possible leaching of ions from nanoparticles. Furthermore, shapes and crystallographic orientation with different surface energies can also affect surface reactivity. To preserve the surfaces for an application like antifouling becomes a significant step, as fabricating a coating may need other supporting material, like polymers. In the above context, material synthesis and their critical physical and chemical properties are of profound interest to resolve and correlate to a specific application. Most importantly, the morphology covering the size, shape, and crystallographic nature is grossly an important aspect to deduce. Very often, phase purity is done by X-ray diffraction study. In addition, simple Scherer's formula (Patterson 1939; Das and Jayaraman 2014; Bonu et al. 2019) allows determination of size which may further be supported by TEM or SEM images. Both later techniques are direct method to map the morphology, shape, and size of the nanoscale materials.

The precipitation method with 1 M $SnCl_4$ and NH_4OH allows the formation of ultrafine SnO_2 nanoparticles as shown in Fig. 5.3. These particles are equivalent to the Bohr exciton radius and show a blue shift to 4.4 eV from the bulk optical bandgap of 3.67 eV (Pradeep 2007; Bonu et al. 2019). Further, annealing those as-prepared quantum dots (QDs) at varied temperatures in the air atmosphere improves crystallite sizes as depicted in TEM images in Fig. 5.8. High-resolution TEM as an inset shown in Fig. 5.8 provides a d spacing value which supports the Rutile structure of the SnO_2 NPs.

5.4 Applications of Metal Oxide Nanoparticles

Among a plethora of nanoparticles (NPs), copper, silver, zinc, and titanium dioxide NP have been extensively used/applied due to their broad-spectrum antimicrobial activity (Brayner et al. 2006; Jones et al. 2008) and photocatalytic property (Norman et al. 2008; Aziz et al. 2015). As biofilm formation is a surface-associated phenomenon, protective coatings offer promise. This review limits to four oxide nanoparticles, viz., silver, copper, zinc, and titanium. Metal oxide nanoparticle (MON)

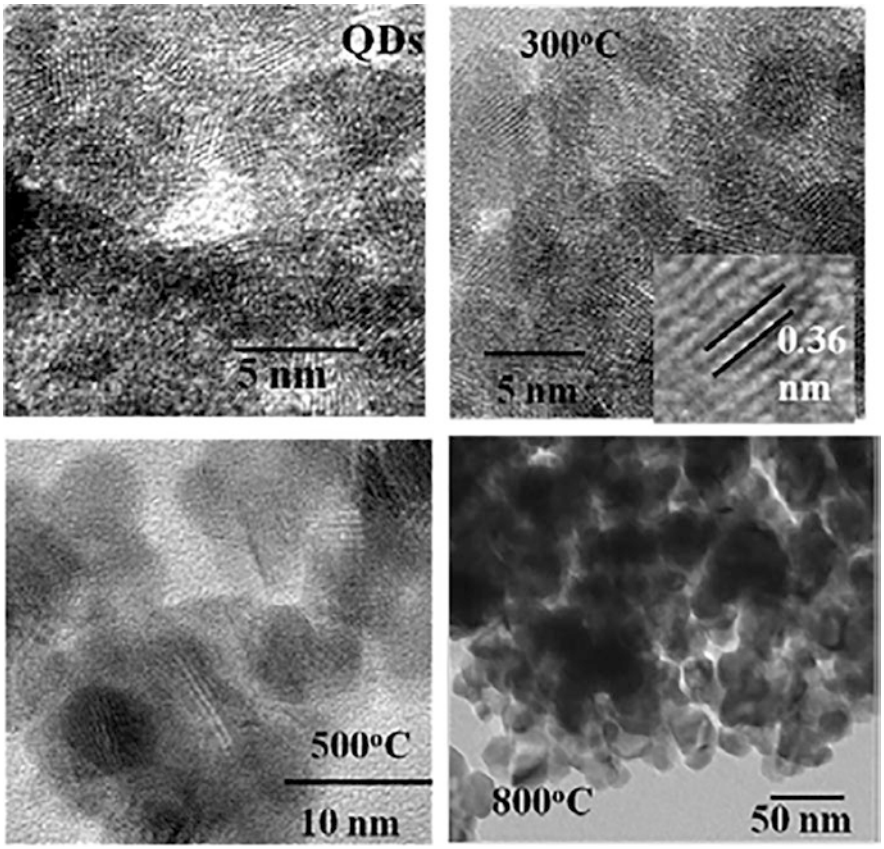

Fig. 5.8 Growth of SnO_2 from QDs to larger nanoparticles by annealing process

coatings find application for the protection of materials in biomedical devices (Stoica et al. 2017), reverse osmosis desalination membranes (Zunita et al. 2018), hospital equipment and biomedical implants (Khatoon et al. 2018), cancer treatment (Ren et al. 2015), biomedicine (Augustine and Hasan 2020) and public hygiene surfaces (Nikalova and Chavali 2019), coatings for food processing and storage equipment (Ogunsona et al. 2020), marine antifouling coatings (Natalia et al. 2012), and exterior protective coatings (Kaegi et al. 2008). In spite of significant improvements in the development of advanced functional coatings, challenges still exist due to the instability of metal oxide nanoparticles with respect to their size, shape, dispersion, aggregation, binding, interaction with polymer matrix, and release of metal ions (Rong et al. 2006; Anyaogu et al. 2008). Among the metal nanoparticles, silver (Ag), gold (Au), and zinc oxide (ZnO) have been extensively used in biomedical settings (Wong and Liu 2010). Qayyum and Khan (2016) have reviewed the antibiofilm activity of different MONs and have outlined the limitations in the application of MONs due to their toxicity concerns as a result of chemicals used during synthesis which are retained in the NP and have urged for developing more

eco-friendly methods for the synthesis of MONs. Silicon dioxide (SiO_2) and nanoclay (zeolites) have also demonstrated excellent antibiofilm properties and have been incorporated into polymer matrices. Single-walled carbon nanotube (SWCNT)-coated surfaces were found to inhibit initial bacterial growth and prevent biofilm maturation of the *E. coli* strain. However, as the biofilm matured, cells became less sensitive to the presence of SWCNT indicating a response similar to the antibiotic resistance which was attributed to the production of soluble exopolymeric substances (EPS) which mitigated the toxic effects of SWCNT (Rodrigues and Elimelech 2010). Interestingly cells without soluble EPS were susceptible and detached from biofilms compared to cells which produced soluble EPS which required a tenfold increase in concentration of SWCNT for inhibition.

5.5 Polymer Nanocomposites as Antibiofilm Agents

The concept of developing antimicrobial surfaces is paramount as bacteria live in biofilms. Metal oxide nanoparticles embedded in polymer matrixes offer release of toxic metal ions which have been demonstrated to inhibit either adhesion of microbial cells or contact killing of adsorbed cells on surfaces. In general ceramics, metal oxide-polymer and of late metal oxide-carbon (graphene oxide) nanocomposites have been developed with sol-gel blending, hydrogels, and in situ polymerization being the most preferred methods of synthesis of polymer NCs. Starting from simple biopolymers like starch, alginate, cellulose, carboxymethylcellulose, guar gum, gelatin, chitosan, polyhydroxyalkanoates, polyhydroxybutrate, poly-caprolactone, and poly-lactic acid to synthetic polymers like polyvinyl chloride (PVC), polyvinyl alcohol (PVA), polydimethylsiloxane (PDMS), polyurethane (PU), polyvinyl pyrrolidine (PVP), polymethylmethacrylate (PMMA), poly-sulfobetaine, poly(amide-imide), poly-vinylidenefluoride (PVDF), polyamide, polysulfone, polystyrene, polyethylene glycol (PEG), polyethylene, and polyisopropanol have all be used to develop metal oxide-polymer nanocomposites for antifouling and antibiofilm applications (Mallakpour et al. 2020). Polymers act as releasing agents which deliver biocides at the surface, and latest developments have resulted in smart antibacterial surfaces which are triggered with surface response. Nanoparticles act as nanofillers in a polymer matrix and are known to improve physical and mechanical strength as well (Fig. 5.9). Moreover, metal oxides or metals for antifouling application need a medium to deliver it suitably. In general, biocides including metal particles are embedded or loaded in a selective polymer by physical and chemical reactions (Sankar et al. 2015; Sathya et al. 2019; Salazar-Hernandez et al. 2019; Ruiz-Sanchez et al. 2020).

An ideal polymer nanocomposite matrix should not aggregate NP, have optimum loading of nanofillers (NPs), and retain the properties of nanoparticles (Chen and Gonsalves 1997). However, due to their high surface free energy, NPs bind strongly to other materials and to each other resulting in agglomeration (Klaus and Sigusch 2009). The strong binding features of NPs are advantageous in a polymer matrix;

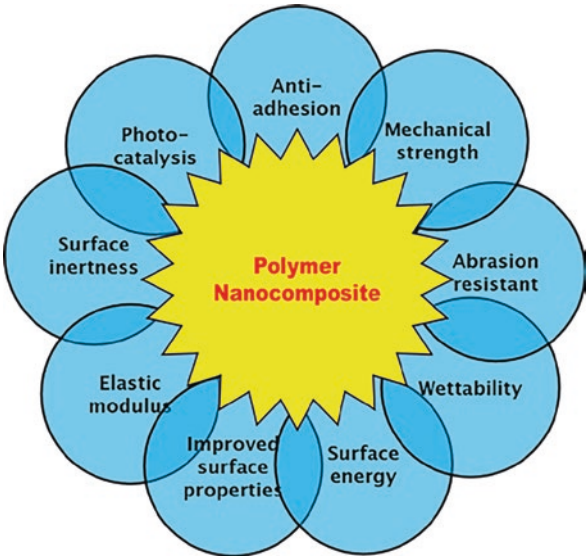

Fig. 5.9 Properties of polymer nanocomposites involved in antimicrobial/antifouling coatings

however, the agglomeration phenomenon affects its uniform dispersion in the polymer matrix. Extensive research has gone into nanoparticle dispersion in polymer matrix as NPs with high surface energy tend to agglomerate and the interaction of hydrophilic nanoparticles in a hydrophobic matrix results in weak interfacial interactions (Rong et al. 2006). Immobilization of nanoparticles into polymer matrix to develop polymer nanocomposites offers the best suitable surface protection strategy as antimicrobial surfaces.

In general, approaches toward developing antibiofilm/antifouling coatings involve (Fig. 5.10) (1) delivery of biocides (oxidizing, quaternammonium compounds-QAC), (2) delivery of antibiotics, (3) metal oxide nanoparticle MON-incorporated coatings for metal leaching and toxicity, (4) phytochemicals and essential oil based (5) polycation based (6) antimicrobial peptide based (AMP) (7) low surface energy & foul release polymeric coatings (PDMS and fluoropolymers) (8) micro / nano structured surface coatings (9) biomimetic coatings (10) superhydrophobic coatings (11) coatings based on quorum sensing inhibitors (12) enzyme based coatings (13) nitric oxide (NO) release coatings (14) sol-gel, hydrogel, xerogel, amphiphilic, zwitterionic coatings (15) photoactive coatings (16) slippery liquid infused surfaces (SLIPS) (Unal 2018).

5.5.1 Silver Nanoparticles

Silver nanoparticle (SNP/Ag_2O) with a bandgap of 1.46 eV has wide application and is the most investigated nanomaterial due to its broad biocompatibility (at low concentrations of Ag ions) and broad-spectrum antimicrobial activity ranging from bacteria, fungi, to virus and even multidrug-resistant strains such as

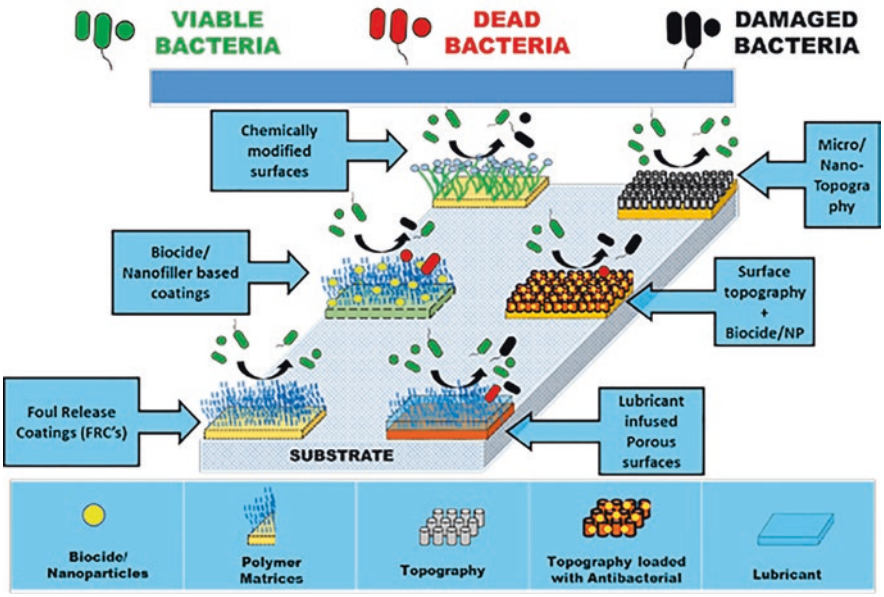

Fig. 5.10 Advancements in approaches toward antimicrobial/antifouling coatings

methicillin-resistant *Streptococcus aureus* (Pal et al. 2007). Silver nanoparticles with less than 100 nm are known to possess 10,000 to 15,000 atoms (Oberdoster et al. 2005). However, the extensive use of silver is still limited by its toxicity to humans, exerted by silver ions (Hamouda 2012). Very low concentrations of silver ions are not toxic, but high concentrations have been reported to exert cytotoxic effects. Nano silver toxicity is still to be clearly understood/established, and in vivo research is a priority area of concern (Chaloupka et al. 2010) for wider application.

Self-assembled monolayers of AgNP on glass surfaces prepared by amino-silanization exhibited strong antibiofilm activity against *S. epidermidis* RP62A which offers prolonged release and increased local release of Ag ions at the surface (Tagletti et al. 2014). A silver-tolerant strain of *Bacillus cereus* was able to produce SNP of ~17.51 nm by biosynthetic pathway which exhibited good antibacterial activity against MDR strains (Khan et al. 2020). Silver NP-loaded polyethylenimine and polyethersulfone membranes developed by electrospinning showed excellent antibiofilm as well as growth inhibition properties (Maziya et al. 2020).

Regarding the effective mechanism, for the well-studied Ag nanoparticles, it is postulated that the binding of Ag nanoparticles onto microbial cells alters their membranes and causes damage to cellular organ after penetrating the microbial cells and the dissolution of Ag nanoparticles releasing Ag+ ions for antimicrobial effects (Yael et al. 2017; Aziz et al. 2014, 2016, 2019). Obviously, release of ions, cell penetration, and toxicity of it will highly depend on the nature of nanomaterials which may have various shapes, crystallographic orientations, and sizes (D'Souza and Richards 2007; Fernandez-Garcia et al. 2004; Jeevanandam et al. 2018; Pradeep 2007; Abioye et al. 2019; Rao et al. 2007).

Small-sized/nano silver of 25 nm has found topical application in biomedical field. In addition, low concentrations as low as 1.69 μg/mL of SNP elicited good antibiofilm activity (Pal et al. 2007). Silver NP has been demonstrated to act against HIV virus at an early stage inhibiting its replication postentry into systems (Al-Jabri and Alenzi 2009) which makes it all the more an effective antimicrobial agent. Incorporation of silver in bone implants offers prophylactic properties (Stanic et al. 2011). The use of bimetallic NP like Ag-incorporated TiO_2 coatings showed excellent AB activity against dental bacterial strains of *S. mutans* and *Lactobacillus* sp. (Lv et al. 2019). The superior action of SNP is also influenced by its surface charge, wherein positively charged NPs have better electrostatic interaction with the predominantly negative charge of bacterial cells (Kim et al. 2007). Silver ions from SNPs are also known to generate ROS in bacterial species and interfere with cell respiration, DNA replication, and translation process (Joshi et al. 2018). Incorporation of silk fibroin into Ag_2O NP enhanced wound healing and improved antibiofilm activity (Babu et al. 2018). However, Tiller (2006) demonstrated that Ag NP embedded in polymer matrix poly (ethyleneimine) required 32 μg cm^{-2} Ag ions to inhibit *S. aureus* whereas Ag NP immobilized on glass surfaces by CVD process required 10 μg cm^{-2} to achieve similar levels of inhibition.

Several silver polymer composites have been developed exhibiting antimicrobial activity. Incorporation of Ag_2O into chitosan, a natural biopolymer, to develop a composite film has increased its antimicrobial properties and finds application in food packaging industries (Tripathi et al. 2011; Chausali et al. 2022). Photocatalytic antibacterial paper has been developed using Ag_2O incorporation into cellulose and graphite fibers (Chen and Liu 2016). Glass ionomer cements have been developed with silver nanoparticles with very low concentrations of 10 μg Ag capsules, reducing biofilm by 99% (Porter et al. 2020). Synthesis of Ag_2O by reducing/stabilizing agents like starch, dextran, polyvinylpyrrolidone, and β-cyclodextrin has been effective in inhibiting biofilms of common pathogenic strains (Bryaskova et al. 2011; Habash et al. 2014; Mohanty et al. 2012). A unique mechanism of action of SNP has been reported by Shrivastava et al. (2007) which involves modulating of cellular signaling activity by dephosphorylating tyrosine residues of peptides, inhibiting bacterial growth. Tyrosine phosphorylation of proteins has been shown to be involved in capsular and extracellular production of polysaccharides in both Gram-negative and Gram-positive bacterial strains (Grangeasse et al. 2003). The superior antibacterial activity of SNP may be due to the inactivation/interference with this signaling pathway.

5.5.2 Copper Oxide Nanoparticles

CuO NPs have wide application in environmental settings where it has been used as biocide for more than half a century. Copper oxide exists in two forms: as (1) copper oxide (CuO with bandgap of 1.21–1.55 eV) and (2) cuprous oxide (Cu_2O with bandgap of 2.2–2.25 eV), like silver depends on release of metal ions to impart toxicity

towards microbial cells. CuO is relatively a more stable MON with respect to its physical and chemical properties as well as cheap compared to silver and gold and blends well with most of the polymer matrices. In general, CuO NPs have been shown to develop as needles, nanoflowers, nanorods, and nanowires. CuO NP has been shown to possess broad-spectrum antibacterial activity with Cu_2O NP showing better antibacterial activity than CuO nanoparticles (Kumar et al. 2019). However, CuO have been shown to produce more hydroxyl radicals compared to Cu_2O nanoparticles (Meghana et al. 2015). CuO NP has also been shown to generate ROS with its electron donor nature. Copper oxide NP has been combined with antifungal agents like fluconazole for medication. Copper nanoparticles functionalized with acrylic monomers were found to be stabilized in the polymer backbone which exhibited better release rate of biocidal ions. Copper acrylate surfaces showed good antimicrobial activity which was not dependent on the concentration of the NP; viz., 1.0 wt% showed similar activity as 10% and 25%; however, higher loading resulted in enhanced release rates (Anyaogu et al. 2008).

Mallakpour et al. (2020) reviewed extensively about benign synthesis of CuO and applications of different CuO nanocomposites. Cuprous oxide nanocube on graphene oxide (0.5–2 nm) composite sheets synthesized by facile method was effective in inhibiting biofilms with low MIC values of 5.9, 2.9, and 2.929 μg/mL for *E. coli*, *P. aeruginosa*, and *B. subtilis*, respectively (Selim et al. 2020). Silver-copper-graphene oxide (Ag/Cu/GO) nanocomposites synthesized were effective against *Methylobacterium* sp., *Sphingomonas* sp., and *P. aeruginosa* at concentrations which were harmless to humans (Jang et al. 2020). Copper oxide-titanium dioxide nanocomposites synthesized by pulsed laser ablation technique were effective in inhibiting methicillin-resistant *S. aureus* and *P. aeruginosa* by damaging the cell membrane (Baig et al. 2020). Erci et al. (2020) demonstrated that biosynthesized CuO NP from leaf extracts also had higher cytotoxicity to mouse fibroblast L929, with antibiofilm activity against *S. aureus*. A limitation in the study was CuO NPs were effective only against Gram-positive bacteria. This again demonstrates the intrinsic mechanisms involved in action of NP vis-a-vis their synthesis methods and that cytotoxicity of biosynthesized NP also occurs.

5.5.3 Zinc Oxide Nanoparticles

Similar to copper, zinc oxide (a wide bandgap material 3.3 eV; binding energy of 60 meV) nanoparticles possess broad-spectrum antibacterial activity with less toxicity to humans as it is an essential trace element and is widely used in medicine, cosmetics, and wound healing (Antonijevic et al. 2019). Shape and size of ZnO NP influence the photocatalytic activity and hence extensive research into synthesis methods. Zinc oxide exists as wurtzite, cubic zinc, and cubic rock salt. Comparison of toxicity of different nanoparticles revealed high toxicity by $ZnO < CuO < TiO_2 < Co_3O_4$ in normal conditions and $ZnO < CuO < Co_3O_4 < TiO_2$ under light and dark conditions (Dasari et al. 2013). Mechanism of toxicity of ZnO

nanoparticles has been through contact-mediated killing as well as release of toxic metal ions (Li et al. 2011a, b) resulting in generation of ROS, oxidative stress (Dwivedi et al. 2014), cell membrane damage, alteration of membrane permeability (Sirelkhatim et al. 2015), and inactivation of biomolecules and enzymes resulting in cell death (Li et al. 2012). ZnO-PAM.Nc (polyacrylamide) developed by in situ emulsion polymerization technique showed broad-spectrum activity against bacteria and fungi (Morsi et al. 2016). Comparison of activity of different NPs, viz., MgO, TiO_2, CuO, and CeO_2, with ZnO on inhibition of biofilms of *S. aureus* strain RN6390 revealed high activity with ZnO NP (>50%) (Jones et al. 2008).

Zinc oxide is soluble and releases zinc ions, and the net positive charge on ZnO NPs acts on proteases of bacterial cell membrane affecting metabolism. $Zinc^{2+}$ ions have been found to inhibit biofilm formation of the bacterium *Bacillus amyloliquefaciens* FZB42 by suppression of the response regulator SPo0F (Huang et al. 2020). Photoactivation of ZnO releases e- during its transition from VB to CB and results in the formation of hole (hb) (He et al. 2014). The hb reacts with electrons and hydroxyl ions from water resulting in release of oxygen. Singlet oxygen is also a strong oxidant, and the formed OH ions react with nucleic acid, amino acids, proteins, and lipids of bacterial cell membrane. Similar to copper, zinc NP has also shown to exhibit a size-dependent activity with maximum activity observed with smaller-sized particles (3–10 nm). However, wire and rod-shaped ZnO NP has been shown to exert higher activity than spherical nanoparticles. Bare ZnO NP has been shown to exhibit higher antibacterial activity compared to capped nanoparticles (Datta et al. 2012). Carbon-stabilized ZnO showed 100% inhibition of biofilm formation of *S. aureus* and *P. aeruginosa* with loading of carbon to influence photocatalytic activity (Janani et al. 2020).

Enhanced antibiofilm activity was observed with incorporation of Ag into ZnO (Lu et al. 2008) which is attributed to the high positive charge on electroneutral Ag particles adhered on ZnO. The strong electrostatic interaction caused by exchange of electrons between Ag and ZnO as well as between positively charged Ag and negatively charged bacterial cells has been attributed to the enhanced antibiofilm activity. Similar mechanism has been observed with gold (Au) NP incorporation with ZnO which showed good antibacterial activity against *S. aureus*, whereas reduced toxicity to mouse fibroblast cells was observed (Khan et al. 2018). Oxidative stress has been attributed to cell death with Au-ZnO nanocomposites. Changing of bandgap of Au-ZnO composites by UV irradiation increases electron transfer and increases ROS generation (He et al. 2013) leading to increased antimicrobial activity. Low concentration of 0.05 mg/mL of photoactivated Au-ZnO was lethal to *S. aureus* and *E. coli* compared to plain ZnO which required three times the concentration for similar effect (Li et al. 2011a). Combining Cu NP with ZnO decreased survival rate of *E. coli* (3.12%) compared to plain NP, viz., ZnO (58.02%) and Cu (76.12%) (Nithya et al. 2015), which has been attributed to the increase of mesoporous property.

Doping is another mechanism to increase antimicrobial activity which is cost-effective and alters the material property. Mn doping of ZnO (Khan et al. 2017), Fe doping of ZnO (Basith et al. 2014), Ag doping of ZnO (Dutta et al. 2010), and Cu

and CuO doping of ZnO/polyaniline (Liang et al. 2012) have all shown good antimicrobial activity against different bacterial strains. Incorporation of organic molecules is another approach to increase AB property of ZnO. Chitosan with reactive OH- and $–NH_2$ groups binds with ZnO to form composites which have been used as bandage material (Kumar et al. 2012). Di(octyl)phosphinic acid-capped ZnO NP has been incorporated into silicone to reduce implant-related infection (Stefan et al. 2013). ZnO-chitosan with polyaniline and montmorillonite (Trivedi et al. 2014) and nano-ZnO bacterial cellulose (BC) (Dinca et al. 2018) have also shown good AB activity. ZnO-GO (Wang et al. 2014), ZnO-starch (Vigneshwaran et al. 2006), ZnO-SiO_2 (Barani and Hossein 2014), chitosan-ZnO (Malini 2015), PA6/ZnO (Erem et al. 2011), Ag-ZnO (Matai 2014), alginate-silica-ZnO (Ahmed et al. 2018), and ZnO-PMMA (Anzlovar et al. 2011) nanocomposites have all shown good antibacterial activity.

5.5.4 Titanium Dioxide Nanoparticles

Since the demonstration of water splitting ability of titanium dioxide (Fujishima and Honda 1972), TiO_2 has found applications in nanomedicine and nanobiotechnology, magnetic resonance imaging (Zeng et al. 2013); black TiO_2 as cancer photothermal therapeutic agents (Ren et al. 2015); photocatalytic, biocompatibility and low cytotoxicity (Mou et al. 2016); solar and electrochemical cells, wastewater treatment, food packaging technology, gas sensing, paints, cosmetics, paper production, hydrogen fuel generation, ink for printing, plastic manufacturing, self cleaning surfaces, antiseptics and antibacterial creams (Akakuru et al. 2020). Clearances by the US FDA for incorporation into domestic products like toothpastes, fillers in medicines – tablets and capsules – and dental pastes (Gomes et al. 2018; Skocaj et al. 2011) have increased TiO_2 applications. TiO_2 NP exists in nature in three forms, viz., rutile, anatase, and brookite, with maximum photocatalytic activity observed with the anatase form (Su et al. 2011; Pantaroto et al. 2018). Some of the features of TiO_2 like hydrophilicity, chemical inertness and stability, film transparency in the visible region (decrease in size from 200 to 10 nm and changes from opaque to transparency), and low oxygen absorption capability offering good corrosion resistance have made TiO_2 a more attractive material. In addition, TiO_2 has also been used as a coloring agent in paints (Manesh et al. 2018).

Titanium dioxide nanoparticles also exhibit a broad-spectrum antibacterial activity due to its photocatalytic properties which was first described by Matusunga et al. (1985). Titanium dioxide NP has been more effective against the MDR nosocomial pathogen *P. aeruginosa* isolated from endotracheal tract and bronchoalveolar regions at concentrations of 350 mg/mL by free radicals (Arora et al. 2015). TiO_2 NP has been effective against another nosocomial pathogen methicillin-resistant strain *S. aureus* which is known to form prolific biofilms on catheters causing bacteremia and pneumonia in the lungs (Jesline et al. 2015). Biofilms of these MDR strains produce EPS-containing nucleic acids and lipids which withstand the host

immune system as well as decrease the penetrating power of antibiotics resulting in less susceptibility of biofilm cells.

TiO_2 films have shown excellent antibiofilm properties against the three oral pathogens – *Streptococcus sanguinis*, *Actinomyces naeslundii*, and *Fusobacterium nucleatum* – with 99% inhibition on surfaces (Pantaroto et al. 2018). TiO_2 has been extensively applied in polymer matrix, doped with other MONs to improve its photocatalytic and antimicrobial properties (Gupta and Tripathi 2011). Synthesis of TiO_2 nanorods using near-infrared (NIR) source (808 nm) activation has been demonstrated as an effective strategy for killing of single species biofilms using the principle of photothermal therapy and photodynamic therapy. The mechanism of action of TiO_2 nanoparticles is found to be inactivation of coenzyme A; DNA damage induced by hydroxyl radicals; oxidative stress induced in cell membranes; reactive oxygen species generation, hyperthermia; singlet oxygen production; affect iron homeostasis; affect expression of genes involved in growth (Zhang et al. 2021; Akakuru et al. 2020).

5.5.5 *Control of Biofilm in Biomedical Settings and Implant Surfaces*

A prerequisite for an implant material apart from its functionality is to resist bacterial adhesion/colonization to prevent pathogenesis. Even with technological advancements, currently infection of implantable biomaterials still results in significant patient morbidity/mortality (Shah et al. 2013). Biofilm-associated infection of implant devices was reported as early as 1972 (Johanson 2013). Antibiotic resistance in implant-related infections is still a major problem to be circumvented, and this has triggered the search for alternate new materials to prevent biofilm-/biomaterial-associated infection (BAI) (Saldarriaga 2010). Orthopedic implants, nonvalvular cardiovascular stents, and urinary catheters are all prone to BAI. Surface modification of biomaterials through coatings offers protection. Different coating approaches have been tried, viz., use of low surface energy hydrophobic coatings (Everaert et al. 1998), polymer brushes (Norde and Gage 2004), zwitterionic coatings (Cheng et al. 2008), and positively charged coatings (Gottenbos et al. 2001; Roosjen et al. 2006) and use of quaternary ammonium compounds (QAC) (Tiller et al. 2001).

Orthopedic implant materials generally involve polymethyl methacrylate (PMMA), titanium and stainless steel, hydroxyapatite for a range of applications like bone cement, fixation devices, screws, osseointegrated implants for limb prosthesis. Gadd et al. (2012) reported PMMA to be highly fouled polymers followed by stainless steel and then titanium. PMMA implants have been shown to develop biofilms causing acute, chronic, and delayed infections (Trampuz and Zimmerli 2006; Minelli et al. 2011). Even antibiotic (vancomycin)-loaded PMMA has been observed to harbor biofilms with PMMA beads recovered from patients harboring

drug-resistant bacterial strains (Neut et al. 2001). Biofilm development on implant materials has been attributed to local bacterial flora along with genetic factors involved in attachment (Gadd et al. 2012). These findings have led to the development of concept of synthetic delivery vehicles for controlled and sustained release of antibiotics in implant materials. Titanium dioxide-nanostructured films have been effective in inhibiting biofilm formation *Listeria monocytogenes* a common oral /environmental pathogen by about 3 log reduction (Chorianopoulous et al. 2011).

Another osteoconductive material is hydroxyapatite (HAP), ($Ca_{10}(PO_4)_6(OH)_2$), similar in composition to the teeth and bone. *Staphylococcus aureus* is the most widespread pathogen on implants forming biofilms with other groups like *Streptococci*, *E. coli*, *Pseudomonas* sp., and *Enterobacter* sp. Zinc has been demonstrated to increase osteogenesis by promoting osteoblast cell proliferation and differentiation (Mourino et al. 2011). Zinc oxide nanoparticles have been classified as *generally recognized as safe* by the US FDA, which is a broad-spectrum antimicrobial compound (Espitia et al. 2016). ZnO-loaded hydroxyapatite composites were evaluated for antibiofilm efficacy against *S. aureus* and *E. coli* which exhibited ~52–54% inhibition (Beyene and Ghosh 2019).

For over two decades, antibiotic-loaded carrier biodegradable polymers like poly(lactic-co-glycolic acid) (PLGA), poly(e-caprolactone) (PCL), and poly(DL-lactic acid) (PLA) (Shi et al. 2010) have been the workhorse for surface modification of implant materials and antimicrobial coatings. Modification of PCL polymers as fine fibers by electrospinning, microcapsules and microspheres to improve their ability to deliver antibiotics in a controlled and sustained manner; preserve the bioactivity of the antibiotic; and release of the total volume of the antibiotic yielding better results (Shi et al. 2010; Huang et al. 2006). Alteration to morphology of PMMA as PMMA beads showed better antibiotic release lasting in time scale of several weeks (Shi et al. 2010). To this effect, a coaxial spun collagen with PLA carrier gentamicin was able to release antibiotics over a 2-week period (Torres-Giner et al. 2011). Synthesis of novel quaternized chitosan derivate (hydroxypropyltrimethyl ammonium chloride chitosan, HACC) demonstrated strong antibiofilm properties against *S. epidermidis* (Tan et al. 2012). Similarly polyethylene oxide coatings developed on glass surfaces using silyl ether bonds were also effective in preventing adhesion of *S. epidermidis* (Roosjen et al. 2005).

Adsorption of cationic molecules on biomaterial surfaces offers favorable sites for bacterial colonization (Cheng et al. 2008). Hence surface modification of implant material with polyethylene glycol (PEG) has demonstrated extensive anti-adhesive property to biomaterials by inhibiting deposition of plasma proteins (Park et al. 1998). Further improvements to PEG coatings are zwitterionic coatings which possess both positive and negative charges with an overall neutral charge balance. Zwitterionic surfaces created by grafting silver nanoparticles into poly (sulfobetaine methacrylate) (pSBMA) and poly (carboxybetaine methacrylate) (pCBMA) polymer matrix demonstrated killing of bacteria upon contact and releasing dead bacteria (Hu et al. 2013). Further enhancement of killing and release of microorganisms upon contact (smart switching) was achieved by poly (N, N-dimethylN-(ethoxycarbonylmethyl)-N-[2′-(methacryloyloxy) ethyl] – ammonium bromide)

(pCBMA-1 C2, cationic precursor) which were able to kill 99.8% of *E. coli* strains upon contact, and 98% of the cells were released by hydrolysis of cationic derivatives to nonfouling zwitterionic polymers (Cheng et al. 2008).

In comparison with MONs, magnesium fluoride (MgF_2) nanoparticle (25 nm)-coated surfaces were effective in inhibiting adhesion of *S. aureus* and *E. coli* strains. The nanoparticles were also reported to penetrate cell membranes and alter membrane potential, reactive oxygen species (ROS) generation, and binding to DNA (Lellouche et al. 2009) parallel to mechanisms reported for MONs. Antimicrobial property of fluorides is well known as well as their mechanistic activity on microbial cells. Metal fluoride complexes of aluminum and beryllium cations have been demonstrated to interact with F-ATPases and nitrogenase enzymes (Sturr and Marquis 1990), disrupt proton movement across the cell due to formation of HF (Guha-Chowdhury et al. 1997a), and inhibit enzymes like enolase involved in the glycolytic pathway by a complex form of F^- and Mg^2+ (Guha-chowdhury et al. 1997b).

Novel antibiotic-free hydrogels have been developed as wound dressing materials (Zhong et al. 2020). Antibiofilm fabrics have been developed using small molecules and Au nanoparticles using sonochemical techniques which have displayed efficient biofilm inhibition of multidrug-resistant bacteria (Wang et al. 2020). Novel nano-enabled surfaces coated with ZnO or ZnO/Ag composites have exhibited enhanced antibiofilm activity against *S. aureus*, *E. coli*, and *C. albicans* (Rosenberg et al. 2020). Such surfaces find application in high touch surfaces in hospital and medical settings. Sputter coating of catheter materials with silver-copper films reduced biofilm formation by *P. aeruginosa* (McLean et al. 1993). Coating of silver on polyurethane catheters inhibited biofilm formation (Jansen et al. 1994). Similarly ion beam implantation of silver on catheters reduced their susceptibility to biofilm formation (Davenas et al. 2002). Smart polymer surfaces of polypropylene-grafted polyacrylic acid (PP-gPAAc) loaded with antibiotic vancomycin inhibited MRSA biofilm formation (Munoz-Munoz et al. 2009). A significant development is the self-sterilizing materials for intravenous catheters using NIR carbon dots (CD) exhibiting broad-spectrum antimicrobial activity (Mauro et al. 2020). Novel chitosan hydrogels incorporating Ag NP and antibiotic ampicillin have inhibited the formation of biofilms of *Enterococcus faecium* and *S. epidermidis* with a tenfold increased concentration required to inhibit beta-lactamase-positive *E. cloacae* (Lopez-Carrizales et al. 2020).

Magnesium oxide (MgO) and calcium oxide (CaO) nanoparticles comprising of essential elements of magnesium and calcium have extensive application in repair of dental tissues and in dental care (Milosevic 1991). Both these nanoparticles hydrolyze to their hydroxide forms in the presence of water and have strong antibacterial activity due to strong alkaline nature, generation of ROS, and adsorption to bacterial cell membranes. The high pH values of 10.4 generated by $Mg(OH)_2$ and 12.5 by $Ca(OH)_2$ have a cascading effect on microbial cells. This was demonstrated by Dong et al. (2010) wherein *E. coli* cells were not affected by pH of 10 in LB medium whereas in the presence of both these hydroxide particles tested individually at the same pH of 10, the organisms succumbed. High alkaline conditions

disrupt structural proteins in bacterial cell membranes, and in contrast to other MONs, CaO and MgO do release Mg^{2+} and Ca^{2+} ions, which do not impart any toxicity. In fact low concentration of Mg^{2+} and Ca^{2+} ions promote biofilm. An important feature is that CaO NPs have been used as drug delivery agents and chemotherapeutic agents due to their unique structural and optical properties (Meghana et al. 2015). Aluminum oxide NP has been shown to inhibit EPS production and reduced biofilm formation by 50% of MDR *Acinetobacter baumannii* (Muzammil et al. 2020). Combination of selenium and iron oxide NP incorporated into chitosan coatings with pentasodium triphosphate as cross-linker yielded excellent antibiofilm activity as well as less toxicity to human dermal fibroblast cells (Li et al. 2020).

5.5.6 Control of Oral Biofilms by Polymer Nanocomposites

Biocompatibility is an issue in the use of nanoparticles in biomaterials and human medicine. Primitively silver nitrate was the most common disinfectant used in dental surgery for the prevention of dental caries. However, silver and titanium NPs have found wide applications in control of biofilms within the oral cavity and are now used as topically applied agents in dental materials (Hamouda 2012). Ag NP demonstrated strong antibacterial activity with 25-fold lower growths compared to the mouthwash chlorhexidine with little influence of silica and titanium dioxide nanoparticles on the oral pathogen *Streptococcus mutans* (Besinis et al. 2014). *S. mutans* and *S. lactobacilli* are known to colonize dentine, enamel and soft tissues, and prosthetic materials, producing acids resulting in dental carries and damage to the hard tissue. This has resulted in incorporating antimicrobial property to dental materials, viz., filling materials, cements, and sealants orthodontic adhesives (Ahn et al. 2009). Lee et al. (2008) demonstrated superior antimicrobial activity of low concentrations of silver-zinc-zeolite incorporation into polymethyl methacrylate (PMMA), used for tissue conditioners, acrylic resins, denture bases, and orthodontic appliances. Silver-zeolite, powdered zinc citrate/acetate, and titanium dioxide have all been incorporated into mouth rinses and toothpastes as whiteners and plaque control agents (Allaker 2010; Boldyryera et al. 2005; Giertsen 2004).

5.6 Mechanism of Antibacterial Action of MONs

The primary mechanism of action of MONs (Fig. 5.11) is by (1) adsorption to the cell membrane and mechanical damage of cell wall, (2) internalization into cytoplasm, (3) release of metal ions, (4) generation of reactive nitrogen species, (5) oxidative stress by ROS generation, and (6) binding with DNA (Ren et al. 2020). Each of these mechanisms may act independently or in synergy to bring about toxicity. MONs have been effective in penetrating thick and simple cell wall of $Gram^{+}$ (20–80 nm) as well as thin and multilayered (peptidoglycan and

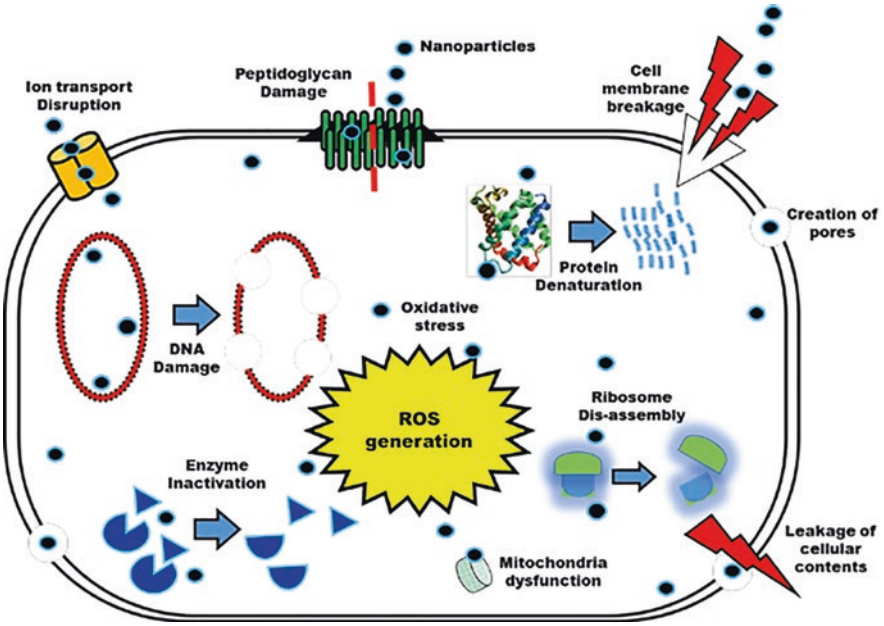

Fig. 5.11 Mechanism of action and toxicity of metal oxide nanoparticles to bacterial cells

lipopolysaccharides) cell walls of Gram⁻ (10–15 nm) bacteria. Mechanism of adsorption of MONs on bacterial cell membrane and its lysis occurs by electrostatic interactions of positively charged MONs with the predominantly negatively charged bacterial (due to teichoic acids in Gram⁺ and lipopolysaccharides in Gram⁻) cell surface (Silhavy et al. 2020). MONs have other advantages; along with adsorption to cell membranes, they also release cationic ions (Beyth et al. 2015) into the media which get further internalized into the cytosol increasing their toxicity.

Bacterial cell membrane provides structural integrity apart from performing functions like transport of solutes, ions, and stimuli and transduction of signals (Gold et al. 2018). Lysis of cell membrane results in leaking of intracellular water from cytosol which actively triggers the proton efflux pumps and electron transport system. Imbalances in ionic composition due to cell lysis impair respiration and gradually result in cell death (Pelgrift and Friedman 2013). Metal ions released from CuO, Ag_2O, TiO_2, and ZnO NP have all been found to bind to thiol groups (-SH), amino groups (-NH), carboxylic groups (-COOH) of cell wall proteins, change in membrane permeability, degradation of lipopolysacchrides, denaturation of proteins, destruction of lipids, cytochrome enzymes, DNA in the cytosol causing homeostatic imbalances. Some bacterial strains have exhibited tolerance to high levels of metal ions like Cu^{++} which was demonstrated by Padmavathi et al. (2017) for a marine strain, *Staphylococcus lentus*, which was not inhibited in the presence of 1000 μg/mL of Cu. Interestingly, concentration of 100 μg/mL of copper ions enhanced biofilm formation, compared to controls. The increased metal ion

tolerance of these bacteria can be attributed to Cu ion efflux pumps, repression of genes, adaptation to Cu ion stress, and plasmid-mediated resistance. Alternatively Cu NPs have also been demonstrated to inhibit antibiotic efflux pumps imparting resistance to bacteria in biofilms. Concentrations as low as 0.065 mM NP showed efflux inhibition of wild-type *S. aureus* and *P. aeruginosa* with less inhibition of efflux pumps in MRSA drug-resistant strain of *S. aureus* (Christena et al. 2015).

In general exogenous events (Bogdan et al. 2015) like binding of MONs to cell membranes and endogenous influx of metal ions have both been associated with the production of reactive oxygen species (ROS) by a Fenton reaction (Sperandio et al. 2013) attributing to antimicrobial activity (Ezraty et al. 2017) and no respite from resistance mechanism (Rout et al. 2017). ROS moieties include hydrogen peroxide (H_2O_2), free radicals such as hydroxyl (OH) and singlet oxygen (O_2), and superoxide ions (O_2^-) among which hydroxyl and singlet oxygen are the most toxic and not neutralized by intracellular enzymes (Ezraty et al. 2017). Hydroxyl radicals with a high oxidation potential of 2.8 V act on proteins, carbohydrates, lipids, and nucleic acids (Stanic and Tanaskovic 2020). Photosensitive MONs like TiO_2, ZnO, CuO, SiO_2, MgO, and Fe_2O_3 have been demonstrated to produce ROS by photo irradiation and UV spectrum absorption due to recombination of electron-hole pairs (Chen et al. 2014, 2018). The mechanism of photocatalytic action is by excitation of electrons from the valence band (VB) to the conduction band (CB) to produce photoexcited electrons (e^-) and an electronic hole (h^+) resulting in an electronic hole pair (e^-/h^+). Smaller-sized particles have increased bandgap energies with enhanced redox potential with photogenerated electrons and holes resulting in enhanced antibacterial activity compared to larger-sized particles.

ROS moieties impact cell membrane, protein, DNA, and electron transport chain and cause oxidative damage to membrane lipids, viz., polyunsaturated fatty acids and phospholipids of membranes (lipid peroxidation). Lipid peroxidation occurs by removal of hydrogen atom from the lipid by the hydroxyl radical resulting in the formation of a lipid radical. The lipid radical reacts with oxygen to form lipid peroxyl radical. The peroxyl radical interacts with biomolecules to form lipid hydroperoxides which in the presence of Fe^{2+} ions results in the formation of alkoxy radicals (Stanic and Tanaskovic 2020). Lipid peroxidation increases membrane fluidity and damages cell integrity. ROS moieties act on membrane proteins oxidizing amino acids, impairing membrane permeability leading to cell death (Cabiscol et al. 2000). ROS acts on nucleic acids by oxidation of double-stranded DNA breaking their backbone and adduction of base pairs and sugar groups (Kim et al. 2013).

5.7 Conclusions

The surge in synthesis and testing of different metal oxide nanoparticles (MONs) arose due to inactivity of conventional antibiotics toward MDR strains and need for combating biofilms in different applications. Significant improvements have been achieved in synthesis protocols, control over morphology, techniques to increase

solubility, and dispersal and understanding of mechanism of action on microbes. Nanoparticle size and dispersion are important parameters influencing activity. The primary reason behind the use of MONs is their nano configuration which aids in mechanical damage to cells, release of ions imparting toxicity, and oxidative stress. Further Cu, Ag, and Zn ions at trace levels are required for organisms and are toxic at higher concentrations. Silver, zinc, and titanium dioxide NPs have transformed from in vitro experimentation to in situ application in biomedical field as implant coatings, antibiotic carriers, and wound dressing agents. Silver has been extensively used in cosmetics and equipment/high touch surfaces in public hygiene due to its certain degree of biocompatibility. CuO finds wide application for biofilm control in industrial settings like reverse osmosis membranes and antifouling coatings. In comparison, TiO_2 finds application as fillers in paint coatings for exterior protection. Fe_2O_3 has applications in biomedical imaging with MgO and CaO finding application in dental settings. However, the cytotoxicity of MONs is a cause of concern which hinders its wide application. However encapsulation and incorporation into polymer matrices have been used as a delivery system wherein the leaching of toxic metal ions at the polymer surface has been exploited and achieved success. However, release of metal ions from NP and depletion of NP with time in polymer matrix render the surfaces benign to microbial colonization. MONs have become a success in marine antifouling coatings, desalination membranes, and antibacterial coatings for public hygiene; however, their in situ use in human medicine is hindered by their residual toxicity caused by long-term accumulation (chronic toxicity) in the skin and internal organs. In general, qualification of new drugs/modification of existing certified devices/disinfectant formulations/antimicrobial nanocomposites depends on two criteria, viz., 1) demonstrating higher efficacy than existing technology for a particular application and 2) that the new product is safer. It is here that research on MONs needs to focus on developing MONs with low MIC values (1–5 μg/L) to minimize environmental toxicity and cytotoxicity. Currently MIC concentration range from 10 μg/mL to 300 μg/mL is reported in the literature for various NPs. To achieve this, synthesis methods should be fine-tuned to obtain NP in the size range of 1–10 nm. Biosynthesized NP in this range is a boon. Lower sizes have been achieved by quantum dots which have immediately found application in imaging and drug delivery. Next clinical safety-related studies should be initiated with potential MONs for successful realization as products.

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Chapter 6
Nanomaterials for A431 Epidermoid Carcinoma Treatment

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6.1 Introduction

One of the most unique fields in today's cutting-edge science is nanotechnology. Nanoparticles show proof of inventive or upgraded properties dependent on their exact uniqueness, for example, measurement, distribution, and surface. Nanotechnology involves blends, delineation, investigation, and apparatus of nano-sized (1–100 nm) materials (Ayyanar and Ignacimuthu 2009). It includes the materials whose structures reveal significantly novel and upgraded physical, substance, and organic properties, wonders, and usefulness due to their nano-scale size. Nanotechnology has an interesting part in contemporary history, with plentiful strategies to join nanoparticles of circumspect shape and size contingent upon explicit necessities. New uses of nanoparticles and nonmaterials are expanding quickly. The idea of nanotechnology was introduced in 1959 by Richard Feynman, who gave a discussion on the idea of nanotechnology. He explained how sub-atomic machines worked with nuclear accuracy and talked about nanoparticles in a lecture titled "There's plenty of room at the bottom." The clinical condition was completely changed in the 1960s, considering the truth that nanoparticles could go about as medication and in addition be utilized as antibodies. The primary paper distributed in 1980 by K. Eric Drexler of Space Systems Laboratory, Massachusetts Institute of Technology was titled "A way to deal with the improvement of general abilities for atomic control." The expression "nanotechnology" was first time utilized as a logical field by Nario Tanigushi in his 1974 paper "Nanotechnology" that for the most part comprises the handling of, partition, union, and distortion of materials by one iota or one atom (Zhang and Zhang 2013).

Nanoscience is the science dependent on nanoparticles whose size is 1–100 nanometers similar to iota's and atoms. Polymers and their subunits together with

nanoscale go about as bio-macromolecules. Nanoscience can be characterized in a progressively consistent way as:

The future holds incredible breadth for organizations fabricating "nanoproducts," which are to beutilized for humanity advances. Nanoparticles are nano sized, and some are easily created and amicable. Nanoparticles are incorporated in three ways: physical, compound, and organic (Jemal et al. 2006). In synthetic blends, an extraordinary measure of nanoparticles are relied upon and the compound substances utilized for the combination and the steady condition of nanoparticles are harmful and non-eco agreeable. The requirement for ecological non-harmful manufactured conventions for nanoparticle combinations prompts enthusiasm for organic methodologies, which eliminate the utilization of toxic synthetic substances as a result. In this way, there is an expanding interest for "green nanotechnology" (Zhao et al. 2015). There are a few reports where a wide assortment of organic substances ranging from amino acids to living microorganisms have been utilized to accomplish this goal.

Plants are the best wellspring of creating nanoparticles. Moreover, utilizing plant extracts likewise decreases the sticker price of confinement of microorganisms and culture media affecting the cost of nanoparticles amalgamation by microorganisms. Part of the esteemed methodology is utilized to save microbial societies. There are different verdures used by specialists and botanists to orchestrate nanoparticles in the organic way, and their concentrates are used as medication. Some plants as well as some microbial species are likewise used to blend nanoparticles, and they are *Fusarium oxysporum, Penicillium* sp. also, microbes, for example, *Bacillus subtilis*. The amalgamation of nanoparticles by methods using plant extracts are the largest part of the strategy for green, biological production of nanoparticles, and furthermore has the uncommon advantage that the plants are widely scattered, easily accessible, a lot more secure to hold and proceed as a premise of various metabolites (Suriyavathana and Kumar 2010). Some of the restorative plants used to execute the blend of nanoparticles are *Oryza sativa, Helianthus annus, Saccharum officinarum, Sorghum bicolour, Zea mays, Basella alba, Aloe Vera, Capsicum annuum, Magnolia kobus, Medicago sativa (Alfalfa), Cinnamomum camphora,* and *Geranium sp.* Pharmaceutical and natural businesses utilize these nanoparticles.

Currently, plants assume an effective job in incorporating silver nanoparticles. In spite of the fact that there are numerous courses accessible for the combination of silver nanoparticles, the natural blend utilizing plant sources offers a few favorable circumstances, for example, best in cost-viability, non-harmful, and eco-accommodating specialist. Silver nanoparticles have a variety of utilizations in vitro and in vivo. Historically, silver has been proven as an antimicrobial operator that destroys pathogenic microorganisms. A plethora of vegetation has been utilized to integrate metal nanoparticles. Because silver is a sensitive white, glossy part, a basic use of silver nanoparticles is to give a thing a silver coating. In any case, the strikingly strong antimicrobial development is the genuine bearing for progression of nano-silver things. Cases are sustenance packaging materials and food supplements,

smell safe materials, equipment, family machines, magnificence care items and remedial advices, water disinfectants, and room showers. Silver is one of the fundamental parts that make up our planet. It is a remarkable, yet naturally occurring part, to some degree harder than gold and outstandingly adaptable and malleable. Unadulterated silver has the high electrical and warm conductivity and has the least contact obstruction. Silver can be accessible in three differing oxidation states: AgO, Ag^{2+}, Ag^{+}. Metallic silver it is insoluble in water, but metallic salts, for instance, $AgNO_3$ and AgCl, are dissolvable in water. Metallic silver is used for prosthesis and supports, fungicides, and coinage. Dissolvable silver blends, for instance, silver salts, have been used to treat afflictions, such as epilepsy, nicotine development, gastroenteritis, and diseases, including syphilis and gonorrhea. Assessments have shown that these groupings of Ag^{+} particles are too low to have a harmful quality. Metallic silver appears to pose an inconsequential danger to prosperity, while dissolvable silver could cause troublesome effects. Owing to the wide arrangement of uses, silver can have presentation through various courses of area into the body. Ingestion is the basic course of entry for silver blends and colloidal silver proteins. Dietary confirmation of silver is surveyed at 70–90 μg/day. Silver in any form is not believed to be perilous to the vulnerable, cardiovascular, nervous, or regenerative structure and it is not believed to be malignancy causing, as such silver is reasonably non-toxic. Silver solicitations will most likely ascend as silver finds new uses, particularly in materials, plastics, and remedial endeavors, changing the case of silver release as these progressions and things diffuse through the overall economy.

6.1.1 Grouping of Nanoparticles

Nanoparticles are grouped by their temperament, measurement, and viability. They are used as medication carriers or imaging specialists in biomedical applications. The characterization of nanoparticles is important to determine their possible applications, and to this end procedures from materials science are used, such as X-beam photoelectron spectroscopy (XPS), electron microscopy (TEM, SEM), nuclear constrain microscopy (AFM), powder X-beam diffractrometry (XRD), bright obvious spectroscopy, Fourier change infrared spectroscopy (FTIR), dynamic light dispersing (DLS), grid helped laser desorption time of light mass spectrometry (MALDI-TOF), and particular surface range and a high division of surface iota's are the qualities of metallic nanoparticles. Because of the extraordinary physicochemical characteristics of nanoparticles, including synergist activity, optical properties, electronic properties, antibacterial properties, and alluring properties, they are receiving attention from scientist to use in novel procedures (Sukirtha et al. 2012a).

The amalgamation of metal and semiconductor nanoparticles is an incredible region of exploration because of its potential applications, which were realized in the progression of novel advances. Nano-crystalline silver particles have found enormous applications in the fields of high influence capacity biomolecular

acknowledgment, diagnostics, antimicrobials, therapeutics, catalysis, and scaled down scale devices. Regardless, there is still a necessity for a fiscally viable and nonpolluting course to coordinate the silver nanoparticles. Nanotechnology is one of the exceptional domains of examination in the current field of materials science. Nanoparticles demonstrate absolutely new or improved properties, for instance, size, transport, and morphology of the particles. Novel uses of nanoparticles and nonmaterials are rising rapidly in various fields. Silver is prominent for having an inhibitory effect toward various bacterial strains and microorganisms commonly shown in restorative and mechanical systems. In drugs, silver and silver nanoparticles have a bountiful application, including skin medicines and creams containing silver to hinder defilement of burns and open wounds, restorative devices, and supplements masterminded with silver-impregnated polymers. In the material business, silver-embedded surfaces are used as a piece of shaking gear. Nanoparticles can be joined using various systems, including creation, physical, and natural. However, an engineered procedure for amalgamation requires a short period of time for association of a broad measure of nanoparticles; this methodology requires beating agents for size alteration of the nanoparticles. Synthetic concoctions used for nanoparticles amalgamation and alteration are unsafe and sometimes non eco-friendly. The necessity for normal non-noxious builds for nanoparticles prompts the use of natural techniques that avoid the use of deadly synthetic substances. As such, there is an extending enthusiasm for green nanotechnology. Moreover, using plants lessens the expense of microorganism's disengagement and culture media, improving the cost centered feasibility over nanoparticles mix by microorganisms (Alam et al. 2011). Various natural procedures for both extracellular and intracellular nanoparticles mixtures have been represented to date using microorganisms, including minuscule creatures, parasites, and plants. To a great extent, the amalgamation of nanoparticles using various plants and their concentrates can be good over other common association techniques that incorporate the amazingly mind-boggling procedure of maintaining microbial social orders. A mix of nanoparticles using plant concentrates is the most understood procedure for green, eco-obliging formation of nanoparticles and has a remarkably favored point of view because the plants are comprehensively cycled, easily available, secure to manage and a wellspring of a couple of metabolites.

There has also been a couple of examinations performed on the mix of silver nanoparticles using restorative plants, for instance, *Oryza sativa, Helianthus annus, Saccharum officinarum,*and *Sorghum bicolour, Zea mays* (Sukirtha et al. 2012b), in the field of pharmaceutical applications and natural organizations. In addition, a green association of silver nanoparticles using a methanolic concentrate of *Eucalyptus hybrida* was also investigated. Silver nanoparticles have been incorporated from naturally occurring sources, including green tea (*Camellia sinensis*), Neem (*A. indica*), leguminous bush (*Sesbania drummondii*), distinctive leaf stock, trademark versatile, starch, Aloe Vera plant extract, lemongrass leaves extract, etc. (Jung et al. 2014). With respect to the microorganisms, the silver nanoparticles become joined to the cell divider, as such disturbing the permeability of cell divider and cell breath. The nanoparticles may in like manner invade some place inside the cell divider, inducing cell injury by interfacing with phosphorus and sulfur

containing blends, for instance, DNA and protein, shown inside the cell. In addition, the intensity of the antibacterial effects is dependent on the proportion of the nanoparticles. The smaller particles have higher antibacterial activities because of the practically identical silver mass substance (Panhwar and Abro 2007).

6.1.2 Types of Nanoparticles

Nanoparticles can be widely collected into categories, normal nanoparticles, which fuse carbon nanoparticles (fullerenes), while a part of the inorganic nanoparticles fuse appealing nanoparticles, fair metal nanoparticles (such as gold and silver), and semi-transmitter nanoparticles (such as titanium oxide and zinc oxide). There is a demand for inorganic nanoparticles, for example, of noteworthy metal nanoparticles (gold and silver), as they give overwhelming material properties utilitarian adaptability. As a result of their size, segments, and focal points over available compound imaging drug administrators and prescriptions, inorganic particles have been assessed as likely gadgets for helpful imaging and furthermore to treat ailments. Inorganic nanomaterials have been comprehensively used for cell movement in light of their adaptable components such as wide openness, rich convenience, extraordinary similitude, and capacity of centered drug transport and controlled appearance of medications (Bernal et al. 2010).

6.1.3 Properties of Nanoparticles

The closeness of a high segment of iotas establishing the nanoparticles on the particle surface rather than in the atom and the huge surface range available per unit volume of the material is the best result for the nanoparticles. Both of these properties increase in significance with a decrease in particle size. Consequently, the unique physical, manufactured, and natural properties of nanoparticles start from these two segments. Quantum effects of some nanoscale materials occur, considering different captivating applications (Liu 2004). The colossal specific surface zone of nanoparticles includes the beginning stage of a portion of their novel applications. Catalysis is updated by the high surface range per unit volume and the homogenous allotment of nanoparticles. Regardless, high surface regions provide a strong relationship between the nanoparticles and the solid system wherein they may be united. The platelet morphology and gigantic specific surface areas of silicate nanoparticles improve the limit properties of polymer films by massively growing the pathway for a nuclear vehicle of invading substances (Tang et al. 2006).

6.2 Cancer and Its History

Malignant growth is a class of sicknesses caused by uncontrolled division of cells and the capacity of these cells to attack different tissues, either by direct development into nearby tissue through intrusion or by implantation into remote locales by metastasis. Metastasis is characterized as the phase where malignant growth cells are moved through the circulatory system or lymphatic framework. Cancer may influence individuals at all ages; however, chance will, in general, increase with age because DNA damage is progressively evident in maturing DNA.

The oldest depictions of malignant growth are found in the Edwin Smith Papyrus (referenced a breast tumor), composed in roughly 3000 BC, and the Ebers Papyrus, dating to 1500 BC (referenced a delicate tissue tumor and diseases of the stomach, uterus, skin, and rectum). Until the nineteenth century, blades, salts, searing, and arsenic glue were utilized by the Egyptians to treat tumors. The Indians and Chinese relied upon homegrown medication, including metals such as iron, mercury, and copper in different structures for over 3000 years. Hippocrates (460–375 BC), the father of medicine utilized the expressions "carcinoma" and "carcinos," which in Greek signified "crab." He and his followers had immense information about the various sorts of shallow and deep carcinomas and utilized different moisturizers, searing methods, and deep tumors were extracted with a blade. He thought about a range of treatments from palliative medicines to removal of breast and colon malignancies (Akhani et al. 2008).

Aulus Celsus (25 BC–AD 50), a Roman doctor, in his book De Medicina wrote about diseases of the spleen, liver, colon, and stomach and suggested early medical procedures. He made an interpretation of carcinos to the Latin word disease. Pliny the Roman (AD 23–79), in Materia Medica gathered different solutions for inner use. His solution of a boiled blend of ocean crabs, egg white, nectar, and powdered hawk defecation was generally valued. Aretaeus (AD 81–138) additionally gave a detailed depiction about different diseases. Galen (AD 130–200) is notable for the humoral hypothesis and numerous unyielding speculations (Ribeiro et al. 2010).

Lanfranc (1252–1315) established French medical procedure. Henri de Mondeville (1260–1320) and Guy de Chauliac (1300–1368), two French doctors, dismissed the old Galen hypotheses, prompting headways in treatment of malignant growth. Paracelsus (1493–1541) presented chemotherapy by directing different metals such as lead, zinc, copper, arsenic, and so forth for ingestion. The mid-1900s demonstrated advances in chemotherapy, distinguishing proof of natural cancer-causing agents, impact of hormones in disease, performing mammography, ID of DNA, and so forth. From 1970 onwards, much accentuation was given to malignant growth research, which prompted distinguishing proof of oncogenes, tumor silencers, and infections causing disease. Different screening techniques were created such as MRI (attractive reverberation imaging), tomography, immunohistochemistry, and so on. The campaign against neoplasia has served to effectively treat and

decrease malignancy mortality, which has been conceivable because of the discoveries and commitments made by doctors, specialists, and a multidisciplinary setting, including scientists, oncologists, radiologists, and so forth (Ankanna et al. 2010).

6.2.1 Epidemiology

For malignant growth, the study of disease transmission is the investigation of the frequency of malignancy as an approach to gather potential patterns and causes. The main such reason for malignant growth was distinguished by British specialist Percivall Pott, who found in 1775 that malignancy of the scrotum was a typical ailment among smokestack cleaners. In some Western nations, for example, the USA and the UK, malignant growth is overwhelming cardiovascular disease as the main source of death. In numerous developing nations, malignancy rate (to the extent that this can be estimated) shows up lower, in all probability as a result of the higher mortality rates because of irresistible sickness or injury, with the expanded command over jungle fever and tuberculosis in some developing nations, frequency of disease is expected to rise; this is termed epidemiologic progress in epidemiological phrasing. For malignant growth, the study of disease transmission intently reflects the chance to calculate spread in different nations. Hepatocellular carcinoma (liver cancer) is uncommon in the West; however, it is the fundamental malignant growth in China and neighboring nations, in all likelihood because of the endemic nearness of hepatitis B and aflatoxin in that populace. Also, with tobacco smoking becoming progressively normal in different developing nations, lungs malignant growth rates have expanded in an equal manner (Ankanna et al. 2010).

6.2.2 Cancer and Its Classifications

Malignant growths are grouped by the sort of cells that look like the tumor, and hence the tissue that was the starting point of the tumor. The accompanying general classes are normally acknowledged. (1) Carcinoma – Malignant tumors formed in epithelial cells. This gathering speaks to the most widely recognized diseases, including the basic types of breast, prostate, lung, and colon malignancies. (2) Lymphoma and Leukemia – Malignant tumors formed in blood and bone marrow cells. (3) Sarcoma – Malignant tumors formed in connective tissue or mesenchymal cells. (4) Mesothelioma – Tumors formed in the mesothelial cells coating the peritoneum and the pleura. (5) Glioma – Tumors formed in glia, the most widely recognized sort of synapse. (6) Germinoma – Tumors formed in germ cells, regularly found in the gonad and ovary. (7) Choriocarcinoma – Malignant tumors formed in

the placenta. Carcinogenesis, which implies the commencement or age of malignancy, is the procedure of derangement of the pace of cell division because of damage to DNA. A wide range of malignant growth shares these characteristics (Hanahan and Weinberg 2000a).

Proto-oncogenes are qualities that advance cells development and mitosis, a procedure of cell division, and tumor silencer qualities demoralize cells development, or incidentally end cell division and thus DNA changes to these qualities are required before a typical cell changes into a malignant growth cell. Proto-oncogenes advance cell development through an assortment of ways. Many can create hormones, a chemical messenger between cells that empowers mitosis, the impact of which relies upon the sign transduction of the accepting tissue or cells. Some are liable for the sign transduction framework and sign receptors in cells and tissues themselves, in this way controlling the affectability toward such hormones (Burkill 2004; Hanahan and Weinberg 2000b). They frequently produce mitogens, or they are associated with interpretation of DNA in protein blend, which makes the proteins and catalysts responsible for creating the components advanced biochemical cells utilize and interface with. Changes in proto-oncogenes can alter their appearances and capacity, expanding the sum or action of the component protein. At the point when this occurs, they become oncogenes, and in this manner, cells have a higher opportunity to partition exorbitantly and wildly. The possibility of malignancy cannot be diminished by expelling proto-oncogenes from the genome because they are essential for development and homeostasis of the body (Hanahan and Weinberg 2000b; Suffiness and Pezzuto 1990). Tumor silencer qualities code for hostile to expansion singles and proteins that stifle mitosis and cell development. For the most part, tumor silencers are translation factors that are actuated by cell stress or DNA damage. Frequently, DNA damage will cause the nearness of free-drifting hereditary material just as different signals and will trigger proteins and pathways that lead to the initiation of tumor silencer qualities. The elements of such qualities are to capture the movement of the cell cycle to complete the DNA fix, keeping transformations from being given to daughter cells. Accepted tumor silencers incorporate the p53 protein, which is an interpretation factor initiated by numerous cell stressors, including hypoxia and UV radiation damage. The Warburg impact is the particular utilization of glycolysis for vitality to support disease development. p53 has been shown to control movement from the respiratory to the glycolytic pathway (Emerich and Thanos 2006). Amalgamation of cytochrome c oxidase 2 (SCO2) has been perceived as the downstream middleman of this impact. SCO2 is essential for directing the cytochrome c oxidase complex inside the mitochondria, and p53 can disturb the SCO2 quality p53 guideline of SCO2 and mitochondrial breath may give a potential clarification to the Warburg impact (Brooks et al. 1998). Through complex correspondence between the tumor cells, stromal cells and its microenvironment, tumor cells can attack and metastasize (Chandran et al. 2006).

6.3 Nanotherapuetics to Overcome Cancer

A significant reason for mortality overall is malignant growth. Malignant growth is one of the most widely recognized issues and genuine medical problems worldwide. It has been seen that more than one out of three individuals will develop some type of malignancy during their lifetime. An assortment of starting points for disease exist, for example, thyroid, prostate, bladder disease, kidney malignancy, pancreatic, breast malignant growth, melanoma, leukemia, oral, colon rectal malignancy, and so on. When cells duplicate and develop rapidly, shaping dangerous tumors and attacking nearby parts of the body, it is called malignant growth. A total remedy for this malady is yet to be found to date. Various techniques have been utilized in the past three decades by scientists and clinicians, but often they only forestall or hinder the development of disease (Chandran et al. 2006). The most widely recognized sorts to treat malignant growth are radiation, chemotherapy, medical procedure, immunotherapy, and photodynamic treatment. Medical procedure is for the most part (Altankov and Groth 1994) used to deal with and to break down the disease if there should arise an occurrence of any neoplasm overwhelmingly when the malignancy has not metastasized to lymph nodes or different parts of the body. Elimination of malignant growth cells by damaging their DNA with vitality radiation is a commonly used technique in radiation treatment. This treatment utilizes the host's own resistant framework to help battle disease and is called immunotherapy (Fabricant and Farnsworth 2001).

In photodynamic treatment, extraordinary medications, called photosensitizing agents, are utilized alongside light to destroy disease cells. According to the substance structure and instrument by which they act, they can be separated into four gatherings: (i) Alkalyting specialists, which damage DNA to forestall the development of malignant growth cells. (ii) Anti-metabolites, which meddle with the replication of DNA or translation of RNA by subbing the ordinary structure squares of RNA and DNA and from this time forward can cause standard cell cycle capture. (iii) Antitumor anti-infection agents, which incorporate anthracycline sactinomycin–D. (iv) Plant alkaloids obtained from regular items are mitotic inhibitors that stop mitosis and thereafter hinder the development of the cell cycle. To avoid the issues related to the abovementioned treatments, as of late, researchers have turned to nanoparticles, which can be utilized as targeted medication conveyance for disease treatment where the malignant growth cells will be annihilated instead of normal cells. More significant than fixing is the counteraction of malignancy. We realize that 80% of all tumors are related with lifestyle causes, such as smoking, biting tobacco, dietary substances, alcohol use, radiation, working environment exposure, drugs, and so forth. Cancer is an extensive issue that can involve early discovery, remedial measures, recovery of the patient, and mental issues monitored by a patient and their family members (Cho et al. 2005).

A superior method to wipe out an issue is to wipe out the reason. Nanotechnology is as an impressive means to treat malignant growth. Nanotechnology incorporates promising outcomes to decimate disease cells with insignificant harm to ordinary

cells and organs, and furthermore to wipe out the malignant growth cells before they move up to the tumor. Bismuth nanoparticles have been researched and shown to amass radiation utilized in radiation treatment to treat malignant growth. The specific properties of diseases can be targeted by nanoparticles. An overabundant admission of folic corrosive may likewise secure the malignant growth development. The study of nanotechnology relies upon the way capacities change in an unexpected way when things are at nano-scale (Brooks et al. 1998).

6.4 Epidermoid Carcinoma (Skin Cancer)

Skin disease is a dangerous development on the skin that for the most part forms in the epidermis of the skin. Because of its development in the peripheral layer of the skin, it is effectively discernible in the beginning phases. Skin malignant growths are the fastest developing kind of tumors in the United States. More than one million Americans are determined to have skin malignancy yearly. There are three sorts of skin malignant growth, each of which is named after the kind of skin cell it emerges from. The first is basal cell carcinoma, which emerges from the basal cell. The subsequent one is squamous cell carcinoma also called epidermoid carcinoma, which are thin, flat cells that look like fish scales under a magnifying lens. The third kind is referred to as melanoma, which is the most dangerous type of skin malignant growth since it spreads rapidly all through the body (Habbal et al. 2011a). The word squamous is derived from the Latin word squama, which implies the size of a serpent or fish. They are likewise found in the lining of the hollow organs of the body, the respiratory and digestive tracts. The beginning phases of this carcinoma are named actinic keratosis. They show up as red unpleasant bumps on the face, ears, scalp, and rear of the hands. Men are more consistently affected than women. The manifestation causes changes of the skin that do not heal, staining, ulcers in the skin, and changes in existing moles. Exposure to UV light is a typical reason for skin damage, which is a significant reason for skin malignant growth in people. Constant non-healing wounds, particularly burns or ulcers dependent on their appearance, form into epidermoid carcinoma (Brooks et al. 1998; Dai and Mumper 2010).

The biomimetic properties of nanoparticles are utilized in location, counteraction, and in the treatment of oncologic sicknesses. Nanoparticles can also help to improve the ineffectively water-solvent medications, bioavailability, decreasing immunogenicity, and to lessen sedate digestion. The use of nanoparticles as medications and their objective toward malignant growth cells expands the viability of the particular treatment of disease cells while leaving the solid cells inert. Metastasized (epidermoid carcinoma) usually leads to a 90% chance of death within 5 years. In epidermoid carcinoma treatment, nano medication conveyance is a help. Because of their typical metabolic exercises, all plants can be used to produce synthetic substances. The phytochemicals obtained from plants are separated into two essential metabolites, incorporating sugars and fats, and optional metabolites are mixes that

are found in small scale in plants but have high explicit capacities. They are helpful and financially inexpensive. The bioactive substances present in therapeutic plants are utilized in the treatment of numerous human ailments. When contrasting with advanced medications, the conventional or homegrown medication is generally less expensive (Zhang et al. 2008; Wang and Chen 2011; Roy et al. 2021).

Skin tumors usually occur in the epidermis (the uttermost layer of skin), and appear as clearly unquestionable areas. This makes most skin developments distinguishable in the beginning phases, which is in contrast to that of other tumors such as those beginning in the lung, pancreas, and stomach, where only a small minority of those affected can eradicate the disease. Skin malignancies are the fastest developing kind of tumors in the United States. Skin tumors are the most common danger, beating lung, chest, colorectal, and prostate development. More than one million Americans are determined to have skin sickness yearly. The yearly rates of a wide range of skin tumors are growing each year, creating an open concern. It has been evaluated that almost half of all Americans who live to age 65 will have a skin malady at least once.

6.4.1 Sorts of Skin Growth

Skin growth is of three sorts, each of which is named after the kind of skin cell emerges from. The first being basal cell carcinoma, which emerges from the basal cell. Second is squamous cell carcinoma (as also called epidermoid carcinoma) that emerges from the squamous cells, which are thin, level cells that look like fish scales under a magnifying instrument. These two are the most widely recognized types of skin disease. Together, these two are additionally alluded to as non-melanoma skin growths. The third sort is called melanoma, which is the most dangerous type of skin malignancy since it tends to spread (metastasize) all through the body rapidly (Daniel 2006).

6.4.2 Basal Cell Carcinoma

Basal cell carcinoma is the most frequent tumor among white people. Progression of basal cell carcinoma is due to the interaction between genes and the environment, especially uv irradiation. Several genes have been associated with basal cell carcinoma development. A basal cell carcinoma patient has increased risk of developing further skin cancers (Eg: malignant melanoma, squamous cell carcinoma as well as non-cutaneous malignancies). Increasing and repeated occurrence of basal cell carcinoma in affected individuals make them an imperative community health predicament. Treatment of basal cell carcinoma includes different forms of surgery, radiotherapy, photodynamic therapy, topical fluorouracil, and imiquimod.

6.4.3 Squamous Cell Carcinoma (Epidermoid Carcinoma)

It begins in the squamous cells, which are thin, flat cells that look like fish scales under a magnifying lens. The word squamous is derived from the Latin squama, signifying "the size of a fish or snake" because of the nearness of the cells. Squamous cells are found in the tissue that structures the outside of the skin, the lining of the hollow organs of the body, the respiratory and digestive tracts. Therefore, squamous cell carcinomas can develop in any of these tissues. Men are affected more consistently than women. The timeliest sort of squamous cell carcinoma is called actinic (or sun-based) keratosis. Actinic keratoses appear as unpleasant red bumps on the scalp, face, ears, and back of the hands. They often appear on mottled, sun-damaged skin. They can be sore and sensitive, in relation to the degree of their appearance. In a patient with actinic keratoses, the rate at which one such keratosis may further develop in the skin into a squamous cell carcinoma is found to be approximately 10–20% over 10 years, but it may take less time. An actinic keratosis that quickly becomes obviously thicker raises the concern that it may have changed into a prominent squamous cell carcinoma (Bernal et al. 2010).

6.4.4 Melanoma

Melanoma is the most dangerous kind of skin tumors. If it is seen and treated early, it is approximately 100% reparable. If it is not, the danger can advance and spread to various parts of the body, where it ends up being hard to treat and can be deadly. While it is not the most common of the skin developments, it causes the highest mortality. Melanoma is an undermining tumor that starts in melanocytes, the cells which make the pigment melanin that tone our skin, hair, and eyes. Regardless, some melanomas are skin-concealed, pink, red, purple, and blue or white (Hu et al. 2009).

6.4.5 Signs and Side Effects of Skin Disease

There is a collection of different skin ailment reactions. These include changes in the skin that do not retouch, ulcers in the skin, recoloring, and changes in existing moles.

- Basal cell carcinoma typically looks like a raised, smooth, eminent bump on the sun-exposed skin of the head, neck, or shoulders. Rarely little veins can be seen inside the tumor. Crusting and leaking in the point of convergence of the tumor routinely occurs. It is often stirred up by an irritated area that does not recover.

- Squamous cell carcinoma (SCC) is typically a red, scaling, thickened spot on sun-exposed skin. Ulceration and depleting may occur. When SCC is not dealt with, it may form into an immense mass.
- Most melanomas are darker to dull looking injuries. Signs that may indicate a perilous melanoma include change in size, shape, concealing, or tallness of a mole, the nearness of another mole during adulthood, or new pain, shivering, ulceration or death.

6.4.6 Chance Elements Prompting Skin Growth

Exposure to UV light is common cause of skin damage and the main reason behind skin threat in individuals. Effects of UV light include burns from the sun, aggravation, erythema, immunosupression, DNA damage, and apoptosis; in any case, the epidermal damage caused by extreme UV exposure will disappear within a few weeks. Never-ending or repetitive prolonged exposure to UV light on the other hand, can provoke photoaging and skin threat. In the scope of UV light, UVB and less significantly UVA are involved in the improvement of skin infection (Altankov and Groth 1994). Chronic non-repairing wounds, especially burns, are called Marjolin's ulcers considering their appearance, and can form into squamous cell carcinoma.

Genetic tendency, including "Inherent Melanocytic Nevi Syndrome" (CMNS) is depicted by the proximity of "nevi" or moles of fluctuating size that either appear at or inside a half year of birth. Nevi greater than (3/4″) in size are likely to become harmful. Skin tumor is one of the feasible dangers of significant germicidal light.

6.4.7 Treatment of Skin Tumor

Most skin malignances can be dealt with by excision of the injury, ensuring that the (edges) are free of the tumor cells. These surgical extractions give the best cure to both early and high-chance illness (Djeridane et al. 2006).

6.4.8 Curettage and Drying Up

Dermatologists as often as possible use this technique, which contains scooping out the basal cell carcinoma by using a spoon-like instrument, called a curette. Evaporating is the additional use of an electric flow to control depleting and eliminate the remainder of the development cells. The skin repairs without sewing. This framework is generally suitable for small tumors in non-basic reaches, for instance, the capacity compartment and cutoff points (Matsuo et al. 2005).

6.4.9 Radiation Treatment

Specialists regularly utilize radiation medicines for skin disease occurring in regions that are hard to treat with surgery. A decent restorative outcome often requires 25 to 30 treatment sessions.

6.4.10 Cryosurgery

A few specialists can accomplish great outcomes by solidifying basal cell carcinomas. Commonly, liquid nitrogen is connected to the development to stop and eliminate the anomalous cells.

6.4.11 Therapeutic Treatment

It uses creams that attack tumor cells (5-Fluorouracil- – 5-FU, Efudex, Fluoroplex) or brace the invulnerable system. These are used a couple of times every week for a brief period. They can cause irritation. The advantages of this procedure are that it avoids medical procedure, allows the patient to perform treatment at home, and may give an unrivaled helpful result, weighed against inconvenience and a lower fix rate, which makes clinical treatment unsuitable for treating most skin malignancies on the face. If disease has spread (metastasized) further, chemotherapy may be required. Analysts have recently been coordinating preliminaries on what they have named "safe getting ready." This treatment is still in its beginning phases, but has been shown to suitably deter dangers such as contaminations and lock onto and attack skin malignancies. Even more starting, recently researchers have focused their undertakings on fortifying the body's own regularly delivered "assistant T cells" that recognize and jolt onto damaged cells and help control the killer cells to the disease. Researchers pervaded patients with approximately 5 billion of the associate T cells with no harsh meds or chemotherapy. This sort of treatment whenever demonstrated to be convincing has no side effects and could change the manner in which malignant growth patients are managed. The probability of metastasis makes it essential to break down squamous cell carcinomas early and treat them thoroughly (Singh and Lillard Jr. 2009).

6.4.12 MTT Assay for Skin cancer Cell Lines Using Green Synthesis of Nanoparticles

In the MTT test, test samples were enhanced as 2X convergence of the cell in 100 µl volume and the amounts were: 1000, 100, 10, 1.0, 0.1 µg/ml. Because the mixes are solvent in the medium, the mixes are diminished a reasonable amount

and broke up in DMSO and extra weakening were in the media when 100 µl of stock was added to the cell. The dishes were helper brooded for 48 h in the CO_2 incubator. MTT arrangement was 3-(4,5-dimethylthiazol-2-yl)- 2,5-diphenyl tetrazolium bromide (MTT) at 5 mg/ml in phosphate supported saline (1.5 mM KH_2PO_4, 6.5 mM Na_2HPO_4, 137 mM NaCl, 2.7 mM KCl; pH 7.4), from this arrangement 50 µl was pipette out into each well to achieve 1 mg/ml. The dish was also incubated for 2.30 h in an incubator and the medium was deliberately tapped. The formazan gems were air dried in a desolate spot and broke up in 100 µl DMSO, and the plates were gently shaken at room temperature and the OD was determined utilizing Synergy HT smaller scale plate pore at 570 nm. From the optical densities, the rate developments were expected with the accompanying recipe:

$$\text{Rate growth} = 100 \times \left[\left(T - T_0 \right) / \left(C - T_0 \right) \right]$$

On the off chance that T is more noteworthy than or equivalent to T_0, and if T is under T_0,

$$\text{Rate development} = 100 \times \left[\left(T - T_0 \right) / T_0 \right)],$$

where T is the optical thickness of test,

C is the optical thickness of control, and

T_0 is the optical thickness at time zero.

From the rate developments a portion reaction bend was produced and GI50 values were introduced as of the development bends.

In cell imaging, the preliminary compound of every fixation was made in quadruplicate and combined variety was maintained under 20% among the information targets. Three arrangements of the cell lines were tried in a 96 well plate as portrayed in the under 96 well organization. The test mixes displayed unrivaled cytotoxicity/anticancer activity in both cell lines used. Test sample extract showed high cell development restraint displayed great hindrance in A431 cell lines. RPM indicated the GI50 territory of 9.2 µg/ml as a target in the A431 cell line. The result delineates with the end goal of the cytotoxic impacts of biosynthesized AgNPs more noteworthy than before within the sight of the concentrate on malignancy cell line. These deeds can be applied to the mixes in the concentrate that improved the activity of the AgNPs.

Immovability of AgNPs can be applied to preserver these mixes in the wrapping of nanoparticles. The biosynthesized AgNPs were separated from the concentrate, and their anticancer impacts were inspected. In this investigation, the anticancer exercises of biosynthesized AgNPs were contrasted. As seen in the convergence of AgNPs in blepharis maderaspatensis, cytotoxicity in A431 cells was more

noteworthy than previously. The IG50 estimation of disengaged AgNPs in the concentrate was 64.4 and 9.2 µg/ml. Biosynthesized AgNPs could partake in a basic errand in cultivating their bioavailability similar to remedial applications in illnesses such as malignant growth. This investigation exhibits the chance of utilizing AgNPs to slow the development of malignant growth cells and their cytotoxicity for pending remedial medicines, and offers another strategy to fight different ailments, for example, disease, arthritis, and neovascularization. The test samples have been tried in the MTT test for the cytotoxic potential in A431 cell line. The concentrate displayed superb anticancer action comparable to SNP. The test samples in SNP and concentrates showed a G150 of 64.4 and 9.2 µg in A431 cell line. This concentrate restraint is powerful and groundbreaking; furthermore, the test samples can be taken for other anticancer examinations, including apoptosis and cell cycle examination to find the component of cell development hindrance/cytotoxicity (Aziz et al. 2019). Silver nanoparticles are synthesized by using three routes physical, chemical, and biological, but the biological route plays a vital role because it is eco-friendly in nature (Prasad 2014; Prasad et al. 2016, 2018, 2020; Srivastava et al. 2021), as shown in Fig. 6.1.

The skin cancer detection has the following steps (as shown in Fig. 6.2): the image input, preprocessing by median filter, segmentation of cluster ring cells, extraction of features, detection of them, and then post processing.

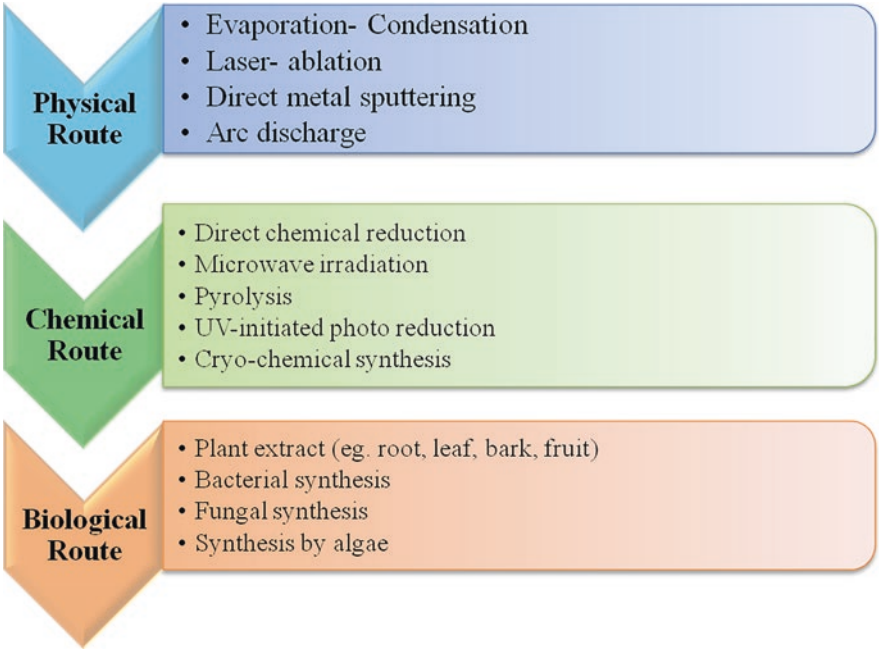

Fig. 6.1 Different routes of AgNps synthesis

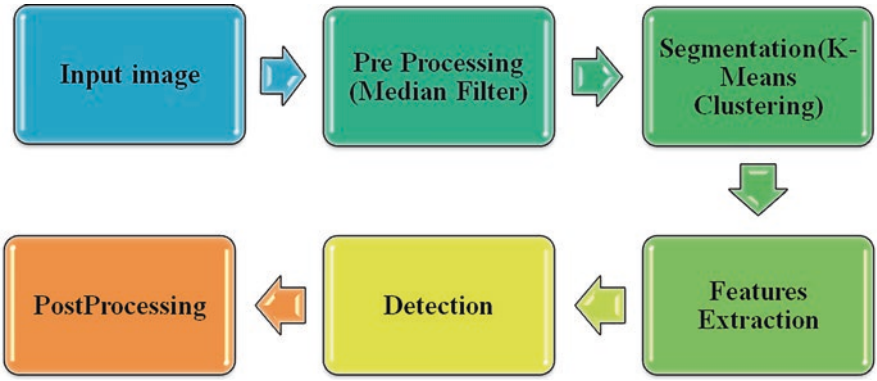

Fig. 6.2 Flow chart of skin cancer detection

6.5 Nano Drug Delivery in Skin Cancer

Numerous nanoparticles have been studied for the treatment of skin diseases, particularly in melanoma treatment, including liposomes, dendrimers, polymersomes, carbon-based nanoparticles, inorganic nanoparticles, and protein-based nanoparticles. In the accompanying sections, the qualities of the regular nanoparticles utilized in skin malignant growth treatment are portrayed.

6.5.1 Liposomes

Liposomes are phospholipid vesicles (measurement of 50–100 nm and much larger) that have a bilayered film structure, similar to that of organic layers, along with a neutral watery stage. Liposomes are grouped by size and number of layers into multi-, ligo, or unilamellar. The fluid center can be utilized for embodiment of water-soluble medications, though the lipid bilayers may hold hydrophobic or amphiphilic mixes. To escape from reticulo endothelial system (RES) take-up after i.v. infusion, PEGylated liposomes, "secrecy liposomes," were produced for diminishing leeway and drawing out course half-life (Sanvicens and Marco 2008).

Early exploration exhibited that liposomes stay in the tumor interstitial liquid close to the tumor vessels. At present, a few liposomal plans in the clinical practice contain a few medications for the treatment of various sorts of malignant growth, including melanoma (Allen and Cullis 2004). A few other liposomal chemotherapeutic medications are at the different phases of clinical trials. In addition, progress with cationic liposomes prompted the fruitful conveyance of small interfering RNA (siRNA). Liposomes can likewise be altered to join amagnetic components for use in checking their development inside the body utilizing MRI or to capture gases and

medications for ultrasound-controlled medication conveyance (Caldecott and Tierra 2006).

6.5.2 Solid Lipid Nanoparticles (SLNs)

SLNs were presented toward the start of the 1990s as an elective conveyance framework to liposomes, emulsion, and polymeric NP. SLNs present a high physical strength; that is, they can ensure the medications against corruption, and they permit a simple control for the medication discharge. The planning of SLNs does not require the utilization of natural solvents. They are biodegradable and biocompatible and have low toxicity. In addition, the production and sterilization on a large scale are rather easy. Solid lipid nanoparticles (SLNs) containing docetaxel improve the efficacy of this chemotherapeutic agent in colorectal (C-26) and malignant melanoma (A-375) cell lines in "in vitro" and "in vivo" experiments (Jabr-Milane et al. 2008).

6.5.3 Dendimers

Dendrimers are unimolecular, monodisperse, synthetic polymers (<15 nm) with layered architectures that are composed of a central core, an internal region consisting of repeating units, and various terminal groups that determine the three-dimensional dendrimer characteristics structures. Dendrimers can be prepared for the delivery of both hydrophobic and hydrophilic drugs, nucleic acids, and imaging agents due to their attractive properties such as well-defined size and molecular weight, monodispersed, multivalence, number of available internal cavities, high degree of branching, and high number of surface functional groups (Torchilin 2005). Several literature sources demonstrate the ability of dendrimer targeting ligands to induce the specific targeting and destruction of tumors. They include oligosaccharides, polysaccharides, oligopeptides, and polyunsaturated fatty acids as well as folate and tumor associated antigens (Yuan et al. 1994). New developments in polymer and dendrimer chemistry have provided a new class of molecules called dendronized polymers, which are linear polymers that bear dendrons at each repeat unit, obtaining drug delivery advantages because of their enhanced circulation time. Another approach is to synthesize or conjugate the drug to the dendrimers so that incorporating a degradable link can be further used to control the release of the drug. They have also found applications in the diagnostic imaging of cancer cells, such as MRI. Gadolinium-conjugates dendrimers have allowed the selective comprehensive targeting and imaging of tumors (Jerant et al. 2000).

6.5.4 *Quantum Dots*

Quantum dots (QDs) are colloidal fluorescent semiconductor nanocrystals (2–10 nm). They possess a broad absorption band and a symmetric, narrow emission band, typically in the visible to near infrared (NIR) spectral range (Ling et al. 2011). Quantum dots are photostable; therefore, the optical properties of QDs make them suitable for highly sensitive, long term, and multi target bio-imaging applications (Tsai et al. 2009). Indeed, in order for QDs to be used for melanoma detection, the surface must be treated to increase hydrophilicity and the desired tumor-targeting ligand must be attached. Possible ligands include antibodies, peptides, and small-molecule drugs/inhibitors. New methodologies, for example, the expansion of a silica covering or a biocompatible polymer covering, have additionally expanded the biocompatibility and diminished their toxicity. In fact, even though quantum dots offer many points of interest in detecting and imaging and as complexity specialists in different procedures such as MRI, PET, IR fluorescent imaging, and processed tomography, there is uncertainty surrounding the toxicity of the materials used (Amstad et al. 2011).

6.5.5 *Nanotubes*

Carbon nanotubes have a place with the group of fullerenes and are made of coaxial graphite sheets (<100 nm) folded up into chambers. These structures can be obtained either as single- (one graphite sheet) or multi-walled nanotubes (a few concentric graphite sheets). They show incredible physical, photochemical, and electrochemical properties. Attributable to their metallic or semiconductor conduct, nanotubes are frequently utilized as biosensors. Carbon nanotubes can be additionally utilized as medication bearers and tissue repair frameworks (Bañobre-López et al. 2013). Tumor targeting single-walled carbon nanotubes (SWCNT) have been integrated by covalent connection of various duplicates of tumor-explicit monoclonal antibodies, radiation particle chelates, and fluorescent tests (Hu et al. 2016). This conveyance framework can be stacked with a few atoms of an anticancer medication, in light of the fact that no covalent bonds are required, so the expanded payload does not fundamentally change the targeting capacity of the counter acting agent. They have likewise been rebuilt to convey gadolinium molecules for MRI of tumors and have been surface functionalized with receptor agonists and foes for tumor targeting (Vannucci et al. 2012).

6.6 Efficacy of Nano Treatment in Future for Skin Cancer

Novel treatments are fast approaching for almost any ailment, and they are intended to be progressively productive, less expensive, and with no penalty to patient security, sometimes even improving it. To accomplish the last mentioned, a perfect

treatment ought to be formed considering acceptable patient consistence, a superior treatment proficiency, a low conceivable harmfulness, and extremely exceptional returns of arriving at the target hand in the body per unit mass of the medication. Nanotechnology based treatments can be progressively effective, since they can be adorned with target moieties (e.g., antibodies) (Sahoo et al. 2011). Both referenced also lead to a decreased toxicity, since lower dosages are important to accomplish a similar impact, as the target and controlled discharge at the target in the vicinity, and renders the harmfulness exceptionally limited. The last is likewise in direct connection to the significant returns of the conveyance (Ma et al. 2012). Knowing these likely points of interest of such plans, it is not unexpected that these are intensely explored and that there is an appeal for their take-up into clinical practice once demonstrated safe. Furthermore, without a doubt, there are at any rate two previously endorsed nanotechnology-based plans utilized in malignancy treatment; Doxil (Janssen Biotech, Horsham, PA, USA), a doxorubicin containing liposome infusion, and Nab-paclitaxel (Abraxane), which contains paclitaxel bound to egg whites' nanoparticles (nm).

Considering all referenced skin malignant growth treatments, there is some encouraging research progress that could mean huge upgrades in the potential treatment result for skin disease patients. A few unique types of novel nano-sized plans have been recently created and are in various phases of testing (Maver et al. 2009). Among others, different lipid-based particles (e.g., micelles, strong lipid particles) are especially mainstream. These not only frequently have the capacity to outmaneuver the host defenses of the living being, which for itself prompts improved yields of the payload conveyance (Navarro-Pardo et al. 2016), but also provide other diverse targeting ways to further improve this yield significantly. Carbon nanostructures remain among the most explored kinds of nanostructures for biomedical applications (Makovec et al. 2009) particularly because of their different applications (e.g., sub-atomic gadgets), and countless adjustment approaches are accessible for them making them intriguing contenders for future viable malignant growth treatment (Siu et al. 2014).

In addition, the most encouraging future treatment approaches lie in the field of theranostics, which joins all the right "fixings" to meet all the prerequisites of the perfect treatment approach. A few novel treatment arrangements in skin malignant growth have been examined (Huber et al. 2015).

It is important that, from our viewpoint, MNPs appear to be among the most encouraging nanoparticulate specialists, particularly in the treatment of "difficult-to-treat" disease structures (e.g., MM). Among MNPs, the most regularly utilized particles are unquestionably based on iron oxides (Lu 2014). The last were joined with different medications (e.g., epirubicin) and are on their own equipped for being utilized to initiate attractive hyperthermia, and since they are generally functionalized so as to forestall agglomeration, their surface is reasonable for securing distinctive targeting moieties (e.g., antibodies) (Sharma et al. 2016).

6.7 Conclusion

Nanomedicine, as a promising instrument for disease treatment, has received increased attention and yielded an incredible number of health advantages. Recently, different sorts of nanomaterials, which could display better cell take-up, tumor site explicitness, and delayed course time after surface change, have been explored for imaging, locating, and treatment of malignant growths. Regarding these points of interest, nanomaterial-based therapeutics have shown equivalent or even better anticancer viability than other industry standards, while showing decreased symptoms, giving new methodologies to battle against carcinomas. An assortment of nanomaterials have been introduced, including polymeric NPs, liposomes, dendrimers, polymeric micelles, polymer-medicate conjugates, silica NPs, carbon nanotubes, nanographene, attractive NPs, AuNPs, and quantum specks. The examination of these nanomaterials through improving their structure and cell targeting capacity has given an increasingly useful restorative conveyance. A large portion of these works have indicated extraordinary potential to make life changing nanomedicine treatments for clinical malignancy treatment. The most significant concern would be nanomaterial toxicity and potential wellbeing dangers, as little is known about how they carry on in people. Liposomes are the most evolved, are clinically affirmed, and currently have the best number of clinical preliminaries with certain plans effectively accessible in the commercial center, while numerous other nanomaterial-based devices, particularly inorganic ones, have not received such endorsement and achievement. Some nanomaterials are not biodegradable and might be held inside the body for extensive periods of time after insertion. The advancement of biocompatible and biodegradable nanomaterials for malignant growth treatment could, along these lines, have an a lot higher clinical worth. Considering everything, tranquilize conveyance has all the earmarks of being a promising methodology for a superior viable melanoma treatment.

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Chapter 7
Efficacy of Nanomaterials and Its Impact on Nosocomial Infections

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7.1 Introduction

Nanotechnology is a multidisciplinary area that covers a tremendous scope from designing, material science and various other science disciplines. Nanotechnology has enabled tremendous advances in science and innovation, opening doors for advances in the fields of medicine, gadgets, nutrition, and the earth. It comprises the group of tiny structures and the prefix "nano" is a Greek expression defined as "diminutive person or scaled down" (Feynman 1959). Nanotechnology gives the ability to design the properties of assets by using their size, and this has led to exploration towards an enormous area of likely uses for nanomaterials. The advantages in edifying available treatments propel established researchers to continue searching for inventive ways to fight contaminations (Kannan et al. 2014).

Nanotechnology is empowering innovation that manages nanometer-sized things. Nanotechnology involves a few levels: materials, gadgets, and frameworks. Nanomaterials are the principal components of the quickly growing field of nanomedicine and bionanotechnology. Nanoscale structures and materials (nanoparticles, nanowires, nanofibers, and nanotubes) have been investigated in many natural applications (biosensing, organic severance, sub-atomic imaging, and anticancer treatment) because their novel properties and capacities vary significantly from their large counterparts. Nanotechnology can be used in medication and medical procedures as designers find novel approaches to apply these particles. There is abundant room for up and coming endeavors with tranquilize conveyance frameworks and cell targeting to create more efficient applications. As shown in Fig. 7.1, the size of

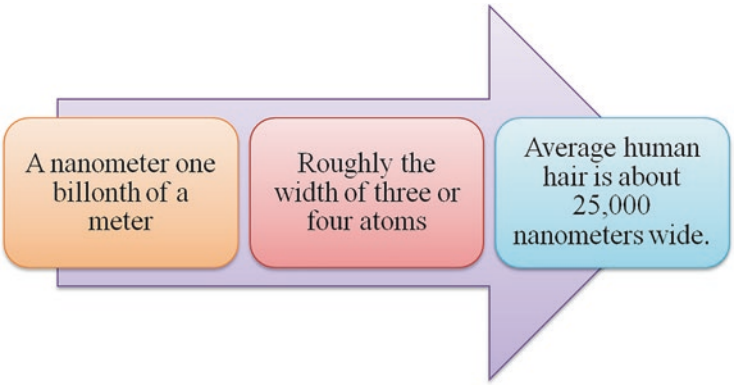

Fig. 7.1 Size of a nanometer

a nanometer is one billionth of a meter, they are roughly the width of three or four atoms, and the human hair is about 25,000 nanometers wide.

The nanoparticles (NPs) have become a fixture because of their use in industry frameworks, along with client items, pharmaceuticals, beauty care products, transportation, influence, cultivating, and so forth, and are continuously implemented in new modern applications. A captivating application of NPs in the field of life sciences is their use in rich freedom frameworks. Metal NPs are of enormous specialized consideration because they connect the gap between the massive and nuclear structures. NPs have supreme physicochemical properties, i.e., raised surface territory, transcending reactivity, tunable pore size, and molecule morphology. Current progress in nanotechnology includes the amalgamation of metallic NPs into changed industrialized, healing, and household items. The size comparison of nanotechnology is shown in (Fig. 7.2) as milliliter, micrometer and nanometer; the examples are five million red blood cells in a drop of blood for millimeter, the blood cells micrometers, and the strand of DNA present in the whole blood cells are 2 nm wide.

Moreover, it is possible that these engaged methodologies could become multiuseful with various procedures and health advantages. The universe of nanotechnology in medicine is currently available, and there is significantly more to learn. In science and medicine, nanotechnology includes the materials, gadgets, and frameworks whose structure and capacity are connected for small length scales, from nanometers (10–9 m) through microns (10–6 m). Various aspects of nanotechnology rely upon the way that it is likely to adjust the structures of assets at extremely

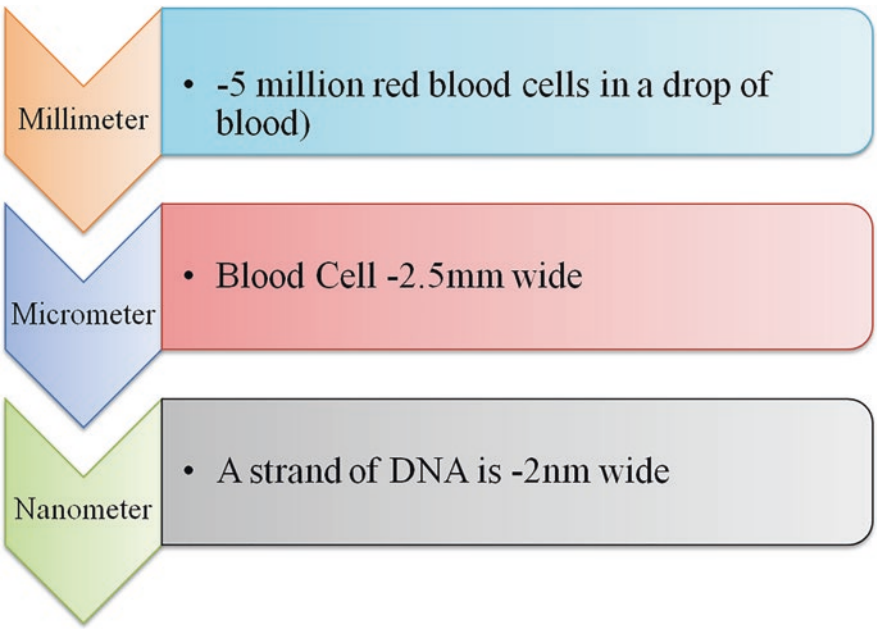

Fig. 7.2 Size comparisons of nanotechnology

small scales to realize specific properties (Buzea et al. 2007). Nano biotechnology is a field that concerns the natural framework streamlined through movement, for example, cells, cell instrument, nucleic corrosive, and proteins to smooth the advancement of utilitarian nano organized and mesoscopic engineering contained natural and inorganic materials. Bio functionalization of nanoparticles is a basic job of current day nano biotechnology. Then again, bio nanotechnology generally refers to how the objectives of nanotechnology can be guided by concentrating on how organic "machines" work and adjust these natural themes into improving available nanotechnologies or making novel ones (Fang et al. 2014).

We can characterize a nanoparticle as a molecule with at least one measurements under 100 nm. The history of nanoparticles dates to the ninth century in Mesopotamia where craftsmen used a few mixes to cover pots. These "paints" molded a glittering impact on the outside of the pots. Because of its size, a nanoparticle shows matchless optical, physical, and compound properties, for example, colossal electrical and warm conductivity, photoemission, and amazing synergist action, among others. Maybe the most common use of nanoparticles in medicine today is in tranquilize conveyance frameworks. The points of interest are numerous over customary conveyance frameworks.

Nanosystems might be utilized for the diagnosis and treatment of viral and contagious diseases. Gainful expository tests dependent on nanosystems are available (Kannan et al. 2013). Differing techniques dependent on nanoparticles (NPs) have been created to recognize unambiguous agents or to separate Gram-positive and Gram-negative microorganisms. Biosensors dependent on nanoparticles have been helpful in viral location to advance reachable basic strategies (Zazo et al. 2017). A few purpose-of-care (POC) tests have been foreseen that can give earlier results, simpler, and at lesser expense than common methods and can even be used in inaccessible locales for viral analysis. Quorum sensing is an upgraded strategy interrelated with population density that microorganisms utilize to authorize biofilms creation. Nanostructured materials that hamper signal particles concerned in biofilm growth have been expanded for the intensity of contaminations involved with biofilm-related diseases. In summary, nanoparticles make an engaging platform for theranostic applications, and frameworks that consolidate drugs and specific sorts of nanoparticles dispense helpful specialist delivery such as the imaging of an objective organ or tissue (Burlage and Tillmann 2017).

7.1.1 Miniature Things with Marvelous Impact

Nanoscience is a promising territory of science that includes the group of materials on an ultra-small scale and the novel properties that these materials possess. One of the most elating fundamentals of administration in the nanoworld is that effects act in an alternate manner when things are ultra-small. At the point when molecule sizes are dense to the nanoscale, the extent of surface area to amount increases extensively. The ability to adjust the center structures of materials at the nanoscale to achieve exact properties is at the heart of nanotechnology. A couple of instances

of contemporary nanotechnology include the following. Nanosensors in wrapping can see salmonella and different contaminants in food. Other blending improvements grasp the chance of utilizing nanotechnology to intensify the extension of nerve cells (for instance, in a harmed cerebrum or spinal string), and by methods for nano strands to encourage fortification of crushed spinal nerves (currently being tried on mice).

Nanotechnology is being used in a progression of energy territories—to recuperate the ability and cost-adequacy of sun-based boards, produce modern sorts of batteries, advance the skill of fuel making by methods for upgraded catalysis, and produce improved enlightenment frameworks. Nanoengineered materials are in a variety of items, including high-power batteries, fuel added substances and energy units, and upgraded exhaust systems, which produce cleaner exhaust for longer periods. Nanostructured channels that can kill infection cells and different flotsam and jetsam from water may in the long run encourage production of soil free, economical, and plentiful drinking water. A nanofabric paper towel, which can sop up multiple times its weight in oil, can be used for oil slick clean up tasks. Nanoscale added substances in textures help resist recoloring, wrinkling, and bacterial development. There is additionally the possibility that nanomaterials may venture out from life form to life form, or completely through natural pecking orders. Despite these worries, most researchers expect that nanoscience will be instrumental in mammoth advances in cures, biotechnology, industry, data innovation, and other territories. Nanoscience is about the ultra-small; however, it has the likelihood to have an epic impact on our lives.

7.1.2 Infectious Disease

Pathogenic diseases have been consistently prosperous. Plants and creatures as well as people are habitually infected by such pathogenic elements causing fierce illnesses; some are even basic and some lead to raised recuperating cost, other prosperity payment, and high mortality hazard. These inconvenient microorganisms can cause high death rates, incapacity, and ailments in plants and creatures. Thinking back to the former times of human maladies, during the nineteenth century, it was thought that microorganisms were liable for a variety of irresistible ailments that had been afflicting mankind from old days. Some bacterial illnesses, for example, tuberculosis, typhus, plague, diphtheria, typhoid fever, cholera, loose bowels, and pneumonia have negatively affected humankind. In 1997, coronary illness and malignancies represented 55% all things considered, with 4.5% owing to pneumonia, flu, and human immunodeficiency infection (HIV) disease (Hoyert et al. 1999). Organisms are likewise the source of various sicknesses in plants, which, if crop plants or woods assets, may have basic practical or social results.

Plant sicknesses have forever been opposed to plant development and yield creation in a few parts of the planet. Plant ailments can influence plants in various ways, for example, the absorbance and translocation of stream and supplements, photosynthesis, bloom and natural product improvement, plant growth and

augmentation, and cell division and amplification. Plant illnesses can be brought about by various sorts of organisms, microbes, phytoplasma, infections, viroids, nematodes, and different agents. Plant maladies are notable to decrease the food available to people by reducing crop yields. This can result in deficient food to people or lead to starvation and death in the most shocking cases. For instance, late blight of potato, which is brought about by *Phytophthora infestans*, destroyed potatoes, which were the principle crop in Ireland during 1845–1850. This brought about the Great Famine (or Great Hunger), where approximately one million individuals died and another million moved to Canada, the USA, and different nations (Nowicki et al. 2011). One of the most widely recognized ways by which plant maladies can trouble people is through the release of harmful metabolites "mycotoxins" by parasites contaminating plant parts. In spite of the fact that the parasites creating these mycotoxins defile vegetation but not people, these mycotoxins can have direct effects on people and creatures, following in maladies and death. Instances of contagious species creating mycotoxinsinclude *Aspergillus flavus, Fusarium* spp., and *Penicillium* sps. (Schaafsma and Hooker 2007).

Aflatoxin B1 is one of the gravest mycotoxins, since it is risky at high fixation and is cancer causing to people in small dosages and can result in condensed liver capacity, retching, and stomach torment. Yearly deaths in certain parts of Africa because of the impact of Aflatoxin have been recorded at 250,000 every year (Hong et al. 2013). In the present situation, it has been seen that the pathogenic organisms, such as microbes, infection, growths, protozoans, and so forth, are battling with antipathogenic substances. The rise of multi-tranquilize resistant (MDR) microscopic organisms has become a thorough hazard to general wellbeing (Tanwar et al. 2014). There are various sought after procedures, including testing for new antimicrobials from common items, change of open anti-infection classes, and the advancement of antimicrobial peptides. Nanoparticles are currently carefully being investigated as anti-microbials and seem to have a high potential to translate the hitch of the surfacing of microbial multidrug obstruction (O'Connell et al. 2013). To start nanoparticles in the field of drugs and to have quality as a matter of first importance, we must be aware of the microorganisms and their impact on living creatures.

7.2 Infectious Agent

A pathogen or infectious agent is a biological agent that causes disease or sickness to its host. The idiom is most often used for agents that interrupt the usual physiology of a multicellular animal or plant. Some pathogens have been shown to be responsible for immense numbers of afflicted groups. Today, while countless remedial advances have been ready to treat illness caused by pathogens, through the use of vaccination, antibiotics and fungicide, pathogens continue to threaten human life. Pathogens are usually divergent from the ordinary flora. Our ordinary microbial populaces only cause trouble if our immune systems are destabilized or if they gain access to a normally sterile part of the body (Alberts et al. 2002).

7.2.1 Types of Infectious Agent

7.2.1.1 Bacteria

Microscopic organisms are innocuous or gainful; a couple of pathogenic microbes can cause irresistible illnesses. They are *Staphylococcus aureus, Pseudomonas aeruginosa, Xanthomonas compestris.*

Staphylococcus aureus – It is Gram-positive microscopic organisms, of the family *Staphylococcaceae*. These microorganisms are fundamentally responsible for causing skin virus in people; however, they may also transmit an infection to different pieces of the body, for example, respiratory system, cerebrum, and can likewise be destructive for plants. *S. aureus* causes serious sicknesses, for example, pneumonia, meningitis, osteomyelitis, endocarditis, poisonous stun condition, bacteremia, and sepsis. It is as yet one of the five most regular reasons for clinic obtained contaminations and is frequently the reason for wound diseases following medical procedure (Masalha et al. 2001). *Pseudomonas aeruginosa* – It is a Gram-negative bacterium that is in the family Pseudomonadaceae. These microorganisms are found broadly in soil, water, plants, and creatures. It is an entrepreneurial microorganism and only sometimes causes affliction in strong individuals yet can expand effectively in immunocompromised patients. It can cause serious nosocomial contaminations (Itah and Essien 2005). *Xanthomonas compestris* – It is responsible for the dark decay in crucifers such as bacterial wither of turfgrass. It is known as the most horrible microbe, which obliterates the entire vegetation of *Brassica* (Slusarenko et al. 2000).

7.2.1.2 Fungi

Growths include the eukaryotic realm of microorganisms that are generally saprophytes (absorb dead and decaying things); however, it can establish illnesses in people, creatures, and plants. Organisms are the most well-known reason for maladies in crops and different plants. The average contagious spore size is 1–40 micrometer long (Chauhan et al. 2014).

Fusarium graminearum – *Fusarium graminearum* is in the phylum Ascomycota of family nectriaceae. It is a pathogenic organism causing *Fusarium* head curse, which happens in wheat and different grains. The illness has the ability to obliterate a possibly high yield inside half a month of reap. It causes despair and greatness misfortunes because of sterility of the floret and arrangement of stained, contracted, and light test weight pieces. In people, *F. graminearum* has been linked to nutritious discharging and contact dermatitis poison levels and seizures (Schmale III and Bergstrom 2003). *Colletotrichum gloeosporioidis* – It is one of the most basic contagious microbes of the phylum Ascomycota family phyllochoraceae. It is chiefly known for causing anthracnose, a plant sickness occurring on different hosts going from trees to grass. Side effects of this ailment are shown by shaded withered spots

on practically all the airborne pieces of the host plant. Skin break out might be engorged prompting shrink, shrivel, and hang from the tainted plant. It requires muggy and clingy environmental factors to root infection on a plant. Consequently, this microorganism is significant for plant pathologists as it could impact the money related framework tumbling crop production worldwide (Waller 1992). *Mycosphaerella pinodes* – It is a hemibiotrophic contagious plant microbe in the family Didymellaceae. It causes curse on pea, it likewise defiles an assortment of species, for example, *Lathyrus sativus, Lupinus albus, Medicago spp., Trifolium spp., Vicia sativa* (Khan et al. 2013).

7.2.1.3 Virus

Infections typically are approximately 20–300 nanometers lengthwise. Pathogenic viral maladies are generally brought about by the groups of Picornaviridae, Herpesviridae, Togaviridae, Adenoviridae, Orthomyxoviridae, Paramyxoviridae, Papovaviridae, Flaviviridae, Polyomavirus, Hepadnaviridae, Rhabdoviridae, and Retroviridae.

7.2.1.4 Prion

As per the prion hypothesis, prions are infectious microorganisms that do not hold nucleic acids. These exceptionally collapsed proteins are occur in a number of ailments, for example, scrapie, cow-like spongiform encephalopathy (mad cow disease), and Creutzfeldt–Jakob ailment. Even though prions do not adequately to meet Koch's hypothesizes, their recognition as a modern class of microorganism drove Stanley B. Prusiner to get the Nobel Prize in Physiology or Medicine in 1997.

7.3 Antimicrobial Agents

There are numerous antimicrobial agents present in the commercial market that are utilized to treat a group of microbial maladies, for example, bacterial, contagious, viral ailments such as ailment brought about by protozoan's and helminthes. Remembering these conditions together with the expanding responsiveness of medication security, we are as of now confronting conditions of partially altered microbial agents. The opposition of organisms lined up with common antimicrobial agents is one of the significant dangers to human wellbeing. Anti-toxins are the broadly utilized antibacterial agents; they are chiefly used to treat bacterial contaminations and numerous infections brought about by the spread of microscopic organisms in the human body. There are two kinds of antibacterial agents. Bactericide: These are the most routinely utilized antibacterial agents; they execute the bacterial strains effectively, for instance, cephalosporins, amino glycosides, fluoroquinollines, vancomycin, daptomycin, and metronidazole. Bacteriostatic: They

fundamentally slow the acceleration of microorganisms; however, never executes them, for instance: macrolides, antibiotic medications, trimethoprim, and sulfonamides (Webster 2005).

7.4 Antifungal Agents

These are fungicide or fungi static depending upon the method of activity that is utilized close by contagious contaminations on plants, creatures, or individuals. Amphotericin is the best antifungal agent accessible; however, it caries considerable danger of toxicity and mortality. Fluconazole is an imidazole that is being used as an alternative to amphotericin for grievous contagious diseases. Fungicides, herbicides, and bug sprays are on the whole pesticides utilized in plant assurance. A fungicide is an exact sort of pesticide that controls parasitic illness by explicitly repressing or killing the organism causing the infection (Bhattacharyya et al. 2016). Fungicides have been utilized to lessen mycotoxins virus in wheat influenced by Fusarium head curse, but most fungicides used widely so far have not been sufficiently viable to be valuable for working on mycotoxins related with different sicknesses (Roco 2011).

A difficult microbe is not always affected by the fungicide, which results in the fungicide being less adequate or even futile. Fungicides that are designed for specific catalysts or proteins arranged by growths do not harm plant tissue, in this way they can puncture and move in the inside of leaves empowering helpful properties and expanding the measure of plant tissue shielded to a larger area than where the fungicide was applied. Because the method of activity of these fungicides is so explicit, small hereditary changes in organisms can beat the viability of these fungicides and microorganism populaces can form resistance to future applications. Although ordinary antimicrobial agents have been significant against numerous irresistible infections from old occasions, recently, they have increasingly been used against numerous bacterial and parasitic strains; thus, because of the increase in the quantity of different anti-toxin safe microorganisms and the standing accentuation on social insurance costs, numerous researchers have explored techniques to broaden new productive antimicrobial agents that overcome the protections of these microorganisms and are also cost effective. Nanoscale materials are presently considered to be an adequate alternative to regular substance antimicrobial agents and have a high plausibility to take care of the issue of the bacterial multidrug obstruction.

7.5 Nano War against Infectious Disease

Subsequently, the use of nanotechnology in pharmaceuticals and microbiology is a way to forestall destructive outcomes. A clear and unfortunate case of the necessity for the capacities of nanotechnology to increase and accelerate microorganism uncovering, and to initiate at the purpose of need, is the ongoing Ebola infection flare-up in

West Africa. Nano-empowered targeting discharge offers promising treatment of jungle fever and other intracellular contaminations. Liposomes, nano emulsions, dendrimers, and chitosan nano carriers outline huge success, by improving defense and targeting one of the most persuasive anti-malarial drugs, artemisinin. Nosocomial diseases (NI), otherwise called Hospital Associated/Acquired Infections (HAI), are those contaminations that occur during a patient's stay in an emergency clinic or other kind of clinical offices, which were absent at the hour of admittance. A wide range of microscopic organisms, infections, growths, and parasites may cause nosocomial diseases. Diseases might be caused by a microorganism procured from someone else in the clinic (cross-contamination) or may be by the patient's own already present infectious agent (endogenous disease) (Ducel et al. 2002).

7.5.1 Nanomaterials in Bacterial Detection

Nanotechnology is being expanded to check, break down, and treat transmittable maladies, with some in or approaching the clinical preliminary stage. Irresistible illnesses brought about by irresistible microorganisms are a question of spreading from either a weak host or vector to a strong host. Rapid, vulnerable, and exact understanding of microbes is essential for recognizing the wellspring of contamination, edifying patient consideration with legitimate treatment, and plotting the expansion of sickness (Wilson et al. 2011). Regular techniques utilized for the acknowledgment of microscopic organisms depend on the way of life of the microorganisms on agar plates and the portrayal of their phenotypic properties (Buszewski et al. 2017). Systems dependent on gold or silver nanoparticles, glass nanospheres, or quantum spots, among others, have been created to recognize specific agents or to recognize Gram-positive and Gram-negative microorganisms. Generally, unique physicochemical and immunological techniques have been created for bacterial identification, for example, fluorescence spectroscopy, mass spectrometry, catalyst connected immunosorbent test, and so forth (Lin et al. 1998). Various sorts of nanoparticles, for example, gold, silver, silica and functionalized nanoparticles, among others, have permitted the improvement of specific and sensitive techniques for the finding and eliminating of microorganisms, with various applications in biomedicine and different fields. Fast and careful discovery of pathogenic microscopic organisms is a significant research area for medicinal services, the earth, food production, and so on.

7.5.1.1 Magnetic Nanoparticles

Tuberculosis is a significant medical issue worldwide, *Mycobacterium tuberculosis* strains are aligned with increased depression and shorter lifespan in afflicted patients. A magneto resistive biosensor to recognize *Mycobacterium bovis* (BCG) microorganisms for tuberculosis decision dependent on the use of attractive

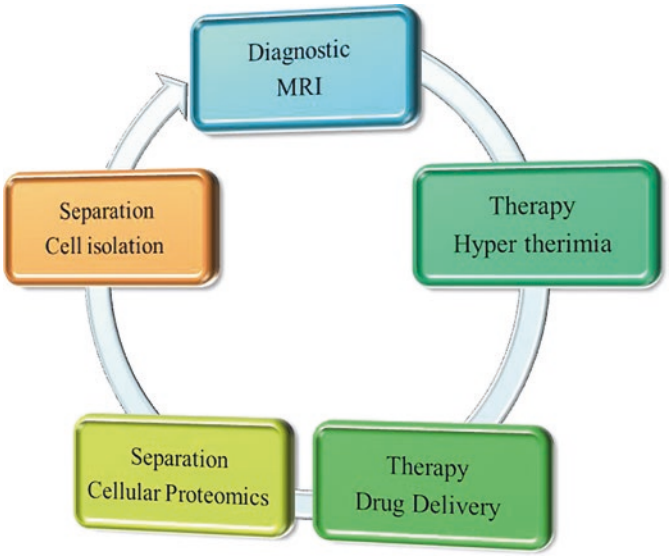

Fig. 7.3 Functionalization of magnetic nanoparticles

nanoparticles has recently been created (Barroso et al. 2018). In addition, a magnetophoretic immunoassay sensor for unfavorable determination of tuberculosis from sputum tests has been created (Kim et al. 2017). Attractive nanoparticles adjusted with a manufactured ligand bis-Zn-DPA can expel *Escherichia coli* (*E. coli*) from ox-like whole blood with practically 100% freedom at streams as high as 60 mL/h. In one ongoing examination, Lowery and associates built up a T2 attractive reverberation (T2MR)-based SPION symptomatic stage that can quickly and reproducibly recognize five Candida species in whole blood inside 3 h. Furthermore, ligand-altered attractive nanoparticles have additionally been joined with attractive microfluidic gadgets for clearing microscopic organisms and endotoxins from the circulation system (Lee et al. 2014). Use of this remarkable profile of attractive nanoparticles related to novel discovery procedures offers boundless potential in delicate and multiplex identification of microbes (Bizzini et al. 2010). The functionalization of magnetic nanoparticles are shown in (Fig. 7.3) as MRI diagnosis, hyperthermia therapy, drug delivery, cellular proteomics, and cell isolation.

7.5.1.2 Silver Nanoparticles

Silver nanoparticles (AgNPs) are considered an antibacterial agent and are used to alter orthopedic inserts to forestall disease. Silver (Ag) has been determined to have a significant antibacterial impact and has been widely utilized in medicine. Ag can

be imagined into silver nanoparticles (AgNPs) through nanotechnology to have improved physical, synthetic, and natural properties. Many studies have examined the antimicrobial action of AgNPs, but the promising anti-toxin components and planned weakness remain unclear. Planning to increase the biocompatibility of AgNPs, biosynthesis procedure can be useful to alter the morphology and surface qualities of AgNPs. Strategies, for example, biosynthesis, modifications of physical properties, and consolidating with biomolecules to expand the similarity of AgNPs are featured. Two antibacterial systems are broadly recognized: contact slaughtering and particle intervened murdering. It has been shown that AgNPs can append to the bacterial cell divider and subsequently invade it. It was additionally determined that the antibacterial impact of AgNPs on Gram-negative microorganisms was stronger than Gram-positive microscopic organisms. Furthermore, it has been demonstrated that the cell film of microorganisms has a negative charge because of the nearness of carboxyl, phosphate, and amino gatherings. The functionalization of silver nanoparticles are shown as a flow chart in (Fig. 7.4). While tetracycline and silver nanoparticles are under functionalization, it produces tetracycline silver nano complex, which is further sub divided into kinetic of tetracycline binding, instrumental method, and antimicrobial test.

The positive charge presents electrostatic attraction among AgNPs and adversely charges cell layers of the microorganisms, consequently encouraging AgNP connection onto cell films. After attachment to the bacterial divider, AgNPs can likewise puncture the layer and infiltrate the microorganisms and

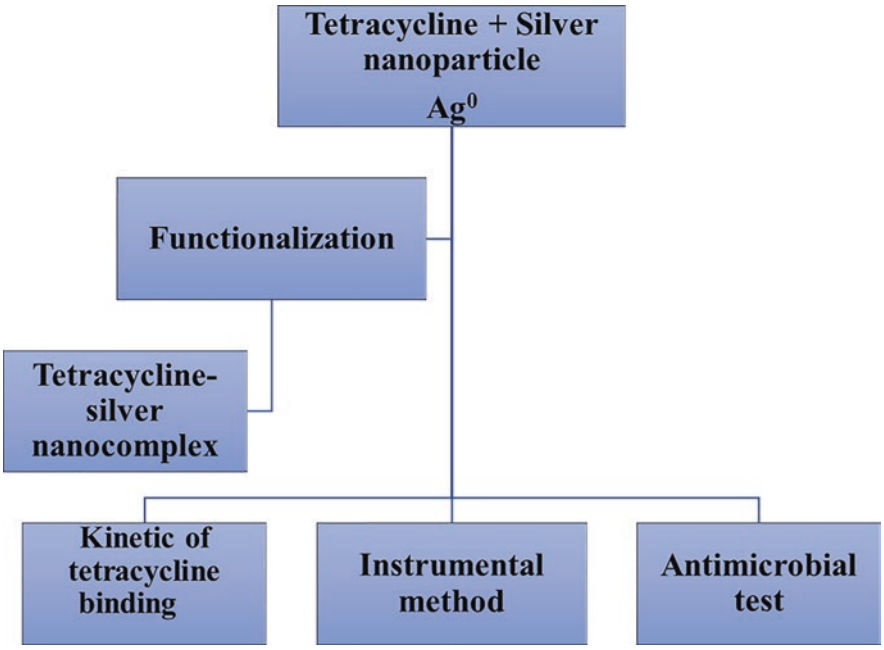

Fig. 7.4 Functionalization of silver nanoparticles

can arrive at the cytoplasm. AgNPs enter inside the microbial cell; it might interact with cell structures and biomolecules, for example, proteins, lipids, and DNA. Communication among AgNPs and cell structures or biomolecules will accompany to bacterial decline and ultimately death (Prasad 2014; Prasad and Swamy 2013; Aziz et al. 2014, 2015, 2016). One of the basic boundaries of AgNPs lined up with microorganisms is the surface zone of the nanomaterials. AgNPs can economically free Ag^+ all through microscopic organisms. In an ongoing report, it is being shown that AgNPs improved bacterial protection from anti-microbials by advancing pressure avoidance through direction of intracellular ROS. Gram-negative microbes *E. coli* 013, *Pseudomonas aeruginosa* CCM 3955 and *E. coli* CCM 3954 can create protection from AgNPs after repeating introduction. The antibiofilm disturbance of AgNPs has been checked in various investigations. One spearheading study was performed to dissect the collaborations of AgNPs with *Pseudomonas putida* biofilms. The outcomes proposed that biofilms are affected by the treatment with AgNPs.

7.5.1.3 Gold Nanoparticles

Au nanoparticles have optical and electrochemical properties that stirred great enthusiasm for their application as detecting materials (Uehara 2010). Au nanoparticles have been broadly utilized as tests for quick distinguishing proof of microbes whose genome arrangement is known to contain remarkable nucleic corrosive marks. Storhoff and colleagues additionally built up a "spot-and-read" colorimetric discovery technique for recognizing the mec A quality found in MRSA strains (Mirkin et al. 1996). Au nanoparticle tests marked with oligonucleotides and Raman-dynamic colors have been used for multiplexed acknowledgment of oligonucleotide targets with increasing affectability and selectivity. Six unique DNA targets are well known with six Raman-named Au nanoparticle tests with a recognition breaking point of 20 femtomolar. Mirkin et al. built a bio-standardized identification test for exceptionally discerning nucleic corrosive and protein targets (Hill and Mirkin 2006). Sandwich structure with Au nanoparticles and attractive microparticles for attractive detachment and dithiothreitol (DTT) intervened in the arrival of scanner tag strands, which are in this manner recognized and evaluated on a microarray. Au nanoclusters embedded inside lysozymes that can tie with peptidoglycans on bacterial cell dividers were created to target pathogenic microbes for MALDI-MS-based recognizable proof (Chan and Don 2013). Human serum egg whites or its coupling peptide with Au nanoclusters also settled unequivocal partiality with *S. aureus* and MRSA for their separation detection. Au nanoparticles can likewise be utilized to set up antimicrobial weakness by estimating the movements in the surface Plasmon band, upon the Con An instigated grouping of dextran-covered Au nanoparticles near starch in bacterial suspension (Nath et al. 2008). The applications of gold nanoparticles are shown in (Fig. 7.5). They are controlled drug delivery, catalyst, used in cancer therapy & diagnostics, and molecular detection.

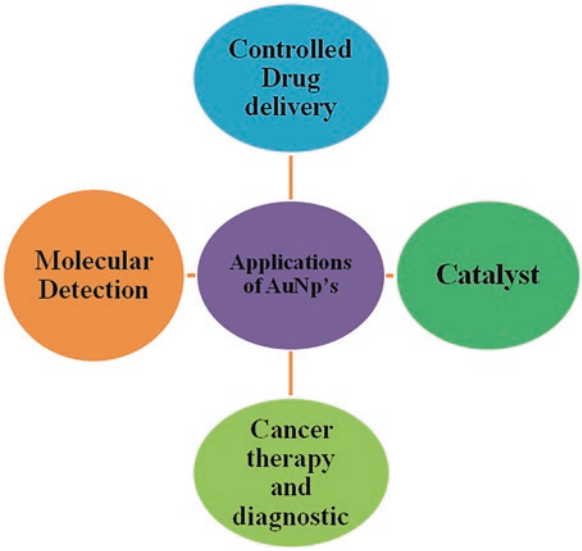

Fig. 7.5 Applications of gold nanoparticles

7.5.1.4 Localized Surface Plasmon's

A limited surface plasmon (LSP) is the outcome of the constrainment of a surface plasmon in a nanoparticle of size equal to or smaller than the frequency of light used to invigorate the plasmon. At the point when a small circular metallic nanoparticle is illuminated by light, the wavering electric field influences the conduction electrons. A solitary nanohole in a metal layer is equipped for supporting an LSP (Spackova et al. 2016). Innovations dependent on nanocavity-formed photonic precious stones with solid plasmonic signals have been created with expected applications in bacterial identification. Thue–Morse (T–M) exhibit nanoholes in a polymeric film to procure metallic gold nanocavities that allows the declaration of surface plasmons (Rippa et al. 2016). These sorts of structures, together with SERS, grant fast and detailed bacteriophage understanding of pathogenic microscopic organisms, for example, *Brucella* sp. (Zhang et al. 2001).

7.5.1.5 Fluorescent Nanoparticles

When microscopic organisms breathe, they produce acids. The acids decrease the pH and oxidize the carbon atoms, causing changes to arrangement of the particles. As a result, they exude a more splendid fluorescent gleam. The specialists put a couple of *E. coli* microscopic organisms and the fluorescent nanoparticles in a little gel microsphere that holds them. When the microscopic organisms begin to partition the carbon atoms, they started to shine more brilliantly. Nanomaterials with fluorescent properties or nanoparticles named/typified with fluorescent colors have been helpful for microbial identification. They also created diverse fluorescence

reverberation vitality transfer (FRET) silica nanoparticles by co-embodying three colors that radiate interesting hues upon excitation with a solitary frequency (Wang et al. 2005). Fluorescence imaging is a non-obtrusive, sensitive strategy that permits examining natural life forms with high tridimensional achievement continuously, by utilizing reasonable fluorescent differentiation agents. From the perspective of fluorescence splendor, the capacity of NP to create an exceptional fluorescence signal, even in the low force excitation system, results from the co-nearness of a high number of MF in every NP. These nanoparticle combination demonstrative systems depend on knowing the bacterial genome groupings/biomarkers by focusing on tests, and in this way may not classify transformed or potentially new microorganisms strains. As medication safe strains are slowly determined, another noteworthy way is the advancement of symptomatic nanotechnology able to detect the nearness of microbes, with the ability to decide the defenselessness of the microorganisms to antimicrobial medications simultaneously.

7.6 Nanomaterials in Viral Detection

Pathogens are the least known organisms, yet they cause the most significant misfortunes to human wellbeing. More often than not, the most popular remedy for infections is the intuitive immunological resistance system of the host; in any case, the starter counteraction of viral disease is the main substitute. Infections are caused by amazing microorganisms called pathogens that cause an extraordinarily number of maladies and mortality worldwide. Currently, popular contaminations and associated infections are significant reasons for death in humankind, and under the current setting of industrialization and migration, they occur and spread at a quick pace, causing huge human, social, and budgetary expenses. Unfavorable analysis is consistently favorable for the control of irresistible sicknesses. Various methodologies have been established for nanoparticles to liven up explanatory procedure qualities, in any event, permitting the extension of simple and quick purpose-of-care (POC) measures to analyze in situ in remote locales.

Various types of nanoparticles have increased their approaches for the determination, recuperation, and expectation of viral diseases in numerous applications, primarily those nanoparticles with viral material or frameworks that copy infection qualities. This portion centers around the indicative procedures expanded for the understanding and evaluation of infections themselves, and specifically for the infections that have been deliberately researched and are more essential (Hassanpour et al. 2018). It is interesting to see that in therapeutics against infections, some special nanoparticles have emerged: the “virus-like particles” (VLPs). They are nanoparticles formed from viral proteins that aggregate in structures similar to authentic infection particles even though they require irresistible nucleic corrosive groupings (Lee et al. 2016). Early conclusions have been consistently positive for the control of irresistible illnesses. Various procedures have been actualized utilizing nanoparticles to improve systematic strategy qualities, including permitting the

advancement of straightforward and quick purpose-of-care (POC) tests to analyze in situ in remote locales. The exceptional and adaptable properties of nanoparticles themselves and the atoms that can be related with them empower quick, complex, and savvy analyses (Jorquera and Tripp 2016).

7.6.1 SERS

The use of nanoparticles in Raman spectroscopy intensifies the signs, prompting SERS that has been applied for various types of infection (Tanwar et al. 2021; Liu et al. 2021). The nanoplasmonic properties of gold nanoparticles have been helpful in human immunodeficiency virus (HIV) load measurement from whole blood tests. Along these lines, a knowledge platform with specific antiviral antibodies preset to the biosensing surface has been built that has the option to identify and measure various HIV subtypes and could be changed for different microorganisms that have known biomarkers (Halfpenny and Wright 2010). Some of the strategies dependent on these intrinsic properties of gold nanoparticles have been used in respiratory infections, taking into consideration the differentiation among various flu infections and hepatitis viruses (Park et al. 2012). An optofluidic-nanoplasmonic sensor that could be utilized as a POC for Ebola investigation, even in bio barrier settings, has been structured. This nano opening-based detecting raised zone has increased its capacity to identify unblemished infections from naturally pertinent media with simple model preparation and the creators prescribe that it could be extrapolated to different infections (Yanik et al. 2010).

7.6.2 Electrochemical Biosensing

Distinctive biosensors dependent on nanoparticles have been used in flu infection identification, among others. Because they have ideal attributes for biosensors for POC examines that can suggest insightful result quicker, simpler, at lower cost than traditional strategies and with amazing selectivity and sensitivity (Tepeli and Ülkü 2018). An anode incorporating graphene and polyaniline nanowires has additionally been anticipated as an approach to advance its DNA discovery affectability (Diba et al. 2015). In addition, immunoassays dependent on complementary metal–oxide–semiconductors (CMOS) that have sensor innovation utilizing indium nanoparticle (InNP) substrates have been utilized for hepatitis infection recognition (Devadhasan and Kim 2015).

In the examination field of Ebola analysis, specialists have explicitly highlighted the need for a biosensor that permits the identification of Ebola infections at the point of care using the relationship of nanoparticles to symptomatic methods created for different infections and on the premise that scaled down chips with immobilized antibodies have built up their ability to recognize pM levels of different

biomarkers (Vasudev et al. 2013). A few creators suggest that scaling down the electrochemical insusceptible detecting ability would be a sensible way to create gadgets for quick and in situ Ebola screening (Kaushik et al. 2016).

7.6.3 Other Biosensing Methods

Regarding infection, soluble phosphatase (ALP) has been utilized as a sign tag for immunoreactions. Shading change was seen within the sight of the infection because of silver expression on the outside of gold nanoparticles initiated by the catalyst. Combined with attractive advancement, this strategy has been exhibited to be basic, quick, and profoundly sensitive, permitting H9N2 infection identification straightforwardly in complex samples (Chin et al. 2011). Nano arrays obtained by nanolithography have demonstrated an upgrade such as quicker discovery than the ordinary colorimetric enzyme-linked immunosorbent assay (ELISA). Double luminophore-doped silica nanoparticles with various surface changes have been used for multiplexed investigation. Together with stream cytometry, it has been proposed that these frameworks have fascinating worthwhile properties with regard to the identification of microorganisms, particularly for those that have issues with typical colors because of their negligible specific antigens. Results uncovered that these nanoparticles have high sign intensification, superb photostability, and simple surface bioconjugation for biomarker location, which marks this framework as a perfect biolabeling reagent in antigens and nucleic acids identification (Wang et al. 2009).

Different techniques dependent on colorimetric discovery have been applied to infection identification. Through the relationship of gold nanoparticles with switch translation circle intervened isothermal intensification, a straightforward test for hepatitis E was created, whose outcomes can be assessed with the unaided eye because of shading changes. It has been proposed as an option in contrast to other costly and tedious techniques normally utilized (Chen et al. 2014). Fe_3O_4 attractive nanoparticles have been additionally applied as nanozyme tests, tackling their regular inborn peroxidase-like action that can be outwardly distinguished because of the undeniable shading response. By marking them with specific antibodies and close by peroxide substrates, they have been used for immuno attractive Ebola infection discovery (Duan et al. 2015).

7.7 Advanced Nano Biomaterials to Treat Infectious Disease

Clinical gadgets assume a significant job in current medicinal services practice, but their application may increase the dangers of nosocomial disease. The microbes most generally found in contaminated gadgets include *S. epidermidis, S. aureus,* and *P. aeruginosa*. These microorganisms can be amazingly impervious to anti-toxin treatment because of the development of biofilms, and

foundational organization of anti-infection agents as a rule does not show agreeable outcomes (Krishnasami et al. 2002). Medical gadgets with innate antimicrobial properties have been used for quite a long time, with the objective that a good mix with have cells while forestalling any bacterial bond or biofilm development.

7.7.1 Nano Vaccine

The host's immune system response has been exhibited to be extremely powerful in securing them against microbial disease. Different existing immunizations for organisms show a significant variety in immunogenicity and wellbeing. Worries with the utilization of live constricted bacterial antibodies include the conceivable inversion of pathogenicity and the prior insusceptibility to the vector, such as the risk to reward traded off for people (Smith et al. 2013). Advances in biotechnology empower the creation of cutting-edge bacterial immunizations, including disengaged proteins, polysaccharides, and exposed DNA. Novel antibodies are regularly less immunogenic than conventional immunizations, for example, those utilizing live weakened organisms. To address this test, the use of nanotechnologies to upgrade the resistant reactions of these antibodies has pulled in extraordinary intrigue (Reddy et al. 2011). Nanoparticles have likewise been demonstrated to be viable conveyance frameworks for mucosal immunization. A defensive, dependable mucosal insusceptible reaction is imperative to shield the host from likely bacterial contamination. Accordingly, mucosal organization through intranasal, inhalational, or gastrointestinal courses is becoming a supported course of immunization. Distinctive nanoparticle conveyance vehicles have been proposed to improve mucosal immunization through their immunostimulatory exercises (Kammona and Kiparissides 2012).

7.7.2 Nano Adjuvant

Nanoemulsions, or oil-in-water emulsions framed by isotropic blends of oil and surfactant with bead distance across in the nanometer scale, are compelling nonprovocative mucosal adjuvants. The adjuvanticity of nanoemulsions has been proposed to add to expanded cell take-up of antigens, enlistment of monocytes and granulocytes, and upgraded arrival of cytokines and chemokines (Hamouda et al. 2001). Intranasally controlled recombinant *Bacillus anthracis* defensive antigen blended in nanoemulsion prompted both serum IgG and bronchial IgA and IgG antibodies after a couple of mucosal organizations in mice and guinea pigs (Bielinska et al. 2007). In correlation, industrially accessible human *Bacillus anthracis* immunization requires six subcutaneous infusions more than year and a half and yearly promoter. Cationic liposomes complexed with non-coding plasmid DNA were

additionally answered to be compelling as parenteral and mucosal immunization adjuvants (Makidon et al. 2010).

7.7.3 *Quorum Sensing*

Quorum sensing is an upgraded process connected with population density that microorganisms use to manage biofilm development. The drawback to Quorum sensing is the need for a methodology to battling its pathogenicity. Common or manufactured Quorum sensing inhibitors may be hostile to biofilm agents and be helpful in rewarding multi-tranquilize safe microscopic organisms. Microscopic organisms can speak with one another through discharged flagging elements, named autoinducers. These compound signs are combined intra cellularly and discharged to the extracellular medium where they are perceived by the nearby cells enacting the statement of related qualities (Lazdunski et al. 2004). The autoinducer movement and the conduct changes are possibly activated when an edge level is reached (Turan et al. 2017; Sintim et al. 2010; Galloway et al. 2012). These occasions require, at that point, high cell densities (to collect adequate sign).

The base conduct unit has been portrayed as many microbes and, in this manner, this method of bacterial correspondence has been named majority sensing (Mukherjee et al. 2008). The QS procedure among cells was first found to control bioluminescence in the marine microscopic organisms *Vibrio fischeri*, where for low cell densities a homoserine lactone is discharged to the medium, while for high cell densities, it is aggregated inside when it triggers the interpretation of radiance qualities (Stevens and Greenberg 1997). In *Pseudomonas aeruginosa*, whose Quorum sensing framework has been the most considered, it manages the creation of a few intensifies that assume significant jobs in biofilm arrangement. This includes rhamnolipids, lectin A (LecA)/LecB, and pyochelin and pyoverdine siderophores. The least complex Gram-positive quorum sensing framework was first found in *Lactococcus lactis* and *Streptococcus pneumoniae* (Tielker et al. 2005; Diggle et al. 2006).

Currently, the expansion in safe bacterial strains and the absence of new antitoxins make it important to scan for new techniques to battle contaminations. Because of the significant job that quorum sensing plays in bacterial harmfulness, the interruption of this bacterial correspondence framework is drawing in a lot of enthusiasm as another antimicrobial methodology (Defoirdt 2017). The mediation methodology is named "quorum quenching" (QQ), a term used to incorporate any methodology that meddles with legitimate microbial QS flagging. This should be possible at various focuses: restraint of autoinducer amalgamation, corruption of the autoinducer, and capture of its collaboration with the receptor (Brooks and Brooks 2014). Numerous restorative plant species, for example, garlic, ginger, basic oils of cinnamon and clove are additionally known to have QSI uses. Carrot, chamomile, garlic, and numerous peppers have been

demonstrated to have hostile to QS action, even though the systems for a significant number of them have not yet been recognized. Additionally, flavonoids, for example, baicalin, quercetin, naringenin, kempferol, and apigenin, have all been found to be effective in threatening bacterial QS. In many examinations, a prophylactic use has been concentrated by overseeing the counter QS agents simultaneously as the microorganisms inoculum, and a significant improvement in the contamination result has been found (Khajanchi et al. 2011; Musthafa et al. 2012).

7.8 Conclusion

Various advances in nanoparticle-based frameworks for the demonstrative and treatment of bacterial contaminations have been distributed with possible applications in the battle against multidrug resistant strains and bacterial biofilms, among other areas. The possible effect of nanotechnology on microbial irresistible sicknesses has just been exhibited by the clinical endorsement of numerous nanotechnology-based items for the location of bacterial contamination, the conveyance of anti-toxins, and the improvement of clinical gadgets with antimicrobial coatings. Nanoparticles with elite physiochemical properties have empowered the detection of microbial sickness with high affectability, selectivity, and quick readout. The attributes of particular kinds of nanoparticles and extra functionalization present perfect properties for application in indicative examination, permitting scaling down and improvement of some customary procedures of microbe location. Progressed explanatory strategies, for example, SERS, joined with the utilization of metallic nanoparticles are magnificent apparatuses for the location of microbes and infections. Regardless of these enchanting accomplishments, the full potential of nanotechnology in running microbial contamination, especially in the territories of antimicrobial treatment and antibodies, is far from being reached. The epic field of theranostic is very much perceived as possible for specially crafted malignancy treatment, including the hang-up of bacterial quorum sensing systems by the utilization of metallic and different kinds of nanoparticles comprises a promising methodology in the battle against bacterial contaminations. The consolidation of QS inhibitors into these nanosystems expands their effectiveness for biofilm treatment. Antimicrobial nanotechnologies can be encouraged by developing more clinically relevant creature models, recognizing the instruments of microbial pathogenesis and new biomarkers, tolerating the microenvironment of bacterial pollution destinations, and overcoming the authoritarian boundaries. With ceaseless progress in antimicrobial nanomedicine, we can expect that many more nanotechnology-based items will be developed to manage each bit of microbial disease.

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Chapter 8
Nanonutraceuticals in Chemotherapy of Infectious Diseases and Cancer

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8.1 Introduction to Nanotechnology and Nutraceuticals

Nanotechnology, an upcoming field of nanoscience and engineering research, is an empowering technology leading to transformation in food, pharmaceutical, cosmetics, and nutraceutical industry (Prasad et al. 2017a). Nanotechnology involves the ability to control and manipulate the atomic scale, creating and utilizing the small and intermediate size structures, devices, and systems that have novel properties and functions and research and technology development at the atomic, molecular, and macromolecular levels (1 to 100 nanometer). Nanotechnology remains a key research area in the science and engineering field with the enhanced utilization of nanoparticle-based medicines (Godwin et al. 2009; Rostamabadi et al. 2019; Saglam et al. 2021).

Nanoparticles are synthesized using organic or inorganic materials either by top-down methods starting with bulk material and removing the material to attain nanomaterial through milling, fluidization, homogenization processes, or emulsification or bottom-up methods starting with atomic or molecular precursors and combining them to form nanomaterials through precipitation/condensation, evaporation, or controlled sol-gel synthesis methods (Bhushan et al. 2014; Singh and Colonna 2015). Nowadays, encapsulation with the natural biodegradable polymer is the frequently used technique (Zhao et al. 2008; Shukla & Iravani 2019).

Nanomaterials that occurs naturally in food include protein, fats, carbohydrates, and nanostructures are cell membranes, hormones, etc (Powell 2008). As nanoparticles have major advantages and worthy of its value, billions of dollars are invested in the nano research, and scientists are exploring all the possible nanomechanisms to encapsulate nanomaterials in nutraceuticals for its safe and wise use to achieve maximum health benefits.

However, a great challenge in nanonutraceutical research is the efficiency in nanomanufacturing which is dependent (Bernhardt et al. 2010; McClements et al. 2015) on the identification and understanding of naturally occurring therapeutically useful material at the molecular level and large-scale production synthesizing at the nanoscale level (Roco and Bainbridge 2001).

8.1.1 Nano Fabrication

Nanomaterials are categorized into the following:

- Category 1: zero-dimensional structures are synthesized using vaporization (Physical /Chemical), aerosol processing, condensation of inert gas, precipitation etc. Eg; Quantum dots, nanoclusters, nanoparticles, nanocrystallites etc
- Category 2: nanometer-sized thin material processed by PVD/CVD/laser ablation/ion implantation (Geng et al. 2006; Singh and Colonna 2015)

8.1.2 Types of Nanocarriers

Nanoparticles are synthesized from natural (lipids, proteins, and polysaccharides) and synthetic (polymers) sources which are usually well-tolerated, biodegradable, and biocompatible (Nalwa 2004; Andreas Wicki et al. 2015; Doktorovova et al. 2016) (Fig. 8.1).

8.1.2.1 Lipid-Based and Surfactant-Based Nanocarriers

Emulsion types which include nanoemulsion/microemulsion/lipid concentrate (SMEDDS and SEDDS) are prepared from liquid lipid (oils) SLNs (solid lipid nanoparticles and NLCs). Nanostructured lipid carriers are synthesized from solid or semisolid fats (Doktorovová et al. 2016; Jafari et al. 2017).

(i) *Liquid Lipid Preparations*

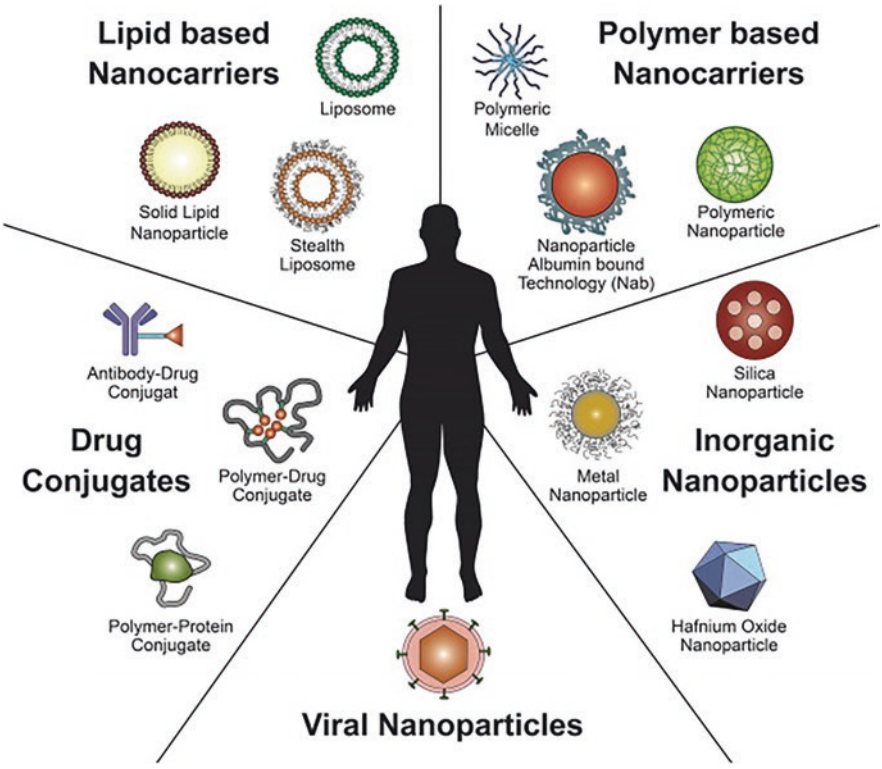


Fig. 8.1 Various types of nanocarriers. (Adapted from Andreas Wicki et al. 2015)

(a) *Liposomes consist* of small (~100–400 nm) amphiphilic artificial vesicles spherical in shape lipid bilayers that are used in the delivery of drugs, nutraceuticals, nutrients, enzymes, vitamins, antimicrobials, and additives (Godwin et al. 2009). Liposomes are an efficacious and safe drug delivery system with increased biocompatibility and are easily biodegradable. Moreover, it is devoid of toxicity or immunogenicity (Lungu et al. 2019), e.g., encapsulation of gallic acid with Zein fibers (Thomas and Sayre 2005).

(b) *Nanoemulsions* (5–200 nm) are kinetically stable, colloidal dispersion of oil droplets in an aqueous medium (O/W, W/O, bi-continuous type). The preparation techniques include the utilization of different energy levels. Low energy techniques include phase inverse and spontaneous emulsification and the techniques that utilize high energy are microfluids and ultrasound-homogenizers. The recent studies include GEON (garlic essential oil nanoemulsion) and Taguchi method(vitamins A, D, and E, encapsulated in O/w nanoemulsion, carotenoids, polyphenols lycopene, β-carotene, and curcumin (Castro et al. 2018; Saura-Calixto and Pérez-Jiménez 2018; Yuan et al. 2019).

(c) *Microemulsion* is a system that is thermodynamically stable comprising of oil, surfactant, cosurfactant, and water. The synthesis includes the self-assembling of surfactant molecules into core micelles and a cosurfactant that minimizes the interfacial energy, e.g., nanoemulsion droplet size (10 to 100 nm) of lycopene (Jafari et al. 2017; Amiri-Rigi and Abbasi 2019).

(d) *SEDDS and SMEDDS* include isotropic oil solution with the lipophilic component and a surfactant that will form microemulsion or emulsion with water on agitation, e.g., d-α-tocopherol polyethylene glycol 1000 succinate (Kuentz 2012).

(e) *Micelles* can encapsulate the electrolyte stabilized lipophilic or lipophobic drugs (~10–100 nm) usually formed by self-assembled amphiphilic particles. The solubilization capacity is directly proportional to the volume of the hydrophobic domain of the micelle core, e.g., casein (Yoksan et al. 2010; Abbasi et al. 2014).

(f) *Cubosomes* and *hexosomes* are viscous and formed from a dispersion of inversed cubic or hexagonal mesophases in water. They are synthesized by hydrating the unsaturated monoacylglycerols like monoolein, monovaccenin, and monopalmitolein or phytantriol and used preferably in encapsulation of hydrophilic, lipophilic, and amphiphilic food and drug components (Spicer 2004; Meikle et al. 2017) (Fig. 8.2).

(g) *SLNs* and *NLCs* (30 to 1000 nm) are lipid-based nanoparticles produced from lipids (stearic acid) with a high melting point (>40 c) (Ganesan et al. 2018). The advantages of SLNs and NLCS are nontoxic and have maximum encapsulation efficiency (Rostamabadi et al. 2019).

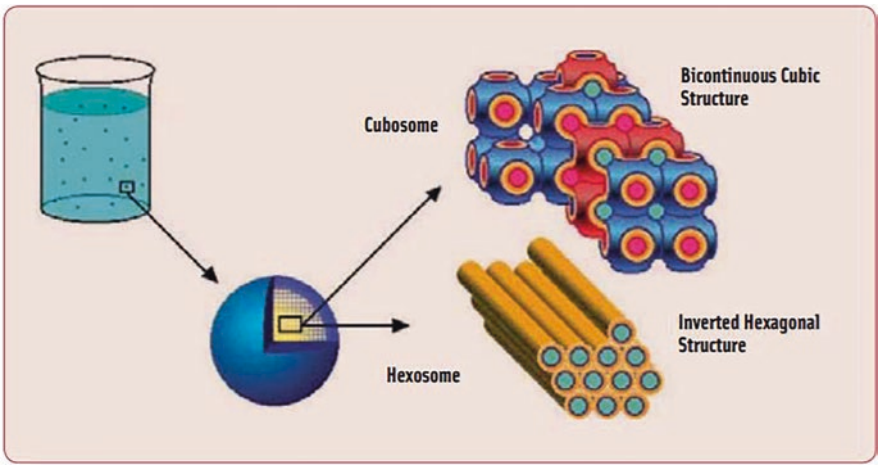


Fig. 8.2 The structure of cubosome and hexosome. (Adapted from Spicer 2004)

8.1.2.2 Biopolymeric Nanocarriers

GRAS (generally recognized as safe) biodegradable and natural biopolymers are used as nanocarriers and classified as follows:

(a) *Polysaccharide-based nanocarriers*
Homopolysachharides (cellulose containing glucose) or hetero polysaccharides (alginates made up of mannuroninc and glucuronic acid) are used as it forms gel by cold, heat set, or isotropic mechanism (McClements 2012).

(b) *Protein-based nanocarriers*
The proteins used for encapsulation are zein, gelatin, casein, myofibrillar, soy, egg, and BSA (bovine serum albumin) proteins (DeFrates et al. 2018).

(c) *Polymeric micelles*
Polymeric micelles (PMs) (10–100 nm) are amphiphilic copolymers containing poly amino acid and propylene oxide (Garti and Aserin 2012; Cho et al. 2015).

(d) *Dendrimers*
Dendrimers (~3–20 nm), a covalently conjugated branchlike structure formed through polymerization reactions (Castro et al. 2018), act as a vehicle to transport hydrophilic nucleic acid-based chemotherapies that cannot pass through the cell membrane (Baker 2009; Bharali et al. 2017; Mendes et al. 2017; Chakraborty 2019).

(e) *Nanocapsules* (~10–1000 nm): Nucleic acid (DNA and RNA) and drugs are restricted in a core-shell-like vesicles with a polymeric coating (Mao et al. 2009; Mendes et al. 2017).

(f) *Nanoparticles* (~20–200 nm): Polymeric nanoparticles include solid carriers that are capable of adsorption, dispersion, and entrapping the active ingredients into the matrix and are synthesized using preformed polymers through solvent

evaporation, dialysis, salting, supercritical fluid technology, and nanoprecipitation. Silicon dioxide, titanium dioxide, and silver nanoparticles are used for sustained release (Arshak et al. 2007; Acosta 2009; Varela-Moreira et al. 2017).

(g) *Nanoconjugate drug molecules are covalently bound to the polymer.* Nanocochleates composed of soy-based phospholipids coil around the micronutrients and enhance the quality of the processed food (Liang and Subirade 2016).

(h) *Virosomes* (~150) are used as carriers in chemotherapy of cancer and vaccine development against viral infections (hepatitis, *H. influenza*) (Krishnamachari et al. 2010).

Nanotechnology based Nutraceutical applications

8.2 Nutraceuticals in Biomedical Applications

Nutraceutical, coined by DeFelice (1989), is an umbrella term used for the intersection of nutrition and pharmaceutical and a food or food product that provides a physiological benefit or provides some protection against chronic disease (DeFelice 1995). About 50%–70% of nutraceuticals are used in developed countries, and this number is increasing by age (Gupta and Prakash 2015). Women use more nutraceuticals than men. Nutraceuticals include functional foods and beverages and dietary supplements.

Classification of Nutraceuticals

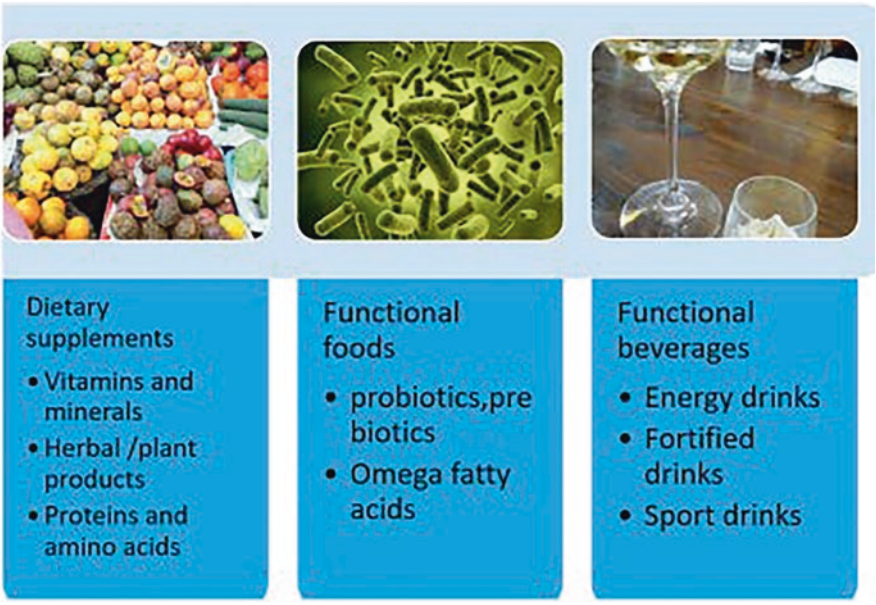
A dietary supplement is a nutrient-containing drug obtained from food or food products that are prescribed in the form of powder, capsule or pills, and liquids (tonics, syrups). Functional food may be whole or fortified food with beneficial health effects (Chaudhry et al. 2008; Isidoro 2020) (Table 8.1).

The bioactive phytochemicals derived from plants have become a greater ingredient (Charu et al. 2007). Out of these phytochemicals, several groups of polyphenols (flavanones, isoflavones, anthocyanins, proanthocyanidins, ellagic acid, and resveratrol) are currently found useful in the nutraceutical industry. Nutraceuticals as dietary supplements provide incredible health and medicinal value for the prevention and treatment of various ailments (Prankash et al. 2012; Charu et al. 2014; Prakash and Sharma 2014).

Primary food elements including carbohydrates, proteins, and lipids necessary for basic life provide energy and normal the function of the body. However, secondary elements like vitamins and minerals are essential but not produced endogenously; hence, they must be administered in the diet or in the form of medicine (Bernela et al. 2018; Assadpour et al. 2020).

Nutraceuticals are minor food elements that regulate normal physiology and provide the defense against invading pathogens and cancer cells by immunomodulating effect (McClements 2012).

Table 8.1 Classification of nutraceuticals



However, when nutraceuticals are ingested orally, poor water solubility, low permeability, reduced absorption, insufficient gastric residence time, and decreased bioavailability are the major factors that limit the efficacy of the nutraceuticals (Augustin and Hemar 2009).

8.3 Nanonutraceutical Drug Delivery System

Nanoencapsulation of food and nutrients with GRAS and ecofriendly biodegradable material facilitate sustained and steady release of the active ingredient (Sen and Pathak 2016; Dima et al. 2020).

Materials used for encapsulation of nutraceuticals are as follows:
- Polysaccharides: plant starch, carrageenan, pectin, etc.
- Microorganism: dextran, xanthan gum, etc.
- Protein food: egg, milk, oat, soy, gelatin, etc.
- Emulsifiers: Tween, sugar esters, monoglycerides, lecithin, etc.

Nutraceuticals are encapsulated and formulated based on shape, particle size, zeta potential, etc. of the nanomaterial to improve the stability, bioavailability, and biocompatibility of the nutraceutical (Fig. 8.3). The basic steps to be considered during the selection of nanocarriers are identification, isolation, purification, and characterization of the properties of incorporated food components (nutritional and

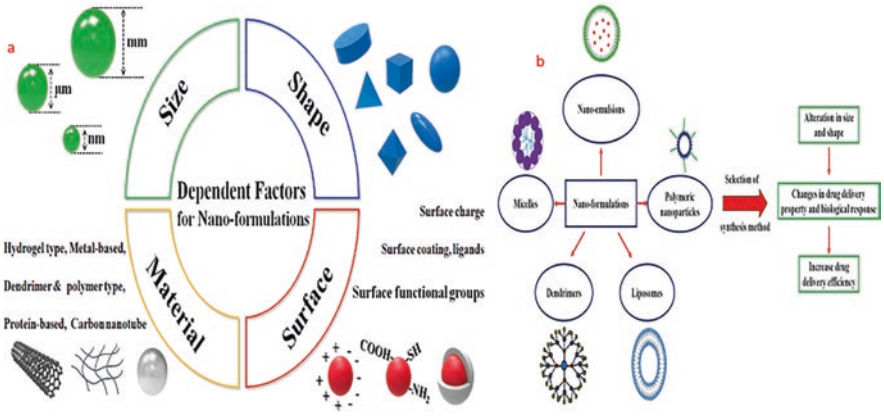


Fig. 8.3 Factors determining synthesis of nanocarriers and biosynthetic process. (Adapted from Jeevanandam et al. 2016; Bajpai et al. 2018)

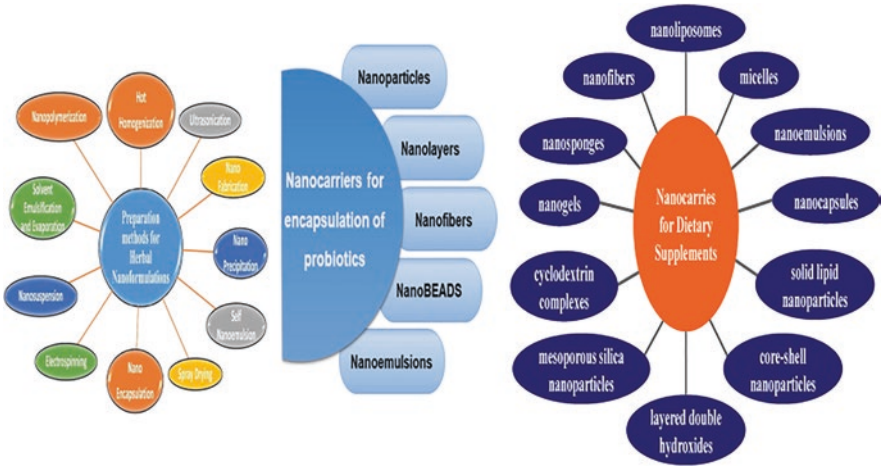


Fig. 8.4 Nanonutraceutical carriers. (Adapted from Dhawan et al. 2018; Jampilek et al. 2019; Machado et al. 2020)

medicinal value) (Jeevanandam et al. 2016; Bajpai et al. 2018). Nanoformulations of vitamins include spray cooling, spray drying, phase separation, liposome, solid lipid nanoparticles (SLN), and inclusion complexation. Figure 8.4 depicts nanoencapsulation of herbal products, probiotics, and dietary supplements (Dhawan et al. 2018; Jampilek et al. 2019; Machado et al. 2020). Archeosome is a nanoencapsulated delivery system for antioxidants pp obtained from archaebacterial membrane lipids. The degradation of milk is prevented by nanoencapsulation of α- tocopherol in fat droplets and canola active oil for the nanoencapsulation of fortified phytosterols with canola oil and Shelf-life of vitamins B9, B12, and vitamin C were increased using chitosan biopolymer (Chaudhry et al. 2008; Ali et al. 2019; Czech et al. 2019).

The instrumental techniques used to characterize the physicochemical parameter of the nanomaterial are the following:

The particle size in nanometer is determined using (TEM, SEM, dynamic light scattering, laser diffraction, static image analysis, etc), crystal morphology (powder x-ray diffraction), magnetic properties (vibrating sample magnetometer), chemical parameters (FTIR, NMR, Raman spectroscopy, organic (LC-MS), inorganic(inductively coupled plasma spectroscopy, Electron microscopy with energy-dispersive X-ray spectroscopy).surface chemistry(Xray photon electron microscopy, scanning probe microscopy) etc.

Limitations of Nutraceuticals

However, physicochemical properties of nutraceuticals have a number of limitations.

All these factors may contribute to reduced bioavailability and hence reduced therapeutic effect.

Nanoformulation of nutraceuticals offers improved pharmacokinetic and pharmacodynamic properties that facilitate target-specific treatment and diagnosis, low systemic side effects, and accurate therapeutic monitoring (Chau et al. 2007) (Table 8.2). Therefore, more innovative research are being carried out for the transition of nutraceuticals into nanonutraceuticals, and most of them are patented (Razak et al. 2018).

The factors affecting pharmacokinetics of nanonutraceuticals include complete absorption, targeted delivery to the site of action, metabolized in the liver and excreted mainly via the kidney in the urine (Fig. 8.5).

The main advantages of nanocarrier-mediated nutraceutical delivery is enhancement of solubility, rate of dissolution and oral bioavailability, and reduction in dosage, time of onset, and systemic toxicity (Fig. 8.6) (Bae and Park 2011; Klajnert et al. 2013; Shende and Mallick 2020).

Major advantages of nanosizing of nutraceuticals are depicted in Fig. 8.7.

Table 8.2 Comparison between nutraceutical and nanonutraceuticals

Nutraceuticals	Nanonutraceuticals
Poor solubility	Chemically and physically stable to environmental stresses while preserving its functional characteristics
Instability of the compound	Improve gastric stability of labile bioactive nutrients
Impermeability across the biological membranes	Maintain constant dosage level within systemic circulation
Disintegration in the stomach due to the presence of an acid	Capable of facilitating lymphatic transport
Widespread distribution	Extend the gastric retention time
Nontargeted delivery	Target-specific delivery
High dose required	
Systemic toxicity	

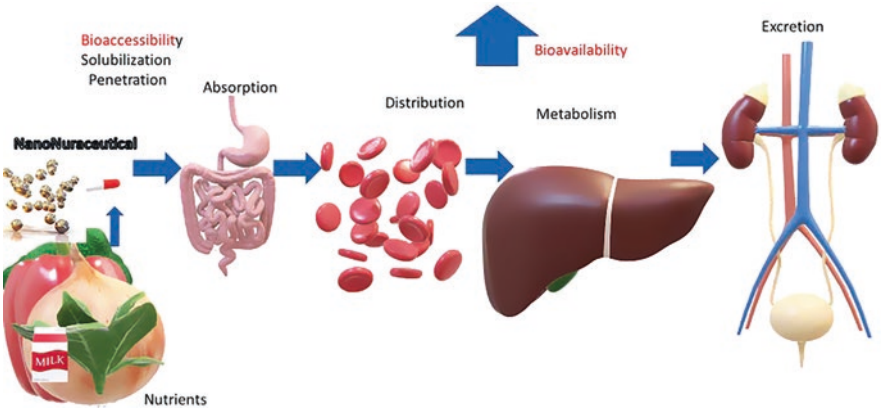


Fig. 8.5 Pharmacokinetics of nanonutraceuticals

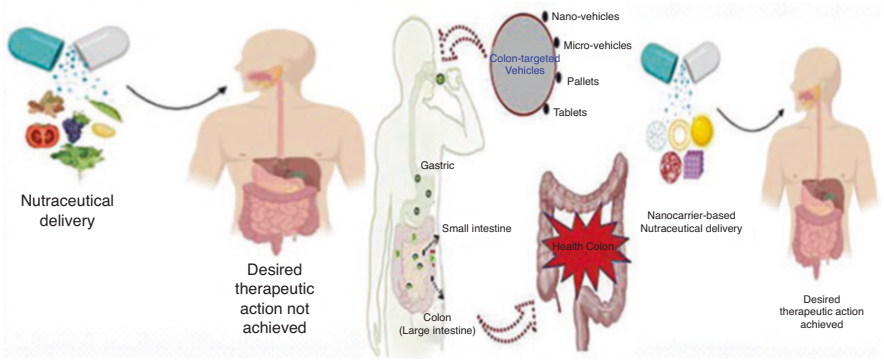


Fig. 8.6 Target-based nanonutraceutical drug delivery. (Adapted from Shende and Mallick 2020)

8.4 Nanosize Nutraceutical Formulations in Biomedical Applications

Nanonutraceuticals in medicine include screening of drugs, gene and drug delivery, and diagnosis, detection, and monitoring of diseases (Fig. 8.8).

Nanoformulated drugs enhance effectiveness in different dosage forms.

Nanonutraceuticals in healthcare: nanovitamins, nano-calcium, nano-magnesium, nano-iron, nanoprobiotics, and nanophytochemicals

8.4.1 Nanovitamins and Nanominerals

Nanoformulation of vitamins and minerals is of foremost importance as it aids in target-specific delivery of vitamins/minerals to the tissues and organs (Iman Katouzian and Seid Mahdi Jafari 2016). Therefore, wastage and adverse effect due

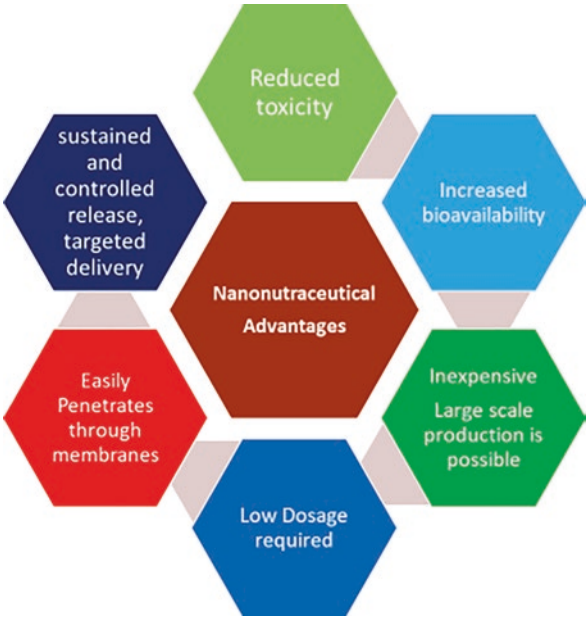


Fig. 8.7 Major advantages of nanonutraceuticals

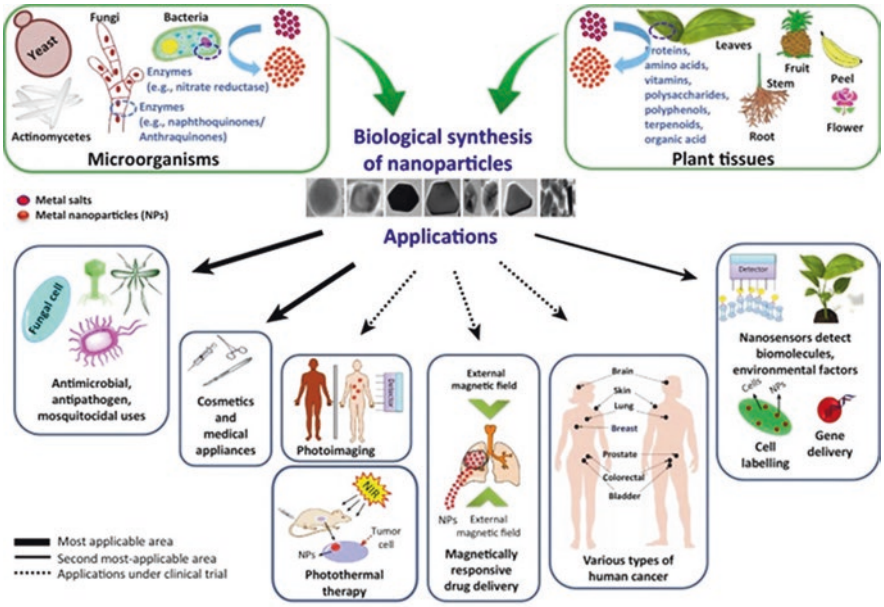


Fig. 8.8 Biomedical applications of nanotechnology. (Adapted from He et al. 2019)

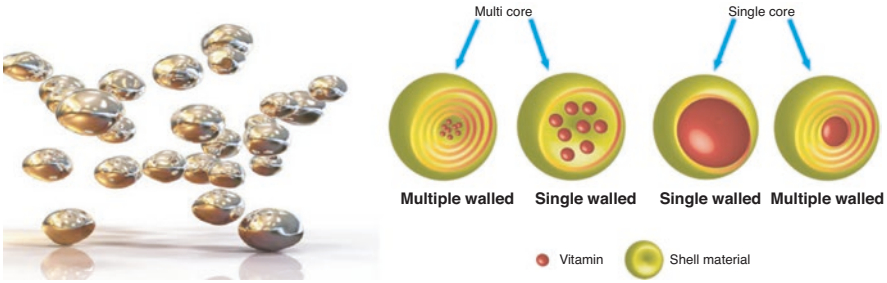


Fig. 8.9 Nanoencapsulation of vitamins. (Adapted from Iman Katouzian and Seid Mahdi Jafari 2016)

to higher dosage is minimized, e.g., nanoencapsulation of vitamins and minerals with liposomes (phospholipids) (Fig. 8.9).

The Merits of Nanoencapsulated Vitamins and Minerals

The dissolution rate of drugs is quick comfortable to swallow, reaches the intestine directly hence complete absorption of vitamins and minerals due to the prevention of first-pass metabolism and destruction by gastric juice, distribution and bioavailability is high and enhanced therapeutic action due to target-specific delivery. Additionally, nanotechnology enables to reduce the usage of additives, fillers, and binders during the manufacturing processes.

8.4.2 Nanoencapsulation of Probiotics

The imbalance or disequilibrium in normal gut flora results in pathological conditions due to disturbances in cellular components. Numerous nutraceutical probiotics counteract the effect of ROS production and thereby can prevent major ailments that include cancer and cardiac and cerebrovascular diseases (MCquade et al. 2019) (Fig. 8.10). Recently, nanoencapsulation of probiotics has been studied with gold and selenium (10–1000 nm) nanoparticles (Pathak and Akhtar 2018; Machado et al. 2020).

The probiotic metabolites produced in the form of secretory proteins (extracellular proteins), short-chain fatty acids, enzymes, extracellular vesicles, bacteriocins, indoles, prodigiosin, and menaquinones enhance the mucus secretion and intervene with the receptor function as a defensive mechanism to afford the protection to the epithelial layer of the intestine (Biersack and Schobert 2012; Kumar et al. 2012; Sumathi et al. 2014).

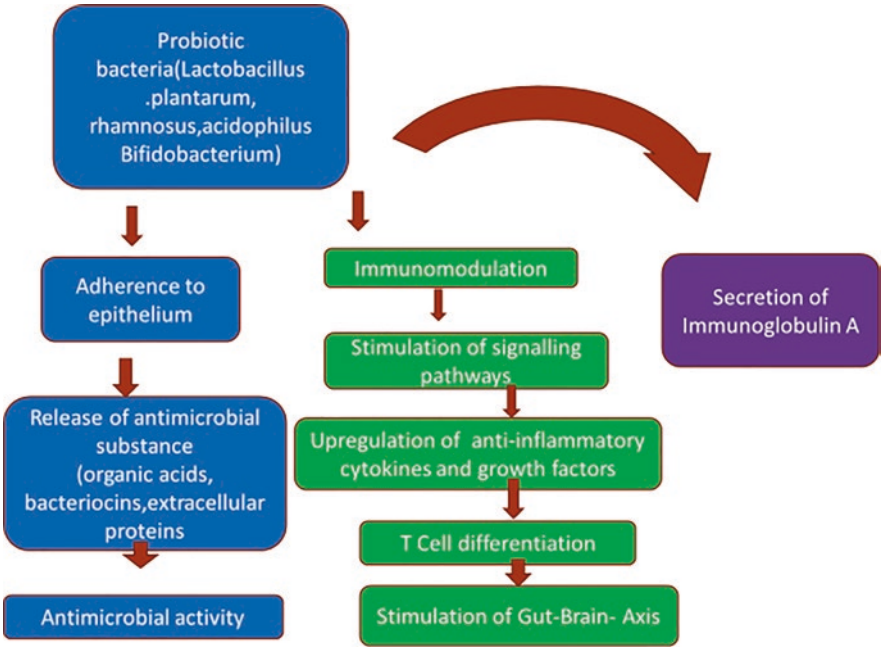


Fig. 8.10 Pharmacodynamics of probiotics

8.4.3 Nanophytochemicals

Similarly, phytochemicals including polyphenols, flavonoids, carotenoids, and glycosides can be effectively utilized in the treatment of hypertension, diabetes, cancer, and GIT disorders and as an immunostimulant owing to their antioxidant potential (Bayir et al. 2019). Nevertheless, the main drawback of the phytochemicals was low bioavailability. Nanoencapsulation of the phytochemicals with small size lipids increases the oral bioavailability and improved therapeutic efficacy due to targeted delivery (Roy et al. 2021; Traitler et al. 2015; Üner 2016; Zachariah et al. 2020) (Fig. 8.11).

Pathophysiology of Cancer, Infectious Diseases, and Inflammation

The imbalance between the ROS production and antioxidant defense mechanism creates oxidative stress that leads to various pathological conditions. ROS interacts with the biomolecules (lipids, a cellular protein, DNA, and RNA) and causes physiological and biochemical alterations in the cell leading to various diseases (Lee et al. 2004; Nosrati et al. 2017; Zewen et al 2018) (Fig. 8.12a).

Nutraceuticals induce the antioxidant mechanism through stimulation of NrF2, ARE and other genes that are involved in antagonizing the adverse effect due to ROS and RNS production leading to deleterious effects (Fig. 8.12b) (Seifalian et al. 2014; Li et al. 2017b; Prasad et al. 2017; Calvani et al. 2020; Godugu et al. 2020).

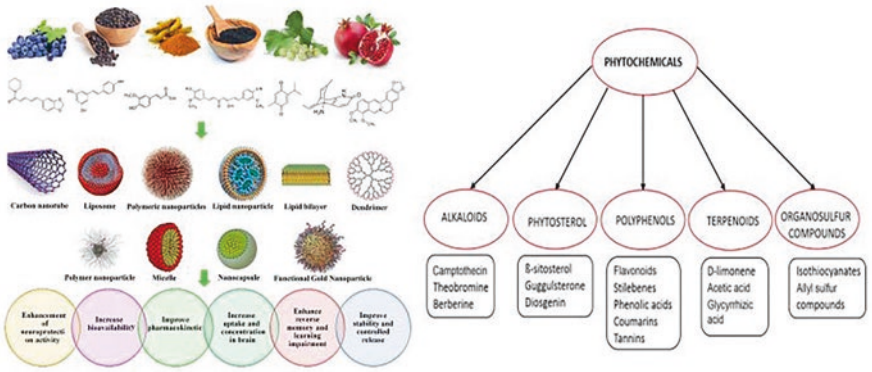


Fig. 8.11 The different forms of phytochemicals and its nanoencapsulation. (Adapted from Bayir et al. 2019; Zachariah et al. 2020)

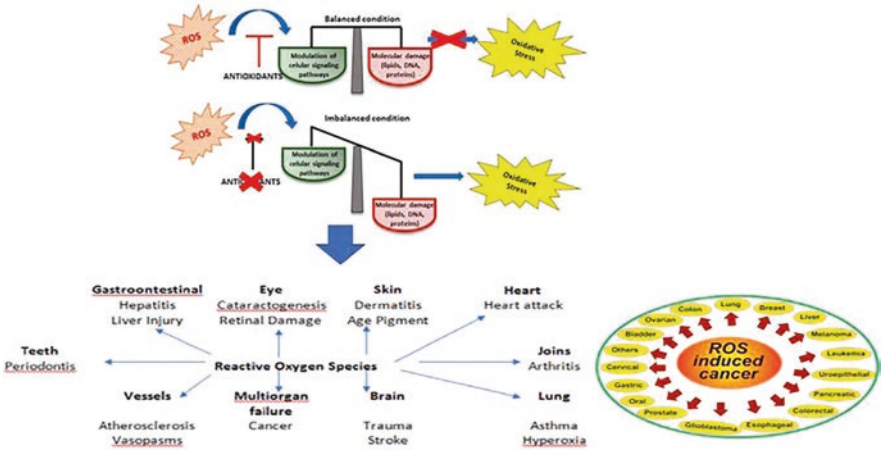


Fig. 8.12 (**a**) Pathophysiological mechanism involved in cancer, infectious diseases, and inflammation. (Adapted from Lee et al. 2004; Prasad et al. 2017; Calvani et al. 2020). (**b**) Nanonutraceuticals in cancer, infectious diseases, and inflammation

8.5 Nanonutraceuticals in the Chemotherapy of Cancer

The mechanism of action of nutraceutical are mainly by affecting epigenetics (up- or downregulating DNA methylation and acetylation of protein, stimulating specific miRNAS, downregulation of B-Cell lymphoma-2(Bcl-2)/ cyclin 01, angiogenic factors, metalloproteinases-9, and IL-6 pathways by blocking inflammatory pathways and NF-kB inhibition (Hegazy et al. 2019). Nutraceuticals reset the normal epigenetic marks and control the metastasis condition including hematological malignancies (Deshantri et al. 2018).

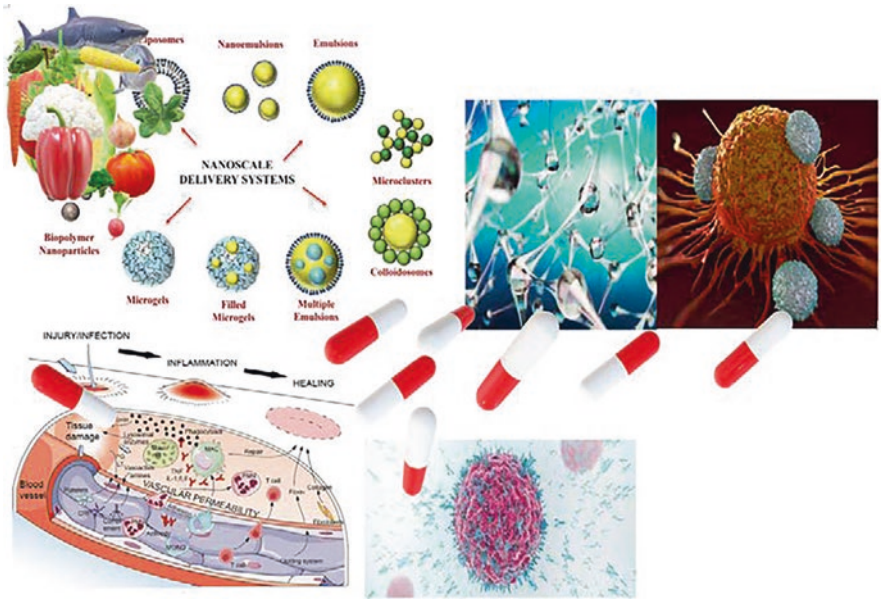


Fig. 8.12 (continued)

Phytochemicals possess antioxidant activity that plays a pivotal role in cancer therapy by preventing the oxidative stress-induced DNA damage, e.g., indoles in cabbage decrease estrogen and thereby the risk of breast cancer (Biersack and Schobert 2012; Singhal et al. 2017). Capsaicin, in chili pepper, protects DNA from carcinogens (Clark et al. 2015). Nanoformulation of these nutraceuticals similar to nanomedicines will facilitate specific and targeted effects with enhanced benefits (Wolfram and Ferrari 2019; Czech et al. 2019; Podsednik et al. 2020).

The probiotic action is mediated through the production of antimicrobial substances, multi-pathogen competition, protection of epithelial layer through secretion of mucus, and immunomodulation. The probiotics adhere to the epithelium and prevent the entry of pathogens. Probiotics affect the immune system by augmenting and upregulating the signaling pathway leading to anti-inflammatory responses via the gut-brain axis (Iacono et al. 2011; Sumathi et al. 2012; Dasari et al. 2017; Langella et al. 2019) (Fig. 8.13b).

Moreover, bioactive nutraceuticals interfere in the electron transport chain mechanism by augmenting phosphorylation and AMPK production. Simultaneously, nutraceuticals will cease the spread of cancerous cells and will provide resistance to ROS-induced cell damage during chemotherapy through synergistic prooxidant activity with anticancer drugs (Hegazy et al. 2019; Pratheeshkumar and Kuttan 2011).

The biotransformation or detoxification process involves phase I (non-synthetic) and phase II (synthetic) pathway. Phase I biotransformation may lead to the accumulation of toxic metabolites that can induce cancer. Hence, activation of phase II synthetic pathway will lead to excretion of these tumorigenic potential compounds.

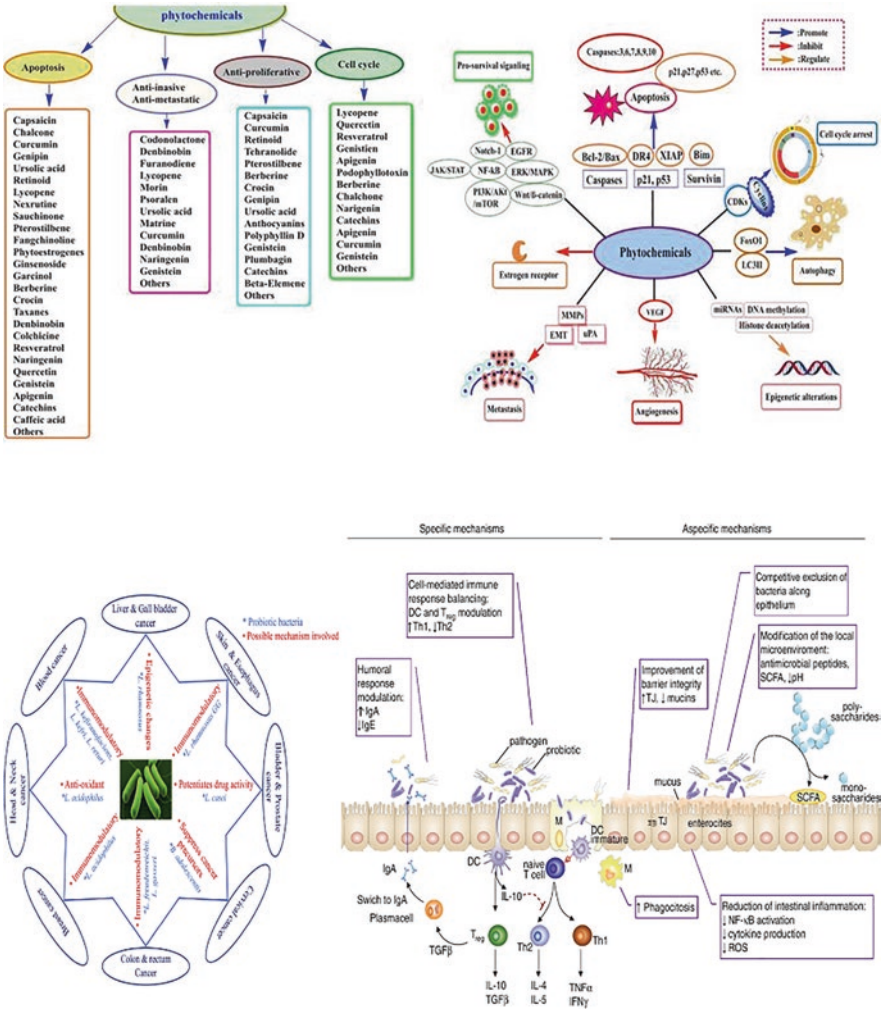


Fig. 8.13 (**a**) The anticancer activity of a. phytochemicals. (Adapted from Iqbal et al. 2018). (**b**) probiotics. (Adapted from Iacono et al. 2011; Dasari et al. 2017)

Nanonutraceuticals upregulate synthetic phase II detoxifying enzymes and lower the excess production of toxic intermediates that can lead to tumorigenic potential and inflammatory responses (Zhao and Agarwal 1999: Zhu et al. 2020).

Nanoformulations of nutraceuticals allow the specific target of tumor cell that surpasses hepatic metabolism and improves efficacy and safety due to dosage reduction and prevention of toxic effects (Flores et al. 2017; Li et al. 2019b).

The phytochemicals possess medicinal value in cancer chemotherapy due to its antioxidant activity and suppression of oxidative stress-induced DNA damage (flavonoids, capsaicin, etc.) and reduce hormone (vinca alkaloids, cabbage in breast

cancer). Nano targeting of tumor requires active high-affinity ligand for interacting with the target moiety which is overexpressed in cancerous cells (Clark et al. 2015; Iqbal et al. 2018; Jampilek et al. 2019; Lungu et al. 2019). Phytochemicals so far studied are noscapine, berberine, brucine, eugenol, homoharringtonne, sanguinarine, taxifolin, quercetin, dihydroartemisinin, gambogic acid, ursolic acid, nobiletin, ellagic acid, curcumin, etc. that acts by inhibiting STAT-3 signaling pathway and vascular endothelial growth factor (VEGF) and regulation of miRNA expression and platelet-derived growth factor (PDGF) receptors (Eun and Koh 2004; Li et al. 2012; Srivastava et al. 2016; Luo et al. 2017; Abdullah et al. 2018; Soto-Quintero et al. 2019; Madkour 2020) (Fig. 8.13).

Vitamins that are used in the therapy of various cancer like colon, rectal, ovarian, and breast include folic acid, B6, B12, and vitamin D that act by interfering with DNA synthesis, receptor-mediated activity, and cell signaling pathways (Liu 2011; Kuppusamy et al. 2014; Pludowski et al. 2019; Singh et al. 2020).

Subsequently, the limitations of physicochemical properties of phytochemicals and probiotics that include polyphenols, phytosterols, carotenoids, vitamins, and minerals are solubility, stability, and permeability that can be overcome by utilizing natural bioactive nanocarriers (PLGA, chitosan, and natural that can improve bioaccessibility and bioavailability) (Boik 2001; Haidar et al. 2008; Sundraraman and Jayakumari 2019). Recent research with nanoencapsulated nutraceuticals has proven effective against various types of cancer cells as it increases the bioavailability of up to 80% (Sahoo et al. 2017; Loutfy et al. 2019; Nayak et al. 2019; Mousa et al. 2020).

Nanocarriers which are proven effective in the encapsulation of nutraceuticals in cancer chemotherapy with highly target-specific delivery and bioavailability are SLN (Date et al. 2019) Biodegradable TPGS-b-PCL NP, Gold NP Triptolide-loaded cationic liposomes, thermosensitive polymer NP hybrid nanomaterial, PEGylated silica NP, dithiodiglycolic acid, Silk fibroin NP, naringenin loaded PCL NP,, naringenin-loaded PLGA NP PLGA, PLA-vitamin E TPGS copolymer, multiwalled carbon nanotubes alginate NPs, PVP conjugate micelle, soy protein NPs α-CD derivatives, liposomal formulation, magnetic nanoprecipitation, NP, hollow capsules, albumin nanosuspension in Brain, cardiovascular system, leukemia, hepatic, colon, prostrate, lung, renal, neuroblastoma, colorectal, breast, prostate cancers (Yoksan et al. 2010; Teleanu et al. 2018; Zhang 2018; Calvani et al. 2020; Fuster et al. 2020; Montalbán et al. 2018; Salama et al. 2020) (Fig. 8.14.)

Similarly, resistance develops to chemotherapy due to lack of specific target and presence of efflux pumps in cancer cells. Nanotechnology can be applied in diagnosis, treatment, and prophylaxis (Divya Arora and Sundeep Jaglan 2016; Zhang et al. 2018; Sarwar et al. 2019). Nanocarrier-mediated drug or nutraceutical delivery aims at the specific target, i.e., tumor cell, and scientists are still exploring in this recent research area.

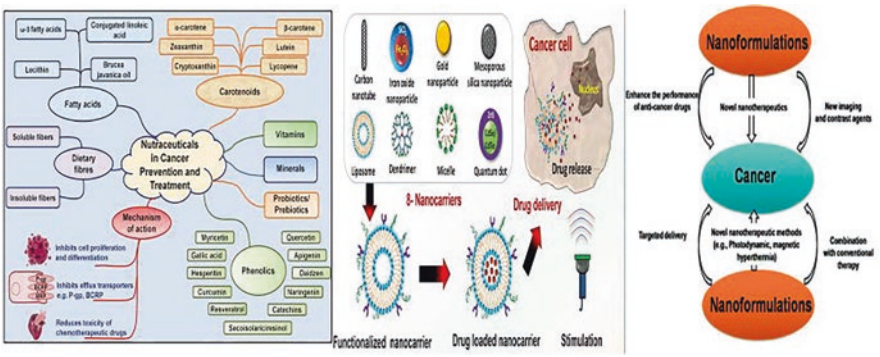


Fig. 8.14 Nanonutraceuticals in cancer therapy. (Adapted from Divya Arora and Sundeep Jaglan 2016; Sarwar et al. 2019; Sahoo et al. 2017)

8.6 Nanonutraceuticals and Anti-inflammatory Activity

Nutraceuticals reduce the reactive oxygen species (ROS) production by either upregulation of anti-inflammatory process or downregulation of inflammatory responses through the alteration of signaling pathways that include NF-κB, M APK, STAT, etc. or mediators (prostaglandins; TNF-α; interleukins 1, 6, and 7; IFN-γ; etc.) (Kim et al. 2013a; Gupta et al. 2016; Afonina et al. 2017) (Fig. 8.15a, b).

Nutraceuticals possess nutrigenomic potential that can alter gene expressions. Utilizing the nutrigenomic principles in the prevention and therapy of major diseases by recovering the normal homeostasis is the novel approach. However, owing to its higher molecular weight and structure and lower bioavailability, it is not recommended for routine use in cancer therapy (Dandawate et al. 2016; Khoder et al. 2016).

Nutraceuticals from plants and animals are extensively studied so as to utilize in chemotherapy and prevention of major diseases owing to their ability to modify inflammatory response and interfere with cellular functions (Chikara et al. 2018; Al-Mssallem et al. 2019).

There exists a cross talk between NF-κB and Nrf2 that regulates the cellular responses to oxidative stress. The anti-inflammatory activity of nutraceutical involves the regulation of multiple gene expression which is influenced by the NF-κB family of transcription factors in coordination with immune responses and inflammatory responses. The most potent activators of NF-κB involved in cell signaling pathways (canonical and alternate) leading differentiation, proliferation, and apoptosis are tumor necrosis factor (TNF-α), bacterial lipopolysaccharide (LPS), and interleukin (IL)-1β (Jesus and Yamamoto-Furusho. 2007; Maithili Karpaga Selvi 2015; Chen et al. 2018; Darwish et al. 2019; Deng 2020).

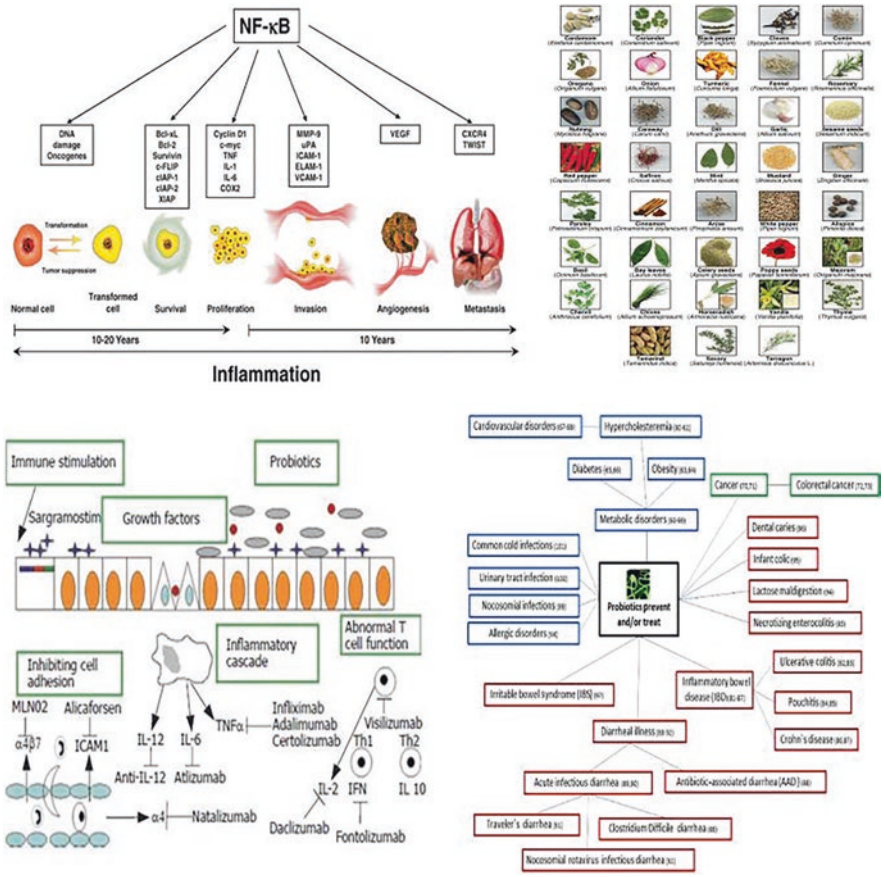


Fig. 8.15 The inflammatory process and anti-inflammatory activity of (**a**) phytochemicals. (Adapted from Agarwal et al. 2009). (**b**) probiotics in inflammatory conditions. (Adapted from Jesus and Yamamoto-Furusho 2007; Khoder et al. 2016)

8.7 Nanonutraceuticals in Medical Imaging

Nanomedicine has been successfully utilized in targeting the specific site and identifying the cancer cells and other serious clinical conditions (Salama et al. 2017).

Nanoparticles that are useful in medical imaging are silica in brain tumor, carbon nanoparticles in colorectal cancer, and ferumoxytol- ironoxide nanoparticles in recognizing the metastasis condition, nanosensors in diseases, nanochips in B- cell lymphomas (Bawarski et al. 2008; Etheridge et al. 2013; Xu et al. 2015; Surendran et al. 2018; Pellico et al. 2019) (Fig. 8.16).

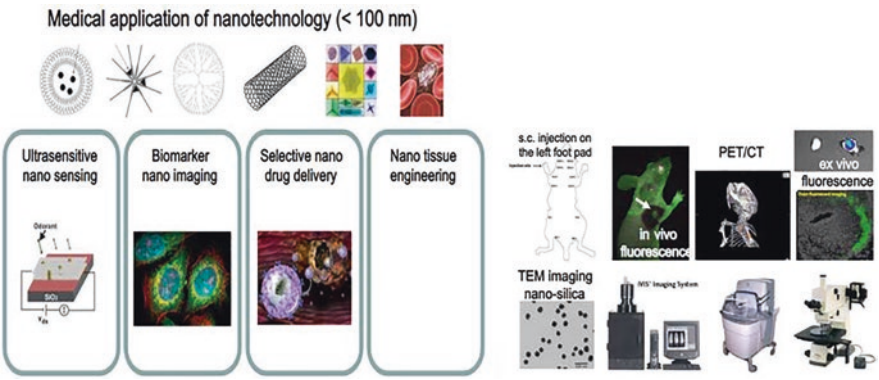


Fig. 8.16 Nanotechnology in medicine and biomedical engineering

8.8 Nanonutraceuticals in Prophylaxis, Diagnosis, and Treatment of Infectious Diseases

Epidemiological studies have indicated that dietary constituents have a major impact on the health of the individual (Chiu et al. 2020). The daily consumption of nutraceuticals in a balanced proportion helps to prevent chronic cardiovascular and neurodegenerative diseases, gallstone, and diabetes. The nutraceuticals regulate the microRNA expression which is involved in the maintenance of normal cellular processes and health conditions (Watson and Preedy 2014; Cameron and Chrubasik 2014; Brüll et al. 2016) (Fig. 8.17).

Furthermore, nutraceuticals cause induction of:

- Glutathione, a major contributor of cellular redox status which gets depleted during oxidative stress and downregulated glutamate-cysteine ligase, a rate-limiting enzyme associated with NF-κB (Zhang et al. 1992).
- Thioredoxin is a disulfide-linked protein involved in thiol-dependent cellular oxidative defense mechanism – signal transduction, cellular growth, and proliferation – and that influences hormones like insulin and glucocorticoid receptors and nitric oxide synthase a transcriptional factor.
- NAD(P)H quinone dehydrogenase, an inducible enzyme that protects cells against the cell damage due to redox cycling of quinones and glutathione depletion.
- Heme oxygenase-1 (HO-1) inducible cytoprotective isoform, a first and rate-controlling enzyme of the degradation of heme into iron, carbon monoxide, and biliverdin that causes direct inhibition of NADPH oxidase activity, hence the SOD generation. HO-1 consists of a binding site for transcription factors of inflammation (NF-κB and activator protein-1 (AP1) and a number of cytokines) (McElvee et al. 2007) (Fig. 8.18).
- The major cardiovascular, cerebrospinal, respiratory, gastrointestinal, and renal diseases and cancer are mainly due to the imbalance between Nrf2 and NF-κB

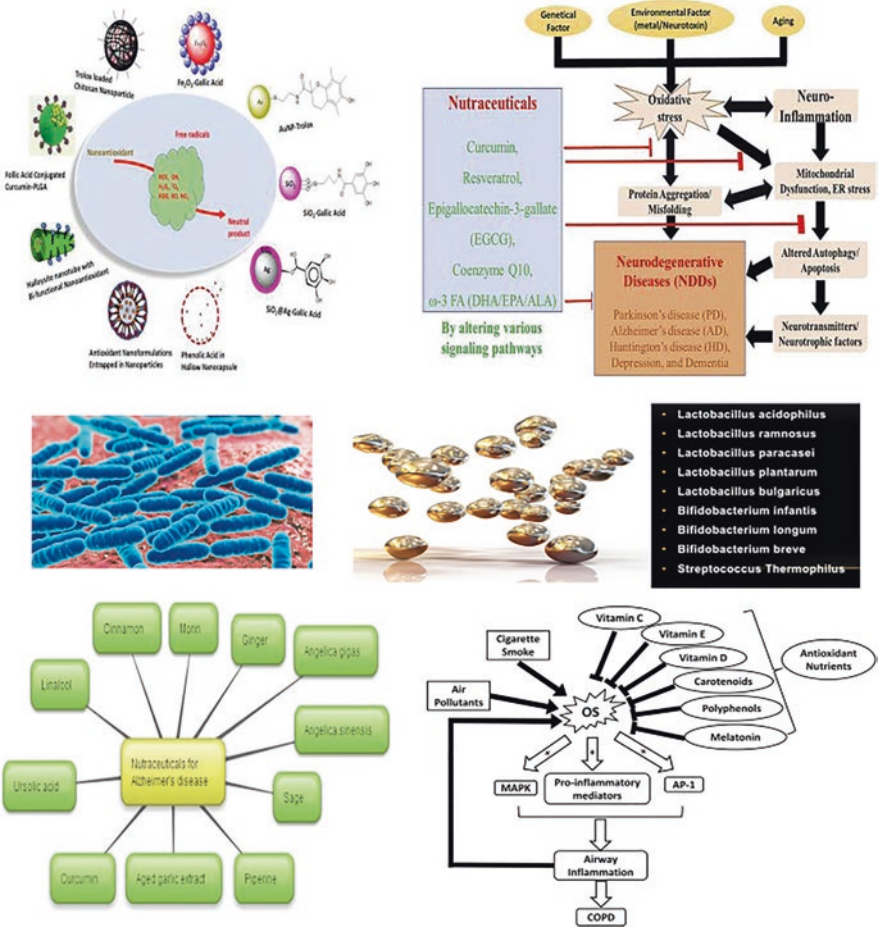


Fig. 8.17 Nanoencapsulation of nutraceuticals in the treatment of diseases. (Adapted from Liu et al. 2018; Chiu et al. 2020)

(Davis et al. 2013; Acevedo-Murillo et al. 2019; Nagaprashantha et al. 2019; Fuster et al. 2020).

Nanoparticles like ω-liposomes can actively penetrate through the immune cells and hence can effectively deliver the nutraceutical (Haidar et al. 2008; Subramani and Ganapathyswamy 2020).

Recent research indicates that fish oil encapsulated with ω-liposomes has a synergistic effect that blocks the production and release of pro-inflammatory cytokines and inflammatory mediators from neutrophils and macrophages and prevents tumor-cell proliferation in head and neck squamous carcinoma (Jampilek et al. 2019; Hamsa and Kuttan 2010).

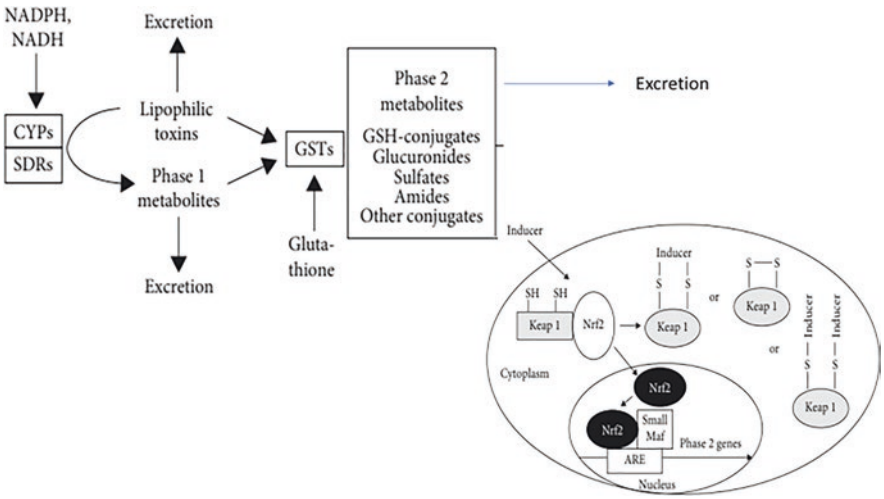


Fig. 8.18 Induction of metabolism by neutraceuticals. (Adapted from Zhang et al. 1992; McElvee et al. 2007)

Similarly, antimalarial herbals include *Ocimum gratissimum*, *Mangifera indica*, *Citrus sinensis*, *Carica papaya*, etc. (Lawal et al. 2015). Peppermint oil and silymarin are effective in the treatment of irritable bowel syndrome. *Artemisia afra*, *Clausena anisata*, and *Haemanthus albiflos* are antitubercular herbals. *Alpinia* and *Acanthopanax* are useful as antiparkinsonian drugs, and *Gardenoia*, *Rubia*, etc. are used in the treatment of gout and arthritis due to its uricosuric effect. *Ficus* have an anthelminthic, antioxidant, and antidiarrheal effect. *Zinger officinalis* is effective against *Leishmania amazonensis. Aloe vera* was effective in reducing chronic ulceration condition that include aphthous ulcer (Pawar et al. 2010; Bhalang et al. 2013; Lage et al. 2015; Duarte et al. 2016). The therapeutic effect of these plant extracts is due to the presence of tannins, alkaloids, terpenes, glycosides, acemannan, brucine, matrine, etc. (Cameron and Chrubasik 2014; Heber et al. 2014; Liu et al. 2016; Saura-Calixto and Pérez-Jiménez 2018; Sudha et al. 2020).

8.9 Nanonutraceuticals as Antibacterial Agents

TLR2 and TLR4 act as innate sensors in the identification of the distinct molecular patterns on the cell wall of invading pathogens and reciprocate with the innate and adaptive immune responses and consequent activation of NF-κB and inflammatory cytokines. Nanonutraceuticals suppress TLR4 oligomerization and reduces hs-CRP, IL-6, and TNF-α. Another gut pathogen *H. pylori*, a pathobiont, is a cancer promoter, causing cancer due to impairment of protein and mineral metabolism due to a rise in pH of gastric content. Nanonutraceuticals afford gastroprotective effect and

modulate the immune response by simultaneous Nrf2 upregulation and NF-Kb downregulation (Grierson and Afolayan 1999; Sahin et al. 2010; Wang et al. 2011; Voukeng et al. 2016; Swanson et al. 2019).

Nanonutraceuticals provide perspective in antimicrobial, anticancer, and anti-inflammatory therapy due to its relatively nontoxic and multiple mechanisms through interference with the activity of phase I and phase II detoxifying enzymes, anti-inflammatory mediators, cancerous cell cycle arrest, apoptosis, and the epigenetic regulation on cyclins, Nrf2-Keap1, CDK, etc. (Sikka and Sethi 2015; Liu et al. 2014; Liu et al. 2016; Mathur et al. 2018; Shende and Mallick 2020).

Subsequently, nanoencapsulation with phytochemicals and probiotics produces a synergistic effect with conventional anticancer antibiotics (nano-TQ with doxorubicin causes upregulation of p53 and downregulation of Bcl2). Nano-TQ offers additional protection against inflammation, diabetes, and cardiovascular and central nervous system diseases due to its antioxidant activity (Alam et al. 2012; Chen et al. 2018). Vitamin E induces apoptosis and enhances the efficiency of chemotherapy (Joshi et al. 2013; Li et al. 2017a; Jampílek and Kráľová 2018; Menditto et al. 2018).

Probiotic produces secondary metabolites with a broad antimicrobial spectrum (*L. salivarius Bacillus megaterium, Pontibacter sps, Lactococcus lactis, L.reutri, Streptococcus lactis antagonizes S. aureus, Listeria monocytogenes, S.hemolyticus, E. faecalis(Ent V)* inhibits *C.albicans*(Boneca et al. 2007; Siezen et al. 2014; Liong 2015; Pathak and Akhtar 2018).

The bioavailability of nutraceuticals depends upon the absorption, bioaccessibility, and biotransformation. Nanocarriers effective in anticancer and antimicrobial therapy include alginic acid, chitosan, titanium dioxide, silver, etc. (Slavin et al. 2017). These nanoparticle acts as a bactericidal agent, alters the metabolic enzyme activities, prevents microbial contamination, and improves the shelf life of the nutraceuticals (Acosta 2009; Alam et al. 2012; Liang and Subirade 2016; Li et al. 2019a).

8.10 Nanonutraceuticals in Antiviral Therapy

Phytochemicals released by *Erythrina abyssinica*, *Mangifera indica*, *Aaloe vera*, and *Warburgia salutaris* are proven effective in the treatment of AIDS patients (Kim et al. 2013b; Konur 2016).

Probiotics that are are commonly used in the treatment of viral infections include *Lactobacillus rhamnosus*, *Lactobacillus gasseri*, *Bifidobacterium bifidum*, *Lactobacillus casei*, *Bacillus coagulans*, *Lactobacillus acidophilus*, *Saccharomyces boulardii*, and *Enterococcus faecium* with or without prebiotic inclusion(galacto oligosaccharide, poly dextrose, hi-maize,rice bran, inulin, pectin are effective in the elimination of viral pathogens by macrophage in HSV-1 and reduced the incidence of (RTIs) through metabolite the production which interferes with the regulation of ca2+ and NSP4 protein involved in reteroviral diarrhea.(Shim et al. 2017; Kanauchi et al. 2018; Liu et al. 2020; Loutfy et al. 2020; Shen 2020).

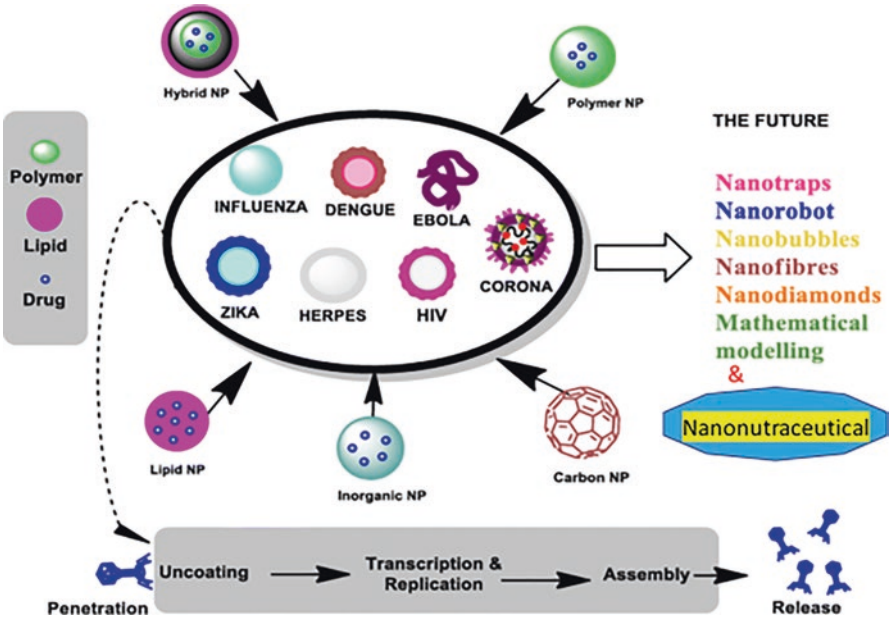


Fig. 8.19 Nanonutraceuticals in antiviral therapy. (Adapted from Chakravarty and Vora 2020)

However, in order to maintain the health benefits of these probiotics and prebiotics, processing, storage, and bioavailability play a crucial role in treatment. Nanoencapsulation with polymers, micelles, and metals has proven to be effective to withstand the adverse conditions of light, temperature, pH, etc. and to regulate the function and viability and also imparts texture, biocompatibility, odor, color, etc. (Fig. 8.19) (Ying et al. 2016; Raddatz, et al. 2020; Rodrigues et al. 2020). The nanocarriers used are nanocomposite, alginate-chitosan capsules, microcapsules, alginate-pectin gels, pectin microparticles, etc. (Chen and Subirad 2006; Ying et al. 2013; Müller et al. 2016; McCarty and DiNicolantonio 2020).

8.11 Utilization of Nanonutraceutical in COVID-19 Therapy: Pharmacological and Toxicological Aspects

The novel pandemic, corona virus disease (COVID-19), a crucial global health calamity, is posing a great threat to the human population as preexisting immune responses may be limited against this new virus (nCoV) strain from Wuhan since December 2019. The new emerging and reemerging animal and human coronaviruses (CoVs) are a major menace and remain challenging to the second world. Most countries around the world have been on lockdown to halt the spread of the virus. Coronaviruses (CoVs) primarily infect birds and mammals but were shown capable

of species crossover by infecting humans in 2002 with SARS and in 2012 with MERS. In spite of intensive efforts taken since the SARS epidemic in 2003, the antiviral drugs to treat CoV infections have not been approved by the FDA so far.

The innate immune system is vital in 2019-nCoV replication. The proteins involved are spike, envelope, membrane, and nucleocapsid protein. The S protein binds to the ACE2 receptor that is most prevalent in the respiratory tract and also present in the heart, kidney, blood vessels, and intestine. ACE2 is protective to the respiratory epithelium (surfactant), and this is one of the reasons for respiratory failure and impact on other organs. The infection causes the overproduction and release of pro-inflammatory cytokines. Most important are IL-1, TNF-a, and IFN. The mostly bind to the Toll-like receptor in macrophages which causes the production of IL-1 beta, destruction and fibrosis of lung tissue, and stimulation of the inflammasome Inflammasomes are formed by the lipopolysaccharide (LPS) that includes pathogen-associated and damage-associated molecular patterns (PAMPs, DAMPs) and pro-inflammatory cytokines (IL1-B, TNF-a). Viruses, bacteria, and fungi mostly contain PAMPs (Bosch et al. 2003; Wu et al. 2020).

The cytokine storm or hypercytokinemia-induced pathological responses play a pivotal role in COVID-19 viral infection. The immune and inflammatory responses include disseminated vascular permeability and coagulation, severe respiratory infections, and natural M protease inhibitors that can be considered as an approach to interfering with viral replication (Conti et al. 2019; Monteil et al. 2020; Fisher and Emdad 2020).

Nutraceuticals have immunomodulating effect and are capable of reducing symptoms of encapsulated RNA viruses that include corona and influenza viruses (Fig. 8.20). Phytochemicals, vitamins, minerals, and probiotics are proven to be involved in host defense mechanism (Pathak and Akhtar 2018; Sander et al. 2019; Adem et al. 2020). Curcumin, quercetin, melatonin, EGCG, resveratrol, vitamins, thymoquinone, and minerals are nutraceuticals that can inhibit M protease and corona viral infection (Alam et al. 2012; Rafiee et al. 2019. Swanson et al. 2019; Jin et al. 2020).

Vitamin D, a fat-soluble vitamin, modulates both innate and adaptive immune responses to respiratory viral infections including *H. influenzae* A and B, respiratory syncytial virus (RSV), parainfluenza 1 and 2, and HCV by production of peptides (cathelicidin) with antimicrobial activity (Liu 2011; Pludowski et al. 2019; Zdrenghea et al. 2016).

Vitamin A stimulates immune function and regulates both cellular and humoral immune responses; vitamins have been effective in chronic hepatitis B and deficiency leading to impairment of cellular and humoral immunity (Stephensen 2017). Vitamin C deficiency may cause dysregulation of host defense mechanism and affects T cell-mediated immune responses and adaptive immunity. Vitamin B deficiency results in immunosuppression due to reduced blood cell count (Liu 2011; Huang et al. 2018; Skrajnowska and Bobrowska-Korcza 2019).

The combined therapy with a multivitamin and multimineral supplement improves the immune responses to corona viral infections (Hemilä and Chalker 2013).

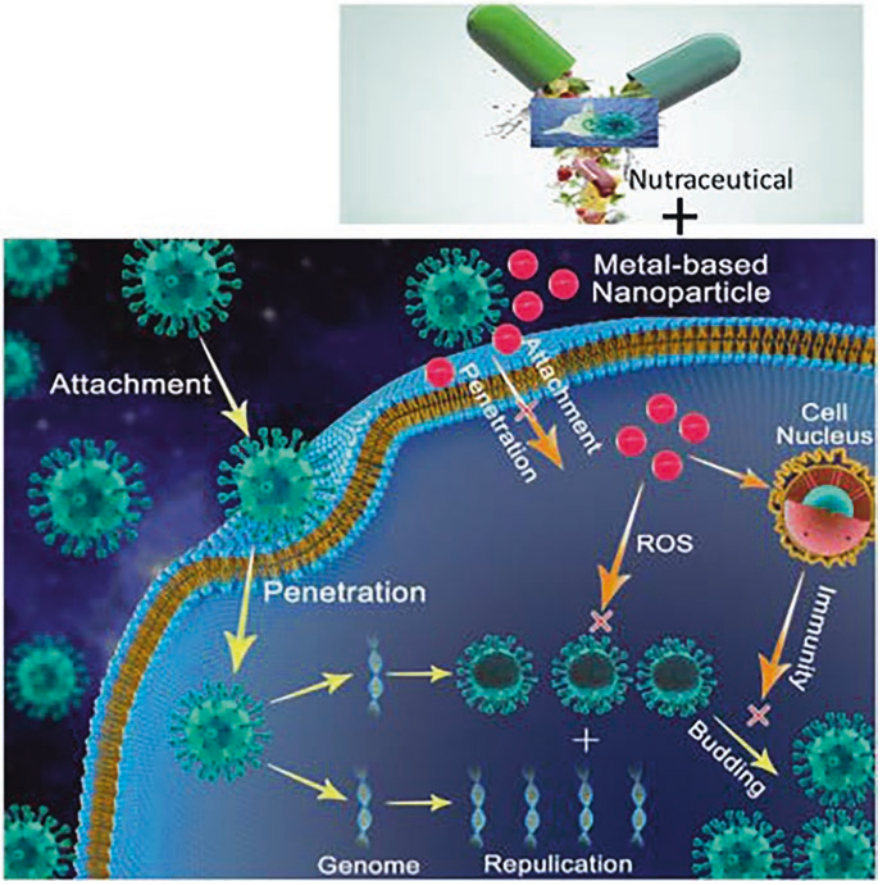


Fig. 8.20 (**a**) Possible utilization of nanonutraceutical in COVID therapy. (**b**) Mechanism of action. (Adapted from Zhou et al. 2020)

Zinc is a crucial trace element involved in immunity, growth, and development. Zinc deficiency leads to a disrupted zinc homeostasis that alters immune mechanism and causes an alteration in intercellular communication, defective lymphopoiesis, and production of reactive oxygen species that results in reduced resistance to viral infections (HIV, HCV) (Acevedo-Murillo et al. 2019; Hemilä Chalker 2019).

Selenium is an antioxidant with anti-inflammatory properties. Selenium in reduced concentration will increase mortality due to lack of immune response and when the concentration is gradually increased offers protection against viral infections in a dose-dependent manner with an increase in IL-10 and T-cell proliferation (poliovirus) (Rayman 2012; Limaye et al. 2018; Mousa et al. 2020).

Magnesium controls immune function through immunoglobulin synthesis and adherence of T helper cells and B cell, affecting the binding of IgM and macrophage response to lymphokines. Iron is essential for the cells that make up our immune

defenses (Liang et al. 2012). Copper is important in the differentiation and development of immune cells. Copper has antioxidant activity and its supplements increased the activity of plasma ceruloplasmin, benzylamine oxidase, and superoxide dismutase activity (Potter et al. 2011; Rosato et al. 2017; Devi and Ahmaruzzaman 2018; Li et al. 2019c; Sevanian 2019).

Omega-3 fatty acids, beta 1,3/1,6 glucan have been recently used as an immune booster for the infection-fighting antibodies and cytokines in viral infections (upper respiratory tract infections, flu, hepatitis, and HPV the phytochemical act as immune boosters and augments the functions of macrophages, white blood cells. Similarly, a Chinese herb *Astragalus* has antiviral property and shortens the duration and intensity of *H. influenza* (Brüll et al. 2016; Müller et al. 2016).

Probiotics are beneficial in COVID therapy. Previous studies indicate that those gut microbes.

Bacteroides ferment dietary fiber into short-chain fatty acids (acetate, butyrate, and propionate that facilitate the formation of the gut barrier and stimulate mucus production that acts as a protective layer against invading pathogens) (VanHook 2015). The researchers found that dietary fiber or butyrate was able to reduce the influx of immune cells called neutrophils into the airways and another mechanism that may be involved is the PPAR pathway. The microbiome competes for binding sites on the intestinal epithelial cells by blocking (i) pathogenic attachment and entry in the host cell, (ii) nutrients in the GI tract to preserve its habitat, and reduces the flourishing of the pathogen by producing antiviral substances. (Sanders 2008; Mackie 2012; Schwabe and Jobin 2013; Rook et al. 2017; Shen et al. 2018a, b; Kanauchi et al. 2018; McQuade et al. 2019; Song et al. 2019).

Recently phytochemical constituents are preferred as immunostimulants for the protection against viral infections. Green tea (polyphenols, catechin epigallocatechin, epicatechin gallate) (Sahin et al. 2010) and lycopene (non-provitamin A carotenoid) provide protection against cellular disturbances due to free radicals (Yang et al. 2017). Curcumin reduces reactive oxygen species and causes degradation of antioxidant enzymes by modulating Nrf2 (He 2012; Wang et al. 2011; Farooqui 2016) bound oligonucleotides that offer stability to DNA triplexes or G-quadruplexes and tumors inhibiting telomerase and topoisomerase (Ortiz et al. 2014) Vanillin used worldwide could reduce free radical cancer promotion (Bezerra et al. 2016). Taurine and curcumin in cactus pear is used for its anticancer, antiviral, and antidiabetic properties (Sabella 2014; Jiang et al. 2018; Meng et al. 2018; Loutfy et al. 2019. Shao et al. 2020).

8.11.1 Toxicities of Nanonutraceuticals

The adverse effects are prominently observed with nanonutraceuticals as there are fewer in vivo studies to assess the efficiency of nanoparticle encapsulation. There are controversial results wherein a set of research have proven that antioxidants, such as vitamins C and E, and carotenoids enhance the efficacy of radiation or

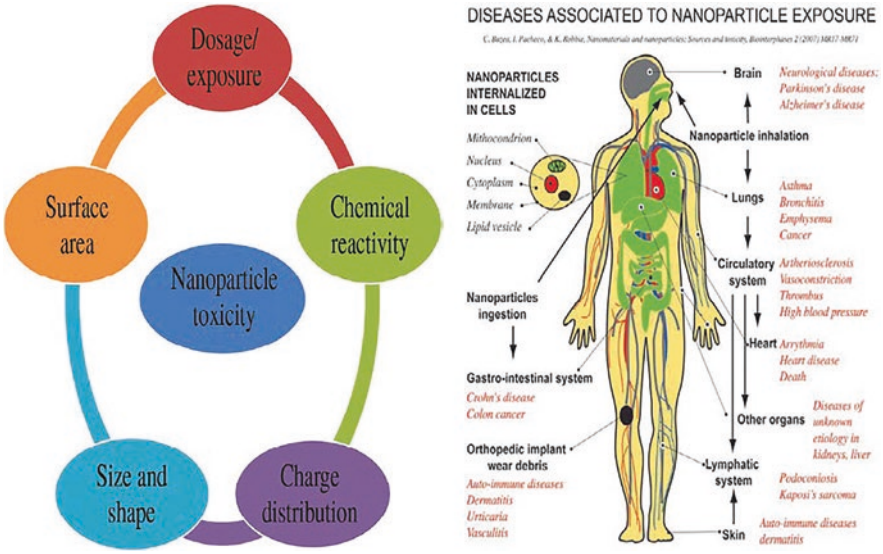


Fig. 8.21 (**a**) Physicochemical parameters of nanotoxicity. (Adapted from Naseer et al. 2018). (**b**) Toxic symptoms of nanoparticles. (Adapted from Cristina Buzea 2007)

chemotherapy by increasing tumor response and minimizing systemic toxicity. Contrastingly, another study reveals that the antioxidants protect the cancer cells from chemotherapy or radiation induced damage (Lam et al. 2004) washed 3 kinds of carbon nanotubes into the lungs of mice;all caused lung granulomas), (Dupont injected nanotubes into rat lungs; 15% died -highest death rate seen in such studies) (Rice University studies show nanoparticles bioaccumulate in living tissues). The toxicities of nanonutraceuticals mainly depend on the dosage of the nutraceuticals and nanoparticles and physicochemical chemical properties of the nanoencapsulation (Naseer et al. 2018) (Fig. 8.21a). The nanocarriers can induce mild to severe toxicities in tissues and organs (Fig. 8.21b) (Cristina Buzea 2007:Andreas Elsaesser and Howard. 2012; Zhao et al. 2015; Limaye et al. 2018; Sukhanova et al. 2018; Marcinowska-Suchowierska et al. 2018).

8.12 Challenges and Future Perspectives

Nanonutraceutical formulations remain a great challenge due to the cost involved in the production. Nutraceuticals are highly complex molecules; hence, the choice of nanoparticles for encapsulation according to size, shape, vehicles, and optimization of dosage for therapeutic purpose is the new area of research. Further, large-scale production requires highly efficient equipment, more space, and time which in turn leads to a higher cost of production and acquisition. Proper planning and implementation of a cost-effective method is the essential criteria for the formulation of

nanonutraceuticals. For therapeutic use, efficacy, potency, and toxicity should be carefully monitored through pharmacokinetic and pharmacodynamic profiling of nanonutraceutical studies based on specific targeting, bioavailability, and toxicity studies. However, nanonutraceuticals seem beneficial in the prevention of infections and inflammation and in cancer therapy. Hence, nanonutraceutical formulations with vitamins, minerals, herbal supplements, and probiotics represent a valuable and promising strategy to prevent diseases and maintain health status in the individual. However, the encapsulation of nanocarriers with nutraceuticals should be strictly monitored with guidelines from regulatory authorities for the safe and efficient use of these nanonutraceuticals.

8.13 Conclusion

Nanonutraceuticals are safe for administration with better bioavailability; however, utilization of nanomaterials in the food and the pharmaceutical industry remains a conflict of the modern world due to inadequate invasive studies. The nanotechnology can increase the shelf life of food and drug, reduce the dosage and toxicity, prevent microbial contamination, and improve food and drug packing using nanosensors and production of nanonutraceutical. However, the major concern is toward the toxicity of engineered nanomaterials in nanofood or nano-drug on human health and environment. The one way that can solve this concern is proper research, information, and regulation of nanofood. Several entities are now in place to govern every aspect of nanofood, starting from the synthesis of nanomaterials to their usage in food industries. Laws and regulation implemented by entities such as the US-FDA, ESFA, etc. need to be followed to have a nanofood that is safe for human consumption. There is an urgent need for natural products as a medicament to overcome pandemic diseases. Recently, standardization of dosage of herbal products after identification and screening with human cell line studies has thrown light in the nanonutraceutical research area. The future work will be to explore and develop novel nanonutraceutical with valid in vivo studies for the utilization in severe pathological conditions leading to life-threatening infections and inflammatory diseases and cancer.

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Chapter 9
Trends of Biogenic Nanoparticles in Lung Cancer Theranostics

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9.1 Introduction

Cancer is a fatal disease that has significant impact on mental health of the diagnosed patients. It imposes emotional, physical, and economic burden on individuals and also on the society. Being noncommunicable in nature, cancer and mental illness are closely interdependent. Cancer patients undergo stress, anxiety, and depression that tend to have a negative effect on the physical stability of the patient and their mortality (Purushotham et al. 2013). Cancer deaths increase each year with the simultaneous increase in the number of new cases annually. According to the estimation of International Agency for Research on Cancer, 22.2 million new cancer cases would be recorded by 2030 with an average of 13.2 million deaths worldwide (Cryer and Thorley 2019). Cancer is certainly an insidious disease that takes away millions of life per year, yet cancer is curable. Lack of knowledge on the possibilities of treatment and exaggeration on the painful deaths are the major reasons that affect the mental health of the patients. Since the past, new treatment strategies are being identified and implemented to treat and cure cancer in a painless manner. However, the hesitation and anxiety among patients to try new treatment strategies remain as a hindrance in the development of diagnostic tools as well as efficient therapies for cancer (Bandyopadhyay et al. 2015).

Lung carcinoma is the most commonly reported cancer among men and the leading cause of cancer deaths. It has been suggested that lung cancer might overtake the incidence of breast cancer among European women by 2050. Globally, 18.4% cancer-related deaths are due to lung cancer and are estimated to have poor survival rate of 15% with a survival extension of 5 years (Mukherjee et al. 2019; Babu et al. 2013). Long-term tobacco smoking and exposure to mutagenic and carcinogenic agents are considered as the major cancer causing agents. Interaction of genetic and environmental factors can aggravate the risk of developing lung carcinoma. Nevertheless, exposure to secondhand smoke; air pollution; and inhalation of toxins such as asbestos, arsenic, etc. also tend to elevate the threat of lung cancer (Que et al. 2019). Histological data suggest that lung cancer can be classified into two main types: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC). NSCLC accounts for more than 85% of cases, and patients are reported to have a life expectancy of 6–18%. Though extreme and innovative measures have been taken in the last five decades to lower the mortality rates of cancer, it has been possible only to an extent. Lack of early theranostics in about 50% of the cases and the confirmation of the disease in stage IV lead to low survival rates (Padmini et al. 2016; Parvanian et al. 2017). Diagnosis technologies that include magnetic

resonance imaging (MRI) and computed tomography (CT) and treatment options such as chemotherapy, hormone therapy, radiotherapy, and surgery fail to treat lung cancer in several patients. Inaccessibility of the deep tissues and barrier penetration within the lungs further complicate the treatment process of conventional therapies (Mao and Liu 2020; Moorthi et al. 2011).

High-quality theranostics for the complete eradication of cancer requires the implementation of new approaches that are safe, eco-friendly, and cost-effective with fewer or nil side effects (Zugazagoitia et al. 2016). Nanoscale materials have the greatest advantage of being smaller in size which ensures their accessibility across the bronchial epithelial barrier to the deeper lung tissues (Fig. 9.1). Nanotechnology has become a part of basic cancer research in recent times. Semiconductor nanocrystals and eco-friendly organic and inorganic nanomaterials have gained the attention of researchers worldwide (Sukumar et al. 2013). These nanoparticles (NPs) are widely employed for cancer theranostics as imagining tools and drug delivery systems. Detection of various cancer metastases that were undetectable in earlier times has now become possible due to the amalgamation of magnetic NPs with MRI scans that help in increasing the contrast of the images (Karkan et al. 2016). Nanoscale formulations such nanogels and nanosprays are efficaciously administered into the respiratory tract by intratracheal routes and showed better delivery results when compared to parental routes. Clinical detections of lung tumors have become possible owing to the efficient use of nanoparticles. For instance, quantum dot-doped polystyrene NPs are utilized to identify the presence of CEA and CYFRA21-1 in lung cancer patient serum (Mottaghitalab et al. 2019). Nevertheless, bioinspired NPs have secured special attention due to their amicable physicochemical properties (Fig. 9.2). Encouraging results have been obtained from bacterial NPs, plant NPs, viral NPs, aptamers, solid-lipid NPs, etc. (Madamsetty et al. 2019). Thus, this chapter addresses the emerging trends of biogenic nanoparticles in lung cancer theranostics due to their manifold applications and promising results in lung cancer diagnosis and therapy.

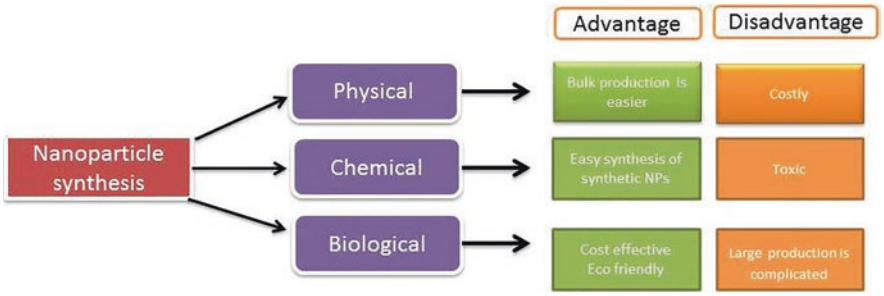

Fig. 9.1 Advantages and disadvantages of different approaches used in NP synthesis

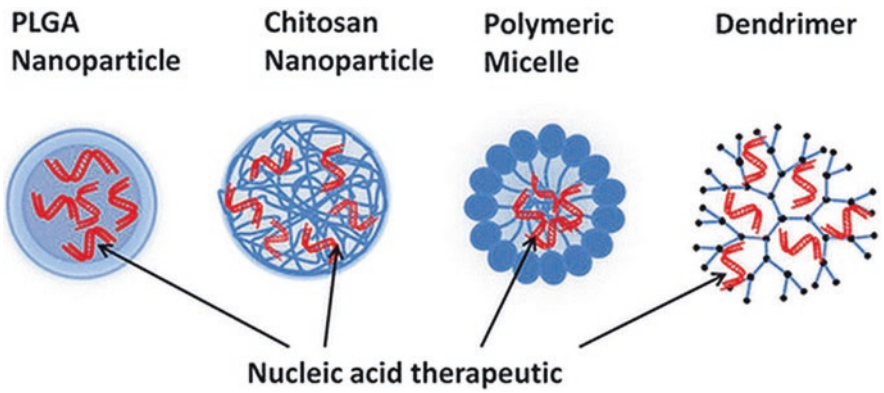

Fig. 9.2 Nanoparticle-mediated gene delivery for lung cancer. (Adapted from Narsireddy et al. 2017)

9.2 Classification and Molecular Biology of Lung Cancer

Neoplastic metamorphosis of the lung epithelial cells results in lung cancer. Progression of the disease is influenced by multiple factors such as molecular aberrations and epigenetic and genetic factors. These factors also have a profound influence in the theranostics and predictive outcomes of lung cancer. In order to identify an unfailing and reliable treatment strategy, it is necessary to understand the underlying molecular and genetic information of lung cancer. Lung cancer is divided into three types based on their histopathological characteristics. SCLC and NSCLC are the major classifications of lung cancer along with malignant pleural mesothelioma (Cooper et al. 2013) (Fig. 9.3).

9.2.1 Small Cell Lung Cancer (SCLC)

SCLC is commonly addressed as the smoker's disease since the incidence of the disease is higher in long-term smokers. The risk of SCLC increases with the exposure to smoke with over 90% of the patients falling into this category. Globally 14% of the reported lung cancer cases are under SCLC category, and more than one million cases are diagnosed and treated each year. According to the World Health Organization (WHO), this category of lung carcinoma is classified as a neuroendocrine malignancy with pathological features characterized by nuclear molding, mitoses, and necrosis (Travis 2012; Padmini et al. 2020). CD56 and thyroid transcription factor-1 aid as biomarkers for the confirmation of lung cancer. Diagnostic exclusion tools that are additionally employed are chromogranin and synaptophysin staining techniques, which act as strong neuroendocrine markers. The least progression is perceived in SCLC genetic studies when compared to other lung cancer

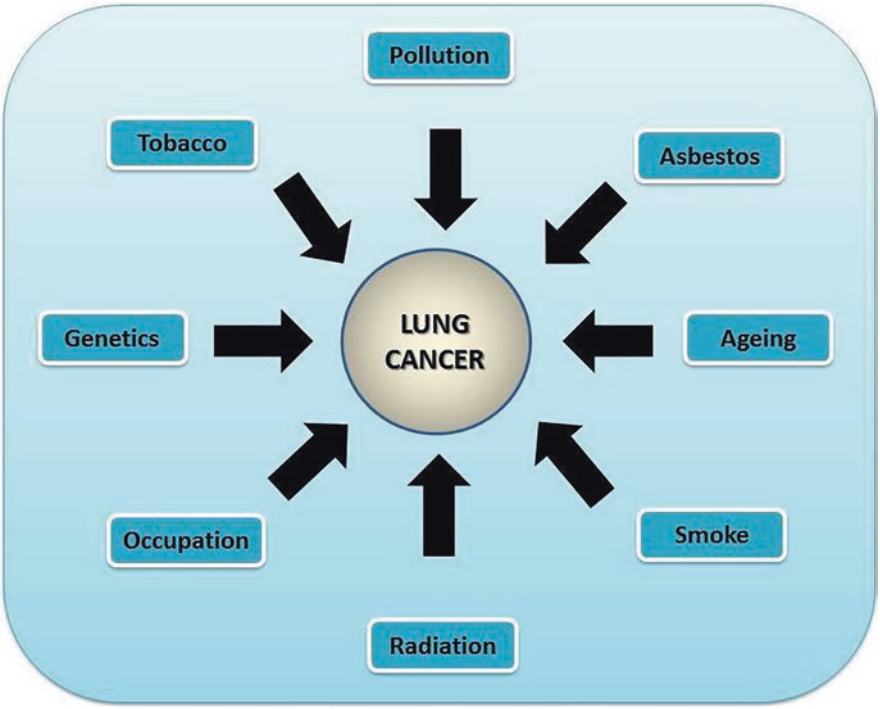

Fig. 9.3 Causes of lung cancer

classifications. The paucity of recognized targets unambiguous to SCLC remains as the plausible reason for the impediment in such cases. Tumor suppressor genes such as TP53 and RB1 are also lost in majority of SCLC patients which leaves them in higher risk (Byers and Rudin 2014).

9.2.2 Non-small Cell Lung Cancer (NSCLC)

Eighty-five percent of the total lung cancer cases are identified as NSCLC that tags the type as the predominant form of lung cancer. Metastasis or local advancement of the disease is identified in more than 50% of the cases. Like SCLC, cigarette smoking is a profound risk factor in NSCLC, yet other factors such as exposure to secondhand cigarette smoke, unhealthy food habits, insalubrious lifestyle, and exposure to carcinogens and mutagens along with genetic variation can trigger the disease (Cryer and Thorley 2019). Active mutations in the epidermal growth factor receptor are commonly diagnosed in NSCLC patients. Squamous cell carcinoma, adenocarcinoma, and large-cell carcinoma are clustered under the umbrella term NSCLC though they are exemplified with different epigenetic, genetic, molecular, and cellular features. Adenocarcinoma is the most prevalent NSCLC with incidence

rates adversely increasing amid women. The major distinction between adenocarcinoma and squamous cell carcinoma patients is the positive expression of mucin, cytokeratin-7, and thyroid transcription factor-1 (Gridelli et al. 2015). Twenty to 30% of NSCLC cases account for the squamous cell carcinoma subtype, and incidence is accounted commonly in men. Familial predispositions, polymorphisms, and cigarette smoking are the major factors that lead to the development of squamous cell carcinoma (Stinchcombe 2014). Keratinization and pearl formation with dense cytoplasm and irregular nuclei are the characteristic features of this subtype. Respiratory malignancies that do not fall under the category of adenocarcinoma and squamous cell carcinoma are grouped under the term large-cell carcinoma and are devoid of differentiating characteristics when viewed under a light microscope. Difference in the characteristics gives rise to various but specific microenvironments that contribute to arduous treatment strategies. Histopathological and immunohistochemical staining, genetic analysis, and imaging techniques are currently employed to understand the disease progression in NSCLC patients (Sholl 2014).

9.2.3 Malignant Pleural Mesothelioma (MPM)

The incidence of MPM is very less when compared to other types of lung cancer. Approximately 2000–3000 new cases are reported each year worldwide, but the incidence rate is considered to increase rapidly in the coming years (Cryer and Thorley 2019). The primary factors that increase the risk of MPM are exposure to ionizing radiations, viral infection due to simian virus, and acquaintance to asbestos. Dyspnea due to pleural effusion is the common symptom noticed in patients diagnosed with MPM. Additionally, patients experience chest pain due to thoracic wall invasion. Other symptoms such as hyperhidrosis, fatigue, weight loss, and tiredness are common in patients. Intrinsic heterogeneity makes it difficult to obtain a genetic footprint; however, TP53 and RB1 mutations occur rarely in MPM (Papp et al. 2001). Cellular proliferation in MPM is not limited to physiological restrictions, since deregulated metabolic pathways play an influential role in determining the disease pathology. Epigenetic alterations and promoter hypermethylation have been remarked at several loci on MPM. Histone deacetylases (HDAC) are inhibited which allows the tumor suppressor genes to remain unfolded and available for transcription (Vandermeers et al. 2009).

Lung cancer is demarcated with the growth of abnormally dividing cells in the lungs that can later infiltrate into different cells of the body. A human body is generally tailored with a remarkable cell cycle assessment system that constraints the growth of new cells as per requirement of the body structure. Additionally, the system is equipped with the ability to eliminate unnecessary and harmful cells naturally by a process renowned as apoptosis. Tumor repressor genes also assist the body systems to control the growth of tumor and proliferation of redundant cells (Mukherjee et al. 2019). However mutations can cause an imbalance in the normal functioning of the cell cycle, for instance, Ras gene (growth promoting gene)

mutations can lead to the uncontrolled growth and multiplication of cells to form tumor- or neoplasm-like structures. Not only oncogenes are altered due to mutations, but the rate of mutations in tumor suppressor genes and genes involved in DNA repair mechanism is also high. It is certain that a fast-growing tumor can consume copious amounts of oxygen and key nutrients that are required for the growth and multiplication of normal cells compelling them to behave abnormally. New territories are gained by invasive cancer cells by vitiating the extracellular matrix with the help of enzyme proteases and penetrate into the normal adjacent cells (Burstein and Schwartz 2008; Muthuraj et al. 2016).

The molecular basis of lung cancer is intricate and diverse. Basic understanding of molecular shifts and genetic, epigenetic, or protein expression along with their functions have an influential role in lung cancer theranostics. Progression and development of lung cancer is a multistep process epitomized by genetic variations and recurrent mutations at high frequency (Larsen and Minna 2011). Insights of genetic variations that affect a common cluster of oncogenic signaling pathways in lung cancer have led to the major improvements in cancer theranostics. New strategies that are being developed effectively target the types and subtypes of lung cancer. The major gene mutations that are correlated with lung cancer have been identified as v-Ki-ras2 Kirsten rat sarcoma viral oncogene (KRAS), epidermal growth factor receptor (EGFR), and phosphatidylinositol 3-kinase (P13K). Recent studies focus on genes such as MEK, HER2, ALK, and ROS1. The major concerns in adenocarcinoma and squamous cell carcinoma are MET and FGFR1, respectively (Cooper et al. 2013; Padmini et al. 2017). Race, gender, and smoking behaviors are commonly associated with the genetic alterations of carcinogenesis. Nevertheless, mutations and alterations associated with host factors such as tumor suppressor genes (TP53, LKB11, RBI, PTEN, and p16) have become a huge concern to researchers in lung cancer development and progression (Lynch et al. 2004; Yip et al. 2013).

9.3 Limitations and Challenges of Conventional Lung Cancer Theranostics

Systematic therapy (chemotherapy, hormonal therapy, targeted therapy, and biological therapy) and local therapy (surgery, radiation) are the conventional methods used to treat lung cancer. At various stages of lung cancer, systematic and local therapy are administered together to reduce the progress of abnormal cell growth in lung cancer patients. Health and age of the patient along with the stage, type, and size of the tumor in the lung determine the type of treatment that has to be administered to the patient. For instance, eradication of the cancerous cells may be possible (curative) or only measure to reduce the pain caused by the cancer can be possible (palliative). Primarily administered therapy is prescribed with an additional therapy in order to enhance the effect of the primary therapy. For example, surgical removal

of the cancerous tissues in the lung is followed by chemotherapy or radiation therapy (Bandyopadhyay et al. 2015).

Surgery is prescribed to patients initially at stage I and stage II where small size tumors present in the lung are excised surgically, or sometimes lobectomy is advised to patients who are exposed to the risk of metastasis. The limitations of surgery in lung cancer are remarked by fewer possibilities to remove large size tumors and the inefficiency to remove cancerous cell completely (Rani et al. 2012). Chemotherapy is the administration of chemicals in the form of drugs into the patient's body either after surgery or as the primary treatment. The major inadequacies of chemotherapy are permeability and retention of the drug within the cells. Chemotherapy may be unsuccessful in patients with poor vasculature and limited interstitial pressure. Moreover, chemotherapeutic drugs can cause cardiotoxicity and nephrotoxicity along with other acute side effects (Mukherjee et al. 2019). Radiation therapy involves the use of X-rays or high energy ionizing radiations to kill the cancerous cells. The possibility of developing radiation-resistant tumors due to the production of reactive oxygen species during the process of radiation therapy is high. Side effects of radiation therapy include nausea, vomiting, fatigue, irritation of the digestive tract, and a sudden drop in the count of white blood cells followed by reduced platelet count (Moorthi et al. 2011) (Fig. 9.4). However, the abovementioned conventional therapies have a prominent effect only during the early stages of lung cancer. Thus, certainly a novel approach to diagnose and treat lung cancer at its various stages effectually without limitations is necessary (Zugazagoitia et al. 2016).

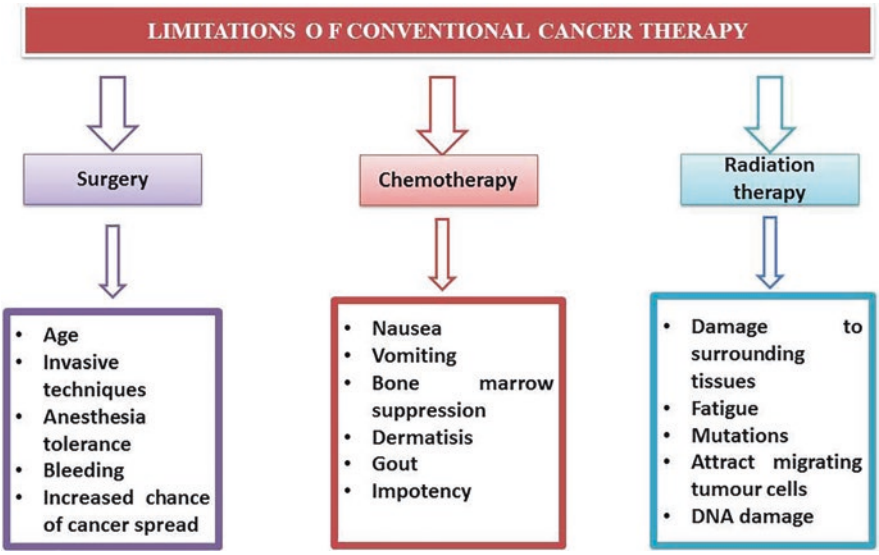

Fig. 9.4 Limtations of conventional cancer therapy

9.4 Nanotechnology: A Promising Theranostic Tool for Lung Cancer

Nanoparticles have enticed substantial attention in the field of nano-medical technology due to their unique and interesting characteristics. Particles that have dimension less than 100 nm are acknowledged as nanoparticles. Nanotechnology has created a cutting edge in cellular imaging, experiment therapies, and theranostics (Fig. 9.5). There is no uncertainty in the appreciable outcomes of nanoparticles in the medicinal field since nanoparticles have claimed their applications in various other fields such as electronics, cosmetics, solar cells, textiles, optical devices, and even more (Bandyopadhyay et al. 2015; Parvathi et al. 2015). Detection at the right stage and proficiency of the prescribed treatment can aid in new prospects of lung cancer theranostics. Interestingly, nature has fabricated the human system with numerous nanoscale biological entities which emphasizes the need of theranostic notions in the same scale. The major advantage of nanoparticles lies in their small size with large surface area. This enables them to absorb or bind micro- and macromolecules that are either hydrophobic or hydrophilic in nature. Nanoparticles can easily carry molecules such as DNA, RNA, drugs, and probes through the intricate barriers of the human body (Ahmad et al. 2011).

Drug targeting and drug delivery of sparingly water soluble drugs have become possible through the use of NPs. Interaction between the NPs and drug ligand to be

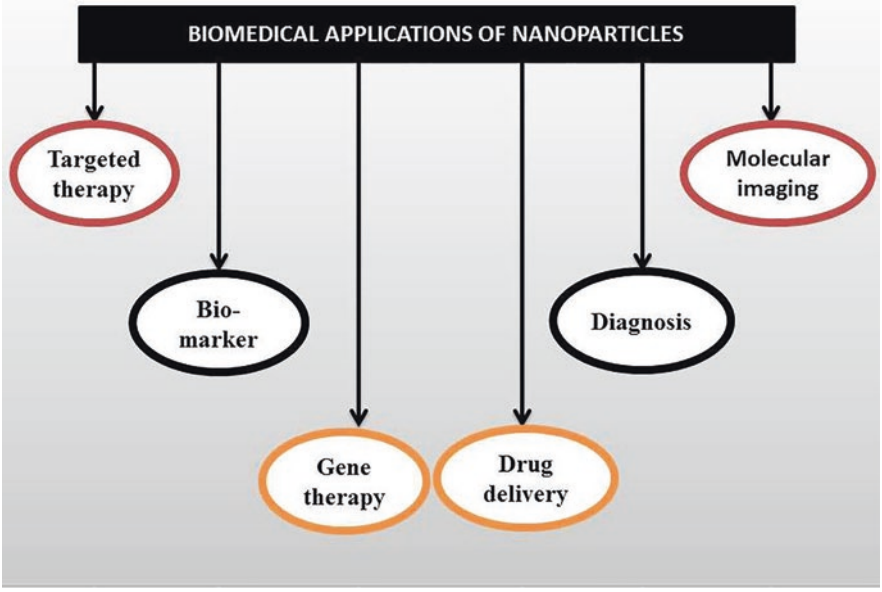

Fig. 9.5 Biomedical applications of nanoparticles

delivered determines the efficiency and the success of the experimental therapy. Diagnosis has reached better apices due to the opportunity of integrating poorly soluble probes to NPs. Attachment of the drug or the probe to the NPs that have smaller size and large surface area improves their dissolving ability in the bloodstream. This in turn increases the bioavailability and retention of the drug in the human system, thus delivering the drugs to specific tissues at the right time (Sattler 2010; Jong and Borm 2008). Degradation of the drugs or the probes is a major concern when it comes to oral and intravenous administration since the acids present in the gastrointestinal tract as well as the stomach can have adverse effects on them. On the other hand, the drugs might be easily metabolized by the hepatic portal system and eliminated from the body (Fig. 9.6). These shortcomings have been overcome by the introduction of NPs that are stable over a wide range of pH and temperature. This characteristic of the NPs also helps in effective targeting of the cancerous cells, since the pH of the cancerous lung cells are acidic in nature when compared to the normal cells. Drugs that have failed in previous experiments due to low solubility and toxicity can be retried by conjugating them with NPs that can improve their solubility and reduce the toxicity (Mohanraj and Chen 2006; Sivasankar and Kumar 2010).

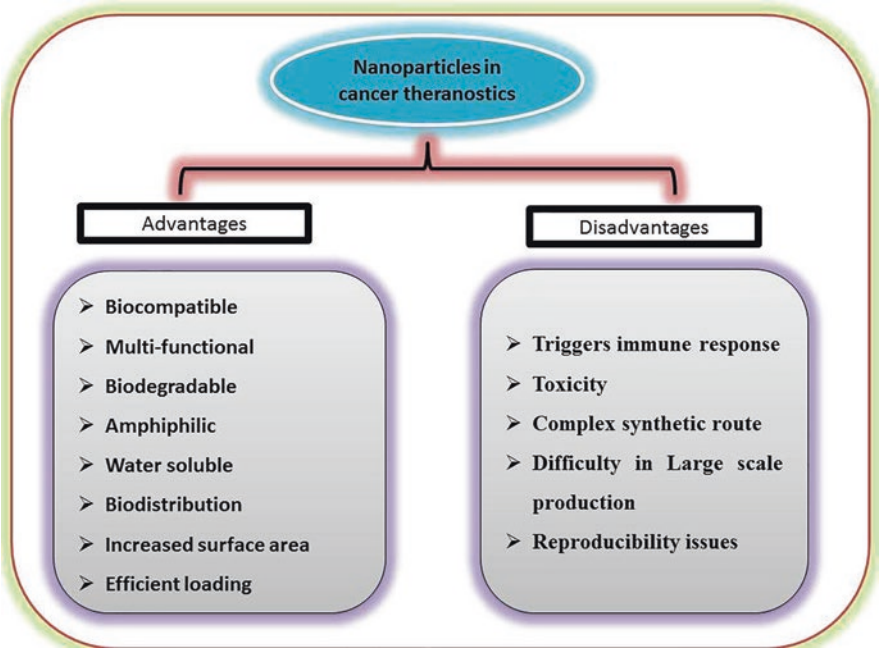

Fig. 9.6 Nanoparticles in cancer theranostics

9.5 Role of Biogenic Nanoparticles in Lung Cancer Theranostics

9.5.1 Synthesis and Mode of Action of Gold Nanoparticles (Au NPs)

Synthesis of gold nanoparticles from plant extracts has been an easy process, and Au NPs are harmless when compared to other NPs (Kumar et al. 2011). Au NPs can produce reactive oxygen species that creates oxidative stress within the tumor environment leading to cell apoptosis. Au NPs synthesized from Dendropanax morbifera leaf extract exhibited potential anticancer activity against HaCaT cells by inducing the production of reactive oxygen species and later persuading the cells to apoptosis process (Wang et al. 2016). Elevated ROS production provoked by Au NPs synthesized from Magnolia officinalis in A549 cells showed nuclear fragmentation and mitochondrial depolarization within the cells (Zheng et al. 2019). Sun et al. (2019) showed that green synthesized Au NPs from Marsdenia tenacissima extract A549 cells serve as effective cancer agents by controlling the proliferation of the cancerous cells through apoptotic pathway. Au NPs downregulated the expressions of Bax, caspase 3, caspase 8, and caspase 9 in lung cancer pathway. Moreover, the modulation of Bax/Bcl 2 induced apoptosis in lung cancer cells (Zheng et al. 2019).

9.5.2 Fabrication and Application of Silver Nanoparticles (Ag NPs)

Ag NPs are widely being recognized as promising candidates in the field of lung cancer theranostics. They not only act as alluring drug delivery vehicles and probes but also as an assuring therapeutic agent (Ratan et al. 2020) (Fig. 9.7). Dried and cleaned powders of various herbal plants are used as reducing, stabilizing, and capping agents in the synthesis of Ag NPs. Purified particles are subjected to characterization techniques to confirm the reduction of the particles to nanosize. He et al. (2016) demonstrated that Ag NPs synthesized using herbal extracts of Dimocarpus longan showed effective chemopreventive activity against human lung cancer H1299 cells. Studies have demonstrated that nanoparticle internalization allows the slow and sustained release of Ag NPs in A549 cells and degradation of the NPs is promoted by the acid environment of the lysozymes. Ag NPs are assumed to regulate the apoptosis process and NF-κB activity. They can effectively slow down the growth of tumors from 28 to 36 days (He et al. 2016; Matsushita et al. 2000). Ag NPs synthesized from *Gossypium hirsutum* leaf extracts, *Syzygium aromaticum*

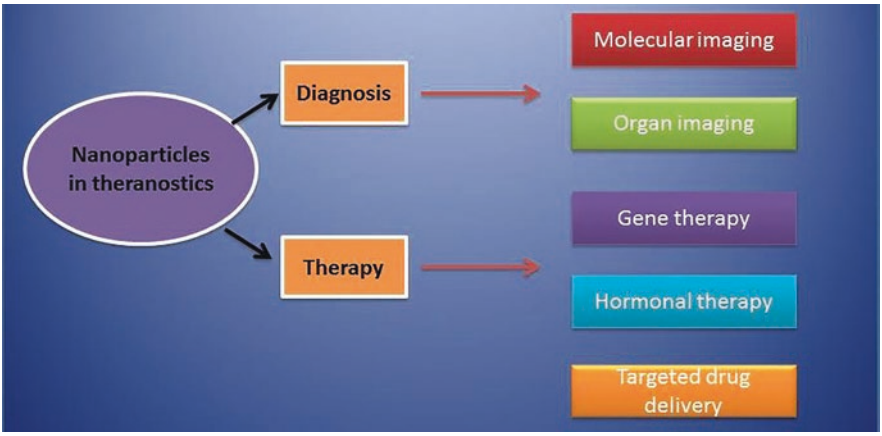

Fig. 9.7 Application of nanoparticles in cancer theranostics

fruit extracts, *Rosa damascene* petal extracts, and *Penicillium decumbens* microbe were effective in inhibiting the growth of A549 lung cancer cells in a dose-dependent manner (Ratan et al. 2020).

9.5.3 Biogenic Synthesis and Use of Magnetic Nanoparticles

Magnetic NPs are progressively gaining consideration as potential lung cancer theranostic agents. Magnetic NPs are advantageous for diagnosis as well as therapy since they evade cytotoxic effects and side effects of conventional cancer therapy. Iron oxide NPs are highly stable and can be fabricated in different shapes through environmentally safe processes. The super magnetic property and the ability to modify their surfaces are an important characteristic that aids in theranostics. Magnetic NPs have superior magnetic signal strength that can be used accurately for cancer detection in the lungs. Most of the magnetic NPs are low toxic in nature, and they increase the level of the contrasts while imaging the lung anatomy in cancer patients. Tumor margins can be precisely identified with the help of NPs as diagnostic tools (Rafique et al. 2017). Magnetic NPs are highly recommended for imaging, targeted drug delivery, slow and subsequent drug release, and site-specific targeting and therapy (Fig. 9.8). Iron oxide NPs are easily engulfed by the macrophages, thus aiding in the clear and accurate imaging of macrophage-rich organs such as the bone marrow, liver, and spleen by targeting the reticular endothelial system. Grape seeds, brown algae, peel extracts of plantain, eucalyptus leaves, sorghum, alfalfa, and *Aloe vera* extract have been successfully used to synthesize magnetic NPs (Karmous et al. 2019). Yusefi et al. (2019) have successfully synthesized iron oxide NPs using *Punica granatum* fruit peel extract and tested its cytotoxic effects on A549 lung cancer cells for which positive anticancer results were obtained.

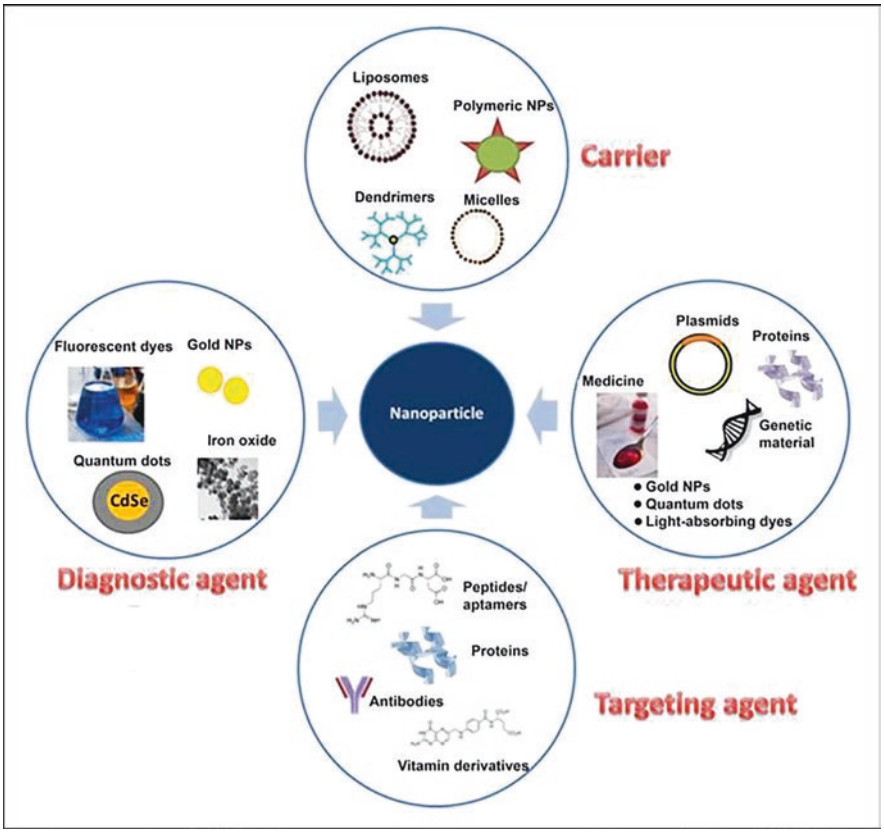

Fig. 9.8 Applications of magnetic nanoparticles. (Adapted from Menon et al. 2013)

9.5.4 Green Synthesis and Theranostic Use of Copper Oxide Nanoparticles (CuONPs)

Copper oxide nanoparticles are transitional metal oxide NPs that have been used as theranostic agents in recent years. Performance and applications of CuONPs depend on the strong absorption capacity that they exhibit. They also show improved and efficient biological photocatalytic activities when compared to other metal oxide NPs. Various approaches such as physical and chemical are being applied for the synthesis of CuONPs, yet biological approach is considered safe and environmental friendly (Fig. 9.9). Plant extracts as well as bioactive metabolites such as flavonoids, tannins, phenolic acids, terpenoids, and proteins are also employed in the synthesis of CuONPs (Rezaie et al. 2017). CuONPs that were synthesized from dried and purified leaf extracts of *Coleus aromaticus*, *Hibiscus rosa-sinensis*, *Murray akoenigii*, and *Azadirachta indica* showed effective anticancer activity against lung cancer cells (Akintelu et al. 2020).

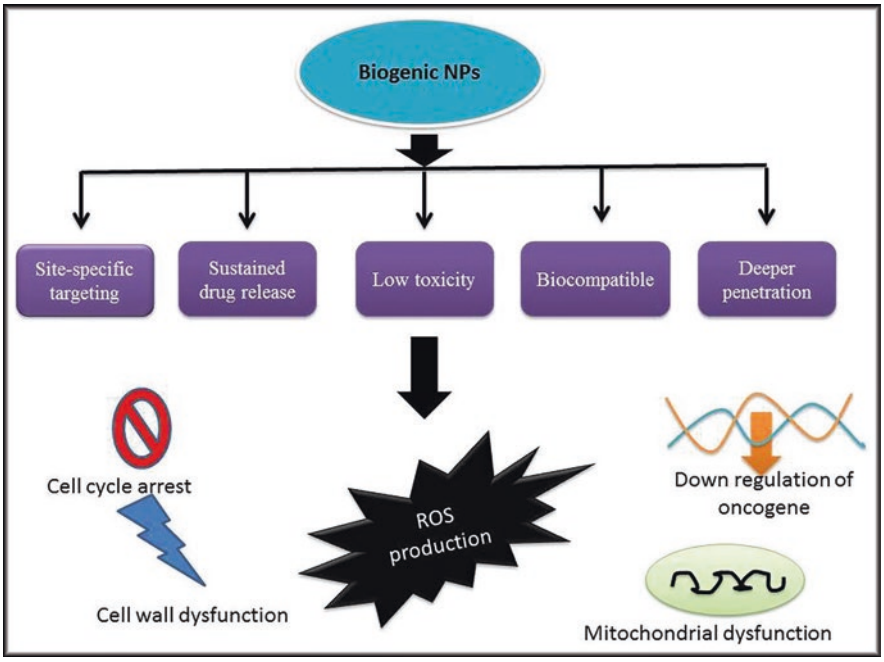

Fig. 9.9 Characteristics of biogenic NPs and their mechanism in lung cancer therapy

9.5.5 Bio-Fabrication and Mechanism of Action of Titanium Dioxide Nanoparticles (TiO_2NPs)

Titanium dioxide nanoparticles have plentiful applications in the field of cosmetics, medicine, energy, and bio sensing (Youssef et al. 2017). TiO_2NPs are being designed successfully to deliver drugs at specific sites without longer retention time in the tissues. Stimuli-trigger drug release and tumor cell targeting are possible with the use of TiO_2NPs. NPs have photocatalytic activity and large surface area, that is, highly functional remarkable cancer theranostic applications can be achieved by TiO_2NPs (Wang et al. 2015). These NPs can be engineered with different structure and size within the nanoscale range to make them highly compatible and bioavailable within the human system. The major limitations of conventional cancer therapies such as drug release, retention, and site-specific targeting are possible when TiO_2NPs are used as theranostic agents. Additionally TiO_2NPs possess low toxicity to the normal cells and are completely environmental friendly when synthesized in biological routes (Skocaj et al. 2011). TiO_2NPs synthesized from C*ynodon dactylon* leaf extract were shown to inhibit A549 lungs effectively at a concentration of 140 µg/ml. The biomolecules present in the plant extract can donate excess electrons to TiO_2 which provides additional opportunity for the TiO_2NPs to produce reactive oxygen species. ROS can generate stress within the cells that induce the cancerous cells to undergo apoptosis. Moreover, ROS is used to break the cell walls

of cancerous cells. The physiochemical properties of TiO_2NPs favor their use as efficient lung cancer theranostic candidates (Hariharan et al. 2017).

9.6 Trends of Semisynthetic Nanoparticles in Lung Cancer Theranostics

Semisynthetic NPs are synthesized by combining natural moieties with synthetic molecules or polymers. The efficacies of the biogenic nanoparticles are improved with the integration of synthetic particles to treat cancer effectively. Further use of natural agents permits environmental-friendly techniques to synthesize semisynthetic nanoparticles

9.6.1 Chitosan Nanoparticles

Chitosan is made up of a nitrogenous polysaccharide with various amino acid groups attached to them. They are biodegradable as well as biocompatible in nature. Positive charge of chitosan molecules and negative charge sites on the cell lines favor strong electrostatic attraction that can promote the penetration of the drugs into the cells. The major advantage of chitosan molecules is their degrading ability when exposed to the cellular lysozyme. This helps in eliminating the chitosan NPs completely from the lungs after the diagnosis process or drug delivery (Bandyopadhyay et al. 2015). A mitotic cell cycle arresting drug PTX which is insoluble in water was loaded with chitosan chloride NPs and was treated to xenografted mouse with Lewis lung cancer cells. This experiment showed successful decrease in the tumor volume with the increase in drug accumulation in the tumor site (Lv et al. 2011). Chitosan microspheres loaded with 2′ 2′ difluorodeoxycytidine and adhered to dextran sulfate exhibited potential anticancer activity when experimented on human lung cancer A549 cells. Chitosan NPs loaded with antisense oligonucleotide that prevents telomere reduction during cell proliferation in NSCLC cells had potent inhibitory effect on A549 and Calu-3 cells. Chitosan-modified semisynthetic nanoparticles also show efficient theranostic properties (Galbiati et al. 2011; Okamoto et al. 2003).

9.6.2 Polyherbal Nanoparticles

Herbal medications are preferred due to their nontoxic property and absence of side effects. A major limitation in the use of NPs for drug delivery has been their accumulation in the target site when they are required to deliver large amounts of drugs.

In order to overcome this limitation, herbal formulations such as ethanolic extract of rattlesnake root and ginger that are reported to have anti-lung cancer activity are encapsulated in polymeric NPs that were biodegradable. It was observed that the cellular uptake of the NPs and sustained release of the polyherbal formulation effectively inhibited the lung cancer cells and were completely eliminated without accumulation in the tissues (Jadhav 2012).

9.7 Recent Trends, Challenges, and Future Prospects of Biogenic Nanoparticles in Lung Cancer

Nanoparticles have refurbished the use of drugs and probes for lung cancer theranostics (Tran et al. 2017). Recent trends of nanoparticles in lung cancer theranostics include the use of hybrid NPs. Hybrid NPs are made from organic/inorganic moieties from multiple origins and are acknowledged to have different functional operations. Hybrid super magnetic iron oxide NPs, lipid-polymer hybrid NPs, stimuli-responsive lipid-polymer hybrid NPs, gene-coupled hybrid nanoparticles, and gene-loaded hybrid NPs that might reduce drug resistance are the recently popular advancements in the use of NPs in lung cancer theranostics (Mottaghitalab et al. 2019). Separate NPs were designed for the purpose of diagnosis and lung cancer therapy in the last decades; recently, researchers are interested in developing single nano-system that can work as a theranostic tool; i.e., the same system is employed to diagnose the location of the tumor within the lung as well as deliver the drug required for the therapy at the specific diagnosed spot. Furthermore, the side effects of the chemotherapeutic agents have been considerably reduced with the use of nano vehicles. Thus, hybrid NPs are promising candidates in the field of cancer theranostics at present (Parvanian et al. 2017).

Nothing is completely perfect on the planet. NPs have their own shortcomings and challenges that have to be further amended to revolutionize the use of NPs in lung cancer theranostics (Table 9.1). The physiochemical properties of NPs must be additionally improvised to meet astonishing theranostic standards. Homogeneity and large-scale production of hybrid NPs are still at a stake due to technical concerns. NPs have the advantage of easily penetrating the tissues yet can get accumulated in the cell and cell organelles. Inorganic nanoparticles at times exert poisonous effects due to their accumulation in the tissues (Bhattacharyya et al. 2011). Further research must also be carried out in the aspects of nano-toxicology and environment safety (Ahmad et al. 2011). Another major hindrance observed in the use of lung cancer therapy is hemolysis. Hemoglobin tends to aggregate on the surface of the NPs that causes its degradation and at worse can lead to anemia resulting in patient's mortality. Opsonization is yet another challenge in the use of NPs, since opsonized NPs are targeted by white blood cells of the system's immune system and easily cleared from the body, thus reducing the bioavailability of the NPs. Moreover, the possibilities of NPs to create oxidative stress and release of reactive oxygen species are also a vital challenge (Sattler 2010).

Table 9.1 Advantages and disadvantages of nanoparticles in biological applications

Contrast agent (NPs)	Advantages	Disadvantages
Metal oxide NPs	FDA approved for clinical use; examples: Combidex, Ferridex Gadodiamide, LumenHance SPIONs exhibit intrinsic magnetic properties	Toxicity and biocompatibility concerns Responsible for inflammatory responses in respiratory system
Gold NPs	Flexible surface modification with different coatings Able to scatter and absorb light with strong excitation peaks in the visible and near-infrared region wavelengths depending on nanoparticle size	Toxicity concern
Quantum dots	Narrow wavelength emission High fluorescent efficiency and photostability with wide range of emission spectra (400 nm–2000 nm) covering both the visible and near-infrared wavelengths	Toxicity and biocompatibility concerns specially heavy metal-containing QDs
Carbon nanotubes	Intrinsic properties, enabling imaging modalities Ultrahigh surface area and hollow inside space available for efficient drug loading	Toxicity and biocompatibility concerns
Radioisotopes and fluorescent molecules	Flexible incorporation into a variety of drug delivering nanoparticle Ability to perform as noninvasive monitoring and early diagnosis capabilities	Lack of targeting specificity, short half-life Toxicity and biocompatibility concerns

Adapted from Howell et al. (2013)

The optimistic future of biogenic NPs in the field of lung cancer theranostics lies in addressing the aforementioned challenges. In vivo toxicity, bioavailability, bio distribution, and retention of hybrid NPs must be evaluated to determine their clinical efficacy. In the near future, hybrid NPs can be used for molecular imaging instead of anatomical imaging which is currently in use. Poor therapeutic consequences, low or poor solubility of drugs or probes, nonspecific targeting, and side effects of conventional cancer theranostics can be convalesced (Yu et al. 2012). Platforms in NP usage must be modified to encourage larger reproducibility, one-pot synthesis and simple hybrid NP synthesis, cost-effective production, environmental safety, higher functional properties, and superior structural properties for appreciable outcomes. Precise and robust research is required to confront the challenges in employing NPs for lung cancer theranostics (Mottaghitalab et al. 2019).

9.8 Conclusion

Every phase of consumer products has seen the eminent contribution of nanoparticles, especially the field of diagnosis and therapy. Extensive research is being carried out worldwide to create nanoparticles for theranostic use that are eco-friendly,

less toxic, cost-effective, safe, and effective at the same time. Despite the overwhelming positive results obtained from laboratory experiments, NP formulations for lung cancer theranostics do not have enough success in clinical trials. The hesitation of public to try new therapies and the producers to invest in novel medications acts as barrier in the development of biogenic nanoparticles as promising therapeutic candidates. NPs can considerably overcome the limitations of conventional cancer therapies such as nonspecific targeting, low solubility, drug retention, bioavailability, toxicity, and side effects. Though NP synthesis is an easy and ecofriendly process when fabricated using biological approach, lack of large reproducibility is considered as the major shortcoming. Fortunately, hybrid NPs and biogenic NPs are being designed to overcome these limitations and will efficiently enter the pharmaceutical markets in the near future.

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Chapter 10
Therapeutic Applications of Nanotechnology in the Prevention of Infectious Diseases

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10.1 Introduction

The word nanotechnology originates from the Greek word *nano*, meaning dwarf. It applies the ethics of engineering and manufacturing at the infinitesimal level. Nanoscience is an interdisciplinary field of research about the study of minute particles on a molecular scale, where the dimension is measured in nanometers. A nanometer means one billionth (i.e., 10–9 m) of a meter. Nanotechnology focuses mainly on how materials respond and function at the atomic, subatomic, or molecular levels (i.e., nanoscale). Nanotechnology involves the handling of the matter in the 1–100 nanometer scale range where atoms are approximately one-third of a nanometer. Thus, particles with a range and dimensions of this size are nanoparticles. The field of medicine, in which nanoscaled particles with dimensions ranging from 1 to 100 nm are built as biomedical tools for research, has been transformed by the use of nanotechnology in numerous therapeutic sectors. In recent years, the widespread and improper use of antimicrobial agents by the residential population has inevitably culminated in the production of pathogenic microorganisms with antibiotic resistance as an alternative to survival strategies. The commercially available antibiotics which are widely used against pathogens demonstrate huge changes in their resistivity. It is therefore well understood that the identification and discovery of new antimicrobial agents are essential to fight against these highly drug-resistant pathogens. The concern regarding the antibiotic resistance of pathogenic microorganisms requires the development of new antimicrobial agents to combat infectious diseases. The evolution of infectious diseases and the emergence of drug-resistant pathogenic microorganisms at an unprecedented pace are a subject of huge concern. Despite the substantial understanding of the pathogenesis of microorganisms and the use of modern therapies, morbidity and fatality connected with microbial infections remain high (Kolar et al. 2001). A significant number of microorganisms causing infectious diseases are known to become multidrug-resistant (MDR), including *Mycobacterium tuberculosis*, *A. baumannii*, *Burkholderia cepacia*, *Escherichia coli*, *Enterobacter* spp., *Campylobacter jejuni*, *Enterococcus faecium*, *Enterococcus faecalis*, *Haemophilus influenzae*, *Proteus mirabilis*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Salmonella* spp., *Staphylococcus epidermidis*, *Staphylococcus aureus*, and *Streptococcus pneumoniae*. All these microorganisms are also called “superbugs” because of their high mutation rate, and they cause a high degree of antimicrobial resistance, amplified virulence, and low susceptibility (Davies and Davies 2010). Hence, there is an urgent need to identify novel methods and new antimicrobial agents and formulations that contemplate the use of nanotechnology to create the next wave of drugs to control microbial infection (Prasad et al. 2019). Nanoparticles are being studied extensively because of their chemical and physical properties. In the field of medicine, nanoparticles are widely studied because of their size-dependent physicochemical properties. Nanoparticles are comparable in scale to those of most biomolecule structures. This makes them a convincing candidate for application in biomedical research. The findings of their implementation in the branch of medicine

have contributed their application mainly in guided drug delivery, bioimaging, and biosensing. Their function as potent antimicrobial agents to target multidrug-resistant pathogens is another fascinating avenue for their medical research (Saglam et al. 2021; Maddela et al. 2021). But, for the application of nanoparticles in the biological study, biocompatibility is the most desirable trait. Biocompatibility is the ability of the substance to function therapeutically without unintended local or systemic consequences (Samia et al. 2006).

10.2 Role of Nanotechnology in the Treatment of Infectious Diseases

Infectious diseases caused by microbes such as bacteria, fungi, viruses, and parasites are responsible for over 15 million deaths worldwide (Panacek et al. 2009). In the latest days, the extensive use of antimicrobial agents by the resident community has undoubtedly led to the emergence of antibiotic-resistant pathogens as an alternative to survival mechanisms and restricts the effectiveness of existing infection treatments and thus faces a significant challenge in the fight against infectious diseases. Recent advancements in nanotechnology allow us to tackle this problem at two levels: diagnostics and therapy. Many new antimicrobial possibilities have been created with the advent of nanotechnology. Nanomaterials present a potential forum for alternate prevention strategies to control infectious diseases. However, relative to other typical antimicrobial agents with short-term action, they deliver sustained antimicrobial activity with minimal toxicity. Nanomaterials provide additional advantages due to their small size, allowing for an improved ability to overcome any physiological hurdles to meet their specific target. The high ratio of surface area to volume allows them for the boosted potential to communicate with the pathogen membranes and cell walls. The most important prerequisite for any successful therapeutic agent is the delivery of medications to the required target at the appropriate doses for the appropriate time. Hence, the nanomaterials serve as one of the most exciting smart drug delivery systems by using the outstanding size and surface properties.

10.3 Nanomaterials in Nanomedicine

Nanomaterials are enormously smaller in scale (dimensions from 1.0 to 100.0 nm), having 100 nm or less in at least one dimension. Nanomaterials may be one-dimensional (such as surface films), two-dimensional (such as wires or fibers), or three-dimensional (such as particles). Nanotechnology uses nanomaterials (nanoparticles, nanofibers, nanotubes, etc.) with novel physical and chemical properties such as their small scale, low toxicity, high biocompatibility, and ability to selectively penetrate the cell membrane of pathogenic microorganisms. These exceptional

properties of nanoparticles could offer significant advantages to nanomedicine. For example, the small size of a nanoparticle can encourage them to cross biological barriers; various nanoparticle architectures can improve the bioavailability of non-soluble or unstable drugs; the configurable surface of nanoparticles can enable the required targeting potential for either imaging or precise delivery of drugs to the diseased region. Nanomedicine is a field of science that uses nanoscale materials for the diagnosis and treatment of human disease. It has arisen as an integral part of therapeutics. By developing new drugs for both diagnosis and care, nanomedicine has made promising advances in clinical practice, allowing it to resolve unmet patient needs through diagnosis, controlled drug release, surveillance, and control; increasing bioavailability, prevention and treatment of diseases, and drug targeting; identifying and managing diseases and analgesic effects; and improving human health. Many drug delivery carriers have been built over time, based on various nanomaterials. Specifically, antimicrobial agents are being placed into polymer-coated crystalline nanoparticles, PLGA, composite hydrogel/glass particles, liposomes, homogenized particulate suspensions, cationic, dendrimers, gold nanoparticles, and silver nanoparticles and are developed for the treatment of a wide variety of microbial infections along with drug-resistant tuberculosis. Nanocarriers have developed a novel vehicle for the delivery of therapeutic agents specifically for the target. Recently, these nanoparticles have arisen as an appealing candidate for the delivery of medications as well as the diagnosis and treatment of many infectious diseases.

Nanomedicine can be divided into two main groups: synthetic nanomedicines and biological-based nanomedicines. The first group consists of nanomedicine derived from synthetic or inorganic materials, and the second group consists of materials based on nanoscale-engineered biological or organic components (shown in Fig. 10.1).

10.4 Synthetic Nanomedicines

10.4.1 Silver Nanoparticles

Silver was most often studied as an antimicrobial agent, and it is used since ancient times to counter microbial infections. Silver nanoparticles (AgNPs) are frequently used as an antifungal (Medda et al. 2015), anti-inflammatory (Hebeish et al. 2014), and antiviral agents (Bekele et al. 2016). Researchers have shown that AgNPs are used as carriers to deliver small drug molecules or large biomolecules to particular targets. They are very target specific. Once the AgNPs have reached their specific target, the release of the drug could potentially be triggered by an internal or external stimulus. Targeted and stored nanoparticles could provide high concentrations of drugs at particular target sites and minimize side effects. Due to the emergence of drug-resistant pathogens which are crass to traditional drugs, the exceptional

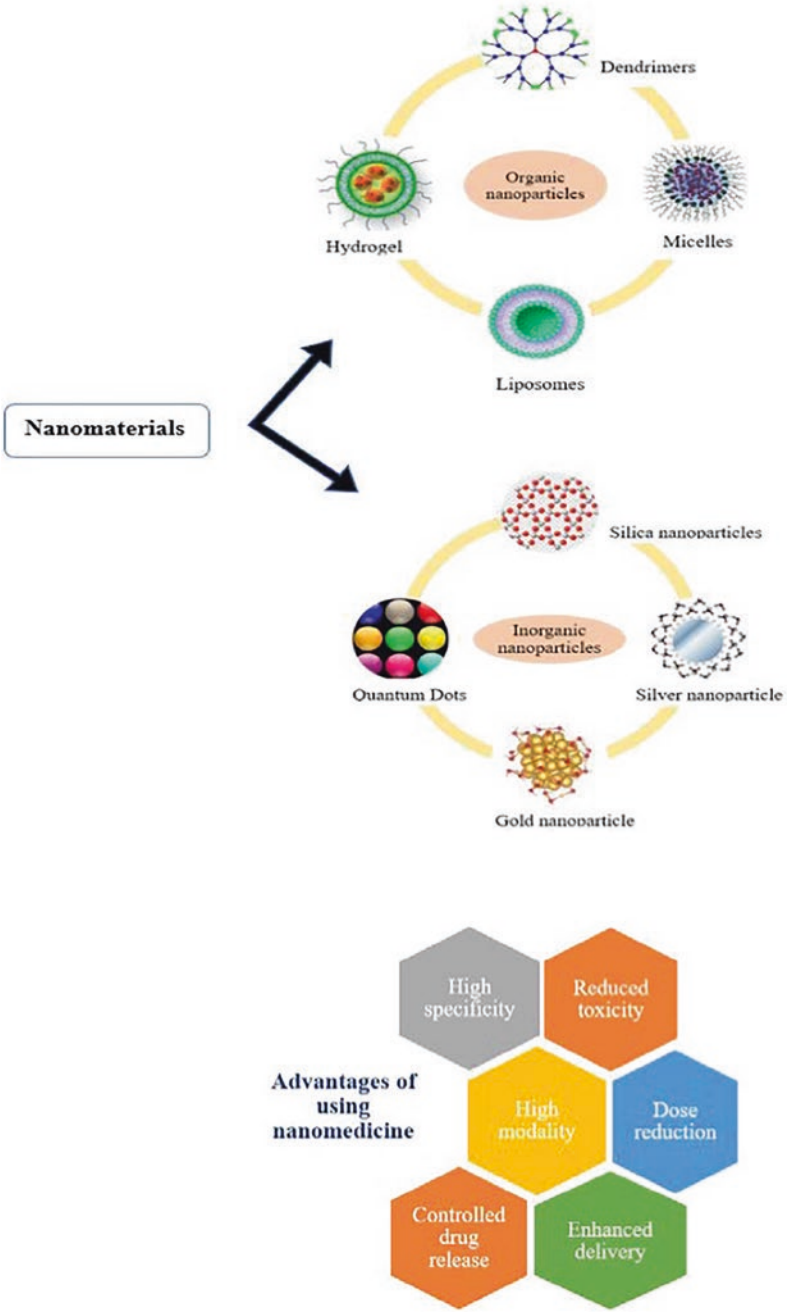

Fig. 10.1 Various types of nanoparticles and their advantages in nanomedicine

properties and broad function of silver and their compounds have prompted scientists from all over the world to investigate their potent antimicrobial behavior. AgNPs showed promising antimicrobial activity against various microorganisms because of their large surface area to volume ratio. These properties are used as bactericides in burned lesions and fillers in dental cavities to deter infection. AgNPs alone or with the combination of other typical antimicrobial agents have been shown to have antimicrobial efficacy against a broad variety of microorganisms. Nano formulated drugs are smart drugs. They are engineered to distribute medications directly to the intended infection sites and in areas of the body that are often impossible to access through available therapies. AgNPs have been reported to display antifungal activity by a mechanism called apoptosis (Hwang et al. 2012). Aggregation of intracellular reactive oxygen species (ROS) was commonly documented as a key feature in cell death and has been related with many of the recognized apoptotic pathways in yeast (Carmona-Gutierrez et al. 2010). AgNP-induced apoptosis cells undergo unique phenomena including ROS production, DNA fragmentation, caspase activation, phosphatidylserine exposure, cytochrome c release, mitochondrial membrane depolarization, nuclear condensation, and cell cycle arrest (Aziz et al. 2014, 2015, 2016, 2019; Bortner and Cidlowski 2007; Prasad and Swamy 2013; Prasad 2014). The injection of silver into bacterial cells triggers a high level of structural and morphological modifications that can contribute to the death of cells. Till now, three main mechanisms for its antibacterial mode of action have been described: (i) dissociation of cell wall and membrane, (ii) intercellular diffusion and damage, and (iii) oxidative stress (Dakal et al. 2016; Duran et al. 2016) (shown in Fig. 10.2). The synergy of AgNPs with bacterial cells allowed the cell wall and cell membrane to disturb and demolish, resulting in the shrinkage of the cell membrane and the leakage of the intercellular products and eventually the death of the bacteria (Abalkhil et al. 2017).

10.4.2 Carbon-Based Nanoparticles

Invariably, the excessive and inappropriate use of antimicrobial agents has led to the establishment of antibiotic resistance. This has been a big concern in recent years. Antibiotics currently available that are widely used against microbial infection display dramatic changes in their resistivity. Thus, the discovery of novel antimicrobial agents for the treatment of these infections is urgently required. In biological studies related to antimicrobial agents, drug delivery, and biosensing, carbon nanostructures are successfully implemented (Bitounis et al. 2013). In particular, carbon-based nanomaterials have shown significant antibacterial properties. Carbon nanotubes and fullerenes are carbon-based nanoparticles. Many biomedical applications of carbon-based nanoparticles have resulted in the development of a new field in diagnostics and therapeutics. The fact that carbon-based nanoparticles exhibit good antimicrobial properties has been well known in the last few years. The size, shape, and surface area are the most important parameters affecting their antimicrobial activity. The mechanism for the activity of interaction with bacterial cells can

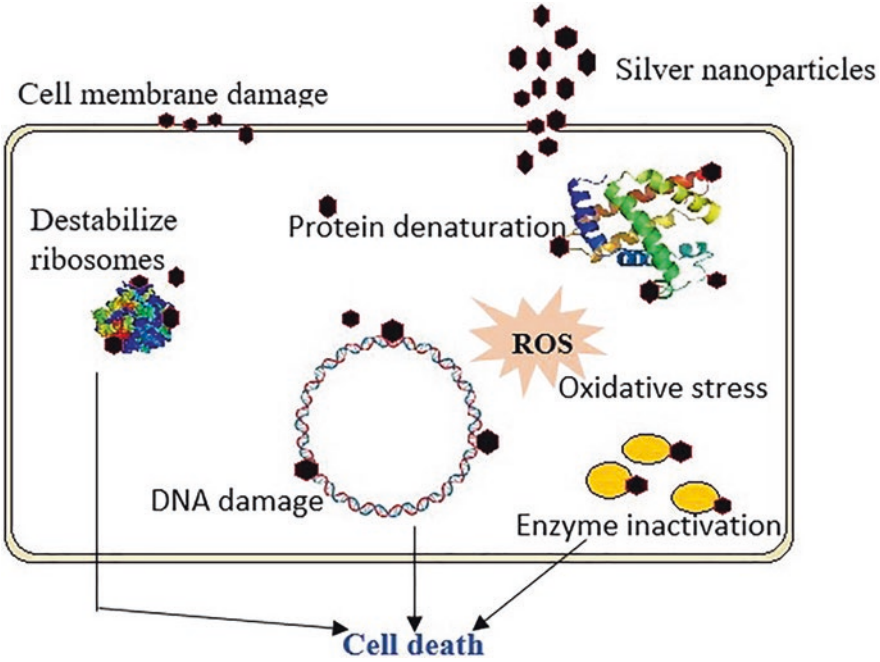

Fig. 10.2 Mechanism of antimicrobial action of silver nanoparticle. (Described by Dakal et al. 2016 and Duran et al. 2016)

be enhanced by increasing the nanoparticle's surface area by decreasing its size (Buzea et al. 2007). In the beginning, it has been revealed that the interaction of carbon-based nanoparticles with bacterial causes damage to the cell membrane due to oxidative stress (Shvedova et al. 2012; Vecitis et al. 2010). But, according to some recent studies, the main cause of the antimicrobial behavior of these nanostructures is the functional association of carbon-based nanomaterials with bacteria instead of oxidative stress (Pacurari et al. 2012; Manke et al. 2013).

10.4.2.1 Carbon Nanotubes

Carbon nanotubes (CNTs) are hollow barrel-shaped nanotubes. They are classified into single-walled carbon nanotubes (SWCNTs) and multiwalled carbon nanotubes (MWCNTs) based on the number of concentric panels. SWCNTs vary in diameter from 0.4 to 2 nm, and MWCNTs vary from 10 to 100 nm. Lijima and Lchihashi, in 1991, synthesized SWCNTs. The antimicrobial activity of SWCNTs on *E. coli* was first described by Kang et al. (2008). In another study (2008), they stated that the size of carbon nanotubes was a significant aspect of exhibiting antibacterial property. In particular, the length of nanotubes during interactions with the cell membrane is crucially significant. In contrast to longer tubes, the shorter tube has better

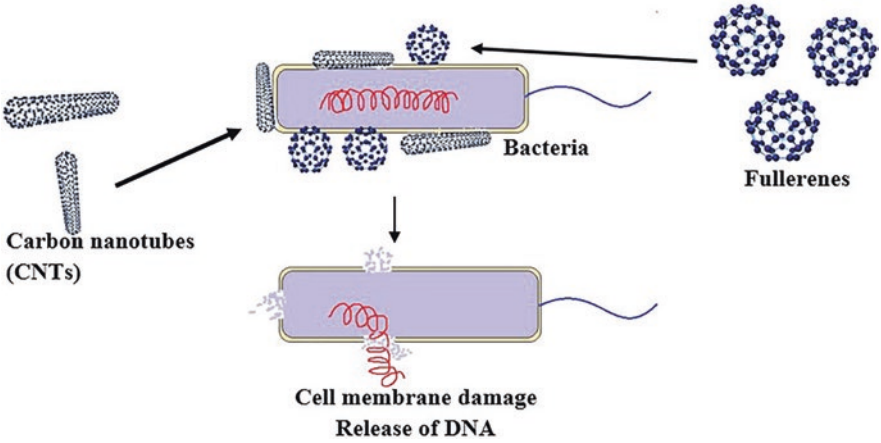

Fig. 10.3 Mechanism of antagonistic activity of carbon nanotubes and fullerenes. (Mechanism described by Kang et al. (2008), Tegos et al. (2005), and Cataldo and Da Ros (2008))

bactericidal efficiency. They have the potential to communicate best with open ends of nanotubes and a microbe, resulting in increased damage to the cell membrane (Aslan et al. 2010). They prepared and tested the antimicrobial effect of SWCNTs and MWCNTs against *E. coli*. Their findings confirmed that SWCNTs were more noxious than MWCNTs to bacteria. Thus, they reported that SWCNTs could be a better choice of antibacterial agents based on their findings. Arias and Yang (2009) tested the antimicrobial efficacy of SWCNTs and MWCNTs against rod-shaped or round-shaped Gram-negative and Gram-positive bacteria with different surface groups. They reported that SWCNTs showed potent antibacterial activity for both Gram-positive and Gram-negative bacteria with surface groups of -OH and -COOH, whereas MWCNTs with the same surface groups did not display any convincing antibacterial activity. Their findings revealed that CNT binding to bacterial cells triggers the cell membrane to disrupt and then release its DNA material, eventually contributing to the death of the bacteria (shown in Fig. 10.3). Moreover, the surface area of SWCNTs proposed improved synergy with the microbial cell wall.

When the bacterial cells come in direct contact with SWCNTs, it influenced the morphology, metabolism processes, and cellular membrane integrity of *E. coli*. SWCNTs easily penetrate the bacterial cell wall due to their smaller nanotube diameter causing severe damage to the cell membrane.

10.4.2.2 Fullerenes

Fullerenes is an allotrope of carbon, composed of carbon atoms connected by single and double bonds. Their design is much like a soccer ball. In discovering new antimicrobial agents for different infectious diseases, the antimicrobial role of fullerenes and their derivatives received considerable interest. They are also known for

demonstrating antagonistic action against various bacteria, such as *E. coli*, *Streptococcus* spp., and *Salmonella* (Tegos et al. 2005). In another study, they mentioned the antimicrobial potency of fulleropyrrolidinium salts after photoirradiation. Their reports revealed that 99.9 percent of bacterial and fungal cells were dead after treatment. After white light irradiation, the cationic-substituted fullerene derivative is extremely efficient in destroying a broad range of microbial cells (Mizuno et al. 2011). They investigated a new category of synthetic fullerene derivatives with prominent antimicrobial activity, carrying either basic or quaternary amino groups. They proposed that in the treatment of superficial infections, for example, in burns and cuts, where light infiltration into tissue is not difficult, quaternized fullerenes can be used efficiently. A bactericidal mechanism that explains the induction of cell membrane disruptions was stated by Cataldo and Da Ros (2008). The hydrophobic surface of the fullerenes can conveniently unite with membrane lipids and intercalate into them. Among three separate groups of fullerene compounds (cationic, acidic, and anionic), cationic derivatives displayed the highest antimicrobial activity on E. coli and Shewanella oneidensis, while the anionic derivatives were nearly inactive. This is due to the robust synergy of cationic fullerenes with the negatively charged bacteria (Nakamura and Mashino 2009).

10.5 Gold Nanoparticles

In recent years, gold nanoparticles (AuNPs) have appeared as exclusive noninvasive drug carriers to target drugs at their site of action. Their site sensitivity has tended to improve the potency of medications at a reduced dosage and reduce their side effects (Kumari et al. 2019). In the field of biomedical research and diagnostics, AuNPs have become an important factor. The unique physicochemical properties of AuNPs make them a superior candidate for an antimicrobial agent (Allaker et al. 2012). The antimicrobial action of gold nanoparticles can be due to the formation of reactive oxygen species (ROS) that increases the oxidative stress of microbial cells. Photothermal therapy (PTT) can be used to improve the antimicrobial efficacy of AuNPs. Gold nanoparticles can produce heat because of the excitation of electrons when irradiated with a laser. This makes it easier to use them as anticancer or antimicrobial agents. For example, AuNPs have boosted the bactericidal effect on *S. aureus* when exposed to laser energy (Riley and Day 2017). The antifungal activity of AuNPs against *Candida* isolates was also reported by some researchers (Ahmad et al. 2013) (Table 10.1).

Table 10.1 Antimicrobial nanomedicines

Nanomedicine	Mechanism of action	Antimicrobial activity
Synthetic antibacterial nanomedicine		
Carbon nanotubes and fullerenes	Cell membrane damage, the release of DNA content, fullerenes can make radical-oxygen species	*E. coli* DH5α, *Vibrio fischeri*, *Bacillus subtilis*
Silver nanoparticles	Cell membrane damage by accumulation, DNA damage, protein denaturation	*E. coli*, *P. aeruginosa*, *S. aureus*
Gold nanoparticles	Disruption of the cell membrane	*E. coli*, *Salmonella typhimurium*
Bioactive glasses	Production of alkaline species	*E. faecalis*
Metal oxide nanoparticles	Electrostatic synergy between nanoparticle and bacteria	*E. coli*, *B. subtilis*, *S. aureus*
Magnesium oxide nanoparticles	Formation of superoxide anions	*Bacillus subtilis*, *S. aureus*
Zinc oxide nanoparticles	Introduction of oxidative stress	*C. jejuni*, *Salmonella enterica serovar Enteritidis*, *E. coli* O157:H7
Silicon dioxide nanoparticle	Discharge of nitric oxide	*S. aureus*
Biological-based antibacterial Nanomedicines		
Chitosan nanofiber	Loss of membrane permeability	*E. coli*, *S aureus*
Targeted drug-carrying phage medicines	Delivery of antimicrobial agents in the target pathogen	*S aureus*, *Streptococcus pyogenes*, *E. coli*
Poly-L-lactide nanoparticles	Release of antimicrobial protein nisin	*Lactobacillus delbrueckii*

Yacoby and Benhar 2008; Matthews et al. 2010; Hajipour et al. 2012

10.6 Biological-Based Nanomedicines

10.6.1 Chitosan-Based Nanoparticles

Chitosan (C) is a semisynthetic linear polysaccharide comprising of randomly assigned β-(1 → 4)-linked D-glucosamine (deacetylated unit) and *N*-acetyl-D-glucosamine (acetylated unit) (Prabaharan 2008). They are developed commercially by chitin deacetylation, which is the principal component in the exoskeleton of crustaceans. The techniques used for the synthesis of chitosan-based nanoparticles are ionotropic gelation, emulsification solvent diffusion, microemulsion, and emulsion-based solvent evaporation (Mohammed et al. 2017), as shown in Fig. 10.4. Chitosan has fascinated numerous biomedical and pharmaceutical industries because of its biodegradability and biocompatibility, in addition to its mucoadhesive and bacteriostatic activity (Nagpal et al. 2010). Chitosan nanoparticles (NPs) are widely studied as carriers of medications, proteins, and genes and have been used as a drug delivery vehicle in polymeric nanoparticle via multiple routes of

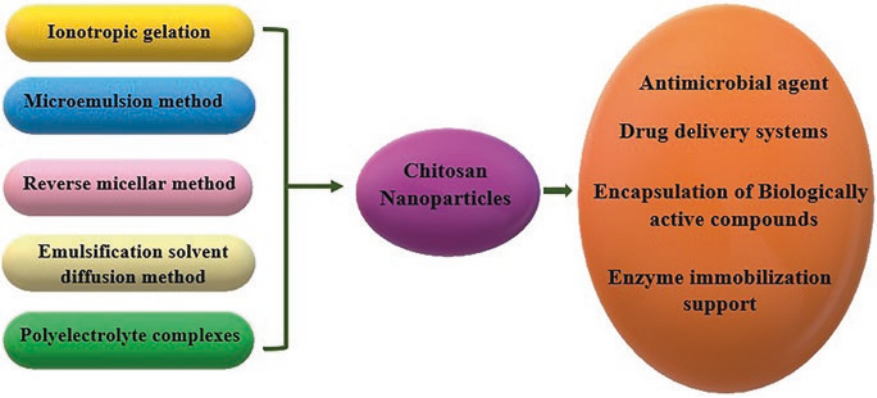

Fig. 10.4 Different methods of preparation and biomedical applications of chitosan nanoparticles

administration (Rampino et al. 2013). Chitosan and chitosan derivative NPs hold a cationic charge on their surface and mucoadhesive features that can bind to mucus membranes and release the drug consignment, in a continuous release fashion (Mohammed et al. 2017). It has an antibacterial and antifungal function as well (Ducheyne et al. 2011). The antibacterial activity of the electrospun nanofiber mats developed from chitosan was reported by Ignatova et al. (2006). The association of protonated quaternized chitosan (QCh) mats with the negatively charged bacterial surface results in the lack of bacterial membrane permeability, cell leakage, and eventually cell death. The QCh mats showed bactericidal characteristic on Staphylococcus aureus and Escherichia coli. Electrospun mats are useful as wound dressings because they can reduce the risk of bacterial infection. Chitosan-based NPs have all the required properties for quick, nontoxic wound healing, hemostatic activity, biodegradability, and the power to affect the function of macrophages.

10.6.2 Poly-L-Lactide Nanoparticles

Poly (L-lactic acid) or (PLLA) is a linear aliphatic thermoplastic polyester produced from sustainable resources (Wang et al. 2012). PLLA has attracted considerable attention because of the combination of its biodegradable property, bioresorbability, biocompatibility, and shape memory effect. It has been broadly practiced in biomedical fields such as bone screws, surgical sutures, tissue engineering, and controlled drug delivery (varkey 2019). Also, its low consumption of moisture and great wicking may benefit the appropriate exudates from the wound (Gupta et al. 2007; Davachi and Kaffashi 2015). In the medicine world, antimicrobial products and biocides are commonly used to kill or inhibit the development of pathogenic and other harmful microbes. Therefore, anti-infection alterations of polymers are introduced to suppress the development of certain microorganisms. Three approaches

can accomplish the anti-infective properties of polymers, specifically anti-infective factors combined with polymers, copolymerization of anti-infective factors with monomers, and adequate surface treatment of medical polymers (Popelka et al. 2012; Kugel et al. 2012). A variety of studies have been performed on the antimicrobial efficacy of PLLA in different formulations, including neat, blended, and composite, and also using various types of antimicrobial agents, along with nisin, Nisaplin, and nano-silver, under a broad dimension of test conditions (Liu et al. 2009; Prapruddivongs and Sombatsompop 2012).

10.7 Nanoparticle Vaccines Against Infectious Diseases

Recently, preventing and immunizing infectious diseases has become a big problem due to the proliferation of numerous novel variants of pathogenic and drug-resistant microbes. As reported by the World Health Organization (WHO) in 2016, there were nearly 3.2 million deaths globally from lower respiratory or lung infections and 1.4 million deaths from tuberculosis alone. No effective medicines against these infectious diseases are available which has become a major obstacle in combating those diseases. The production of the desired vaccines against these diseases is urgent. In vaccine production, nanotechnology plays a major role. Vaccines based on nanotechnology are more effective than traditional vaccines. Any of the essential facets of any regular vaccine include (i) protection, (ii) security, and (iii) ability to provide a long-lasting and sufficient immune response at a minimum dose level (Atkins et al. 2006; Beverley 2002). For the production of new-generation vaccines, nanotechnology-based formulations provide various benefits. In addition to shielding the vaccines from premature degradation, the nanocarrier-based delivery mechanism also offers increased antigen stability, good adjuvant properties, targeted delivery, and gradual release of the drug and helps to deliver an immunogen to the antigen-presenting cells (APCs) (Pati et al. 2018). Several nanoparticle-based therapeutic methods have been introduced recently to monitor the function of T cells against viral, bacterial, or fungal infections. Effective transmission of antigens to APCs, particularly in dendritic cells (DCs), and APC activation are some important factors in the production of successful vaccines. It is now conceivable to target delivery to DCs, APCs activation, and monitor the release of the antigen by nanoparticle-based vaccine delivery systems. In the presence of co-stimulatory compounds and cytokines, the synergy between MHC I and T-cell receptors (TCR) kills the infected cells by triggering cytotoxicity. It provides a cellular immune response. Antigens are also expressed on the surface of the APC by class II MHC molecules to the (CD4+). Subsequently, helper T CD4 + cells stimulate B cells and thus produce antibodies (Pati et al. 2018) (shown in Fig. 10.5). It is responsible for humoral immunity.

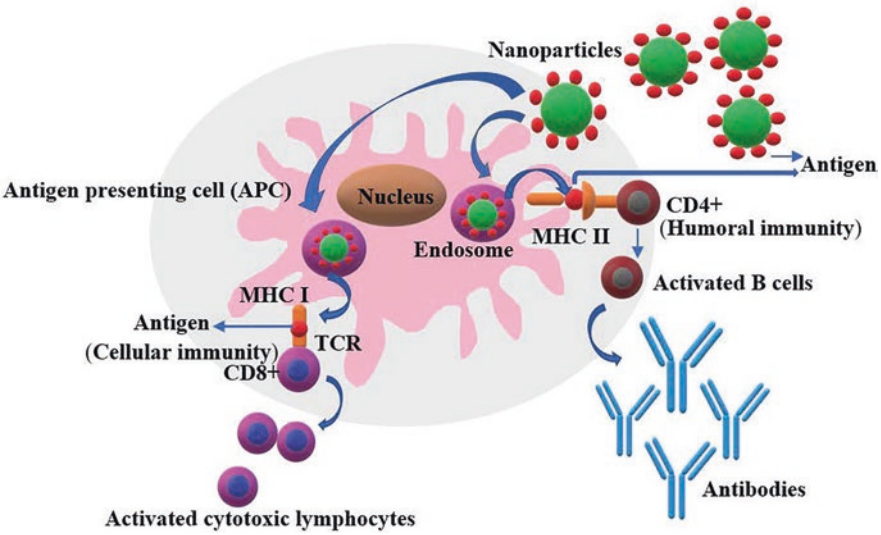

Fig. 10.5 Targeted delivery of antigenic molecules into the antigen-presenting cells (APCs) using surface designed nanoparticles. (Mechanism described by Pati et al. 2018)

10.8 Types of Nano-Immuno Activators

10.8.1 Liposomes

Liposomes are spherical sac of phospholipid molecules ranging from 20 to 30 nm in size. It can imitate cell membranes and directly fuse with microbial membranes. They are the most broadly discovered vaccine and drug delivery tool in nanomedicine. Liposomes can be produced by lipid hydration resulting in the formation of lipid bilayer around the aqueous core (Sharma and Sharma 1997). They are predominantly composed of biodegradable phospholipids (e.g., cholesterol, phosphatidylcholine, and phosphatidylserine). Liposomes carry vaccines by combining them with the target cell membrane (Tyagi et al. 2012). They can encapsulate both hydrophilic and hydrophobic compounds. The aqueous core can accumulate hydrophilic particles, while the phospholipid bilayer encloses hydrophobic particles. According to some studies, the delivery of antigenic proteins trapped in multilamellar lipid vesicles produces active T- and B-cell responses (Moon et al. 2011). Antigenic peptides coupled to phosphatidylserine (PS) liposomes are internalized by APCs to develop T-helper cell-mediated immune responses (Ichihashi et al. 2013), and distribution of heat shock protein-encoding DNA vaccine using liposomes produced active immunity against fungal infections.

The most advantage of liposomes in nanomedicine is that they can not only deliver large amounts of drug payloads but also protect their encapsulated drugs

from degradation, premature inactivation, and dilution in circulation and can be constructed in different forms for various pathways of administration.

10.8.2 VLPs (Virus like Particles)

VLPs are complexes between 30 and 90 nm consisting of self-assembled viral proteins with no nucleic acid genome or lipid envelope. They are more like empty viruses with intact protein hulls and, if desired, membrane envelopes but devoid of genetic material that makes them safe for human use (Naskalska and Pyrc 2015). VLPs contain repeated, high-density distributions of viral surface proteins that display conformational viral epitopes capable of producing robust T-cell and B-cell immune responses (Akahata et al. 2010). Nonprotein antigens and small organic molecules can also be chemically coupled to the viral surface to create VLP bioconjugates (Maurer et al. 2005). Consequently, VLPs can defend against viruses and heterologous antigens (Grgacic and Anderson 2006) and boost the immunogenicity of weak antigens as well. *Salmonella typhi* membrane antigen, influenza A M2 protein, and H1V1 Nef gonadotropin-releasing hormone (GnRH)-mounted VLPs produce boosted antigen-specific humoral and cellular immune responses (Gao et al. 2018).

10.8.3 Dendrimers

Dendrimers contain a blend of amines and amides and with nanostructures that are hyperbranched, three-dimensional, and monodispersed (Pati et al. 2018). Because of their features, such as hyperbranched, well-defined globular structures, excellent structural uniformity, multivalence, variable chemical composition, and robust biological compatibility, dendrimers hold enormous potential for biomedical applications (Kesharwani et al. 2014) as shown in Fig. 10.6. However, the application of dendrimers as scaffolds of prodrugs is chiefly interesting. Therefore, dendrimer has been considered as an efficient bioactive delivery vehicle because of their distinctive biological characteristic such as high drug payload, lipid bilayer interactions, targeting potential, blood plasma retention time, filtration, intracellular internalization, biodistribution, transfection, and strong colloidal and biological constancy (Hawker and Frechet 1990; Kumar et al. 2010).

A single dose of a dendrimer with many antigens produces strong antibody and T-cell responses against the Ebola virus, H1N1 influenza, and *Toxoplasma gondii* (Chahal et al. 2016). Irrespective of their toxicity, dendrimers have been referred as "smart" drug carriers because of their ability as intracellular drug delivery vehicles to cross biological barricades, to distribute in the body during the time required to

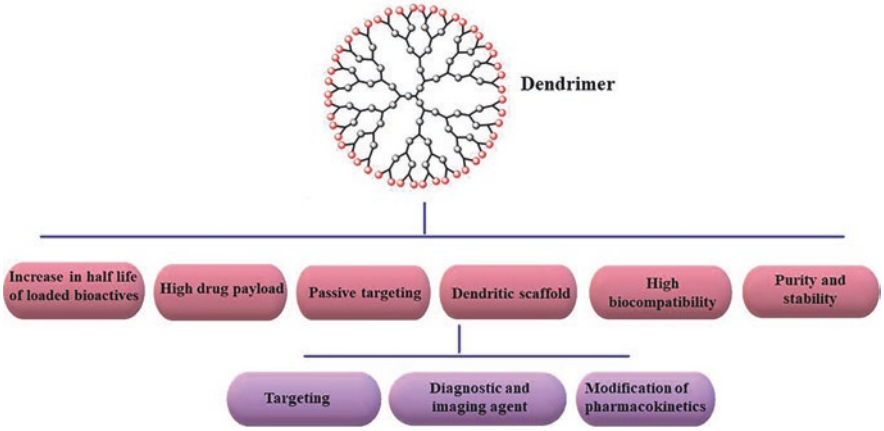

Fig. 10.6 Main features and applications derived from dendrimers

Table 10.2 List of antigens delivered via different nanocarriers for the medication of different infectious diseases

Antigen	Nanocarrier used	Disease	References
Against bacterial infection			
Antigenic protein	Poly (D,L-lactic-co-glycolic acid) nanospheres	Anthrax	Manish et al. (2013)
DNA encoding T cell epitopes of Esat-6 and FL	Chitosan nanoparticle	Tuberculosis	Feng et al. (2013)
Mycobacterium lipids	Chitosan nanoparticle	Tuberculosis	Das et al. (2017)
Polysaccharides	Liposomes	Pneumonia	Abraham (1992)
Bacterial toxic and parasitic protein	Liposomes	Cholera and malaria	Alving et al. (1986)
Antigenic protein	Nano emulsion	Cystic fibrosis	Makidon et al. (2010)
Antigenic protein	Nano emulsion	Anthrax	Bielinska et al. (2007)
Against viral infection			
Antigenic protein	Chitosan nanoparticles	Hepatitis B	Prego et al. (2010)
Viral protein	Gold nanoparticles	Foot and mouth disease	Chen et al. (2010)
Membrane protein	Gold nanoparticles	Influenza	Tao and Gill (2015)

Antigen	Nanocarrier used	Disease	References
Viral plasmid DNA	Gold nanoparticles	HIV	Xu et al. (2012)
Hepatitis B surface antigen	Poly(D,L-lactic-co-glycolic acid) nanospheres	Hepatitis B	Thomas et al. (2011)
Hepatitis B surface antigen	Alginate-coated chitosan nanoparticle	Hepatitis B	Borges et al. (2008)
Capsid protein	VLPs	Norwalk virus infection	Ball et al. (1998)
Nucleocapsid protein	VLPs	Hepatitis	Geldmacher et al. (2005)
Fusion protein	VLPs	Human papilloma virus	Oh et al. (2004)
Multiple proteins	VLPs	Rotavirus	Parez et al. (2006)
Virus proteins	VLPs	Bluetongue virus	Roy et al. (1994)
Viral protein	Polypeptide nanoparticles	Coronavirus for severe acute respiratory syndrome (SARS)	Pimentel et al. (2009)

exert a clinical effect, and to target specific complex (Kesharwani et al. 2014) (Table 10.2).

10.9 Conclusion

To tackle the growing number of antibiotic-resistant strains of pathogenic microorganisms, new antimicrobial agents are urgently required. In the field of medicine, nanoparticles are extensively examined because of their unique physicochemical properties. By providing fast healing of infection without destroying the surrounding cells, nanotechnology achieves impressive outcomes in the treatment of infectious diseases. The current study discusses recent advancements in nanomedicines, including technical innovations in targeted drug delivery and innovative diagnostic methodologies. By manipulating certain diagnostic and treatment criteria, such as controlled slow release of encapsulated medications, nanoparticles make a big leap from conventional diagnosis and treatment to more modern and upgraded one. The diverse types of nanomedicine that have been explored are very promising but still have far to go.

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Chapter 11
Nanotechnology's Promising Role in the Control of Mosquito-Borne Disease

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11.1 Introduction

11.1.1 Nanotechnology

Nanotechnology can be described as the scientific and technological aspects of the architecture, synthesis, features, and functionality of substances at the nanometer scale. This technological know-how opens up innovative role in insect pest management and their opportunities in a blend with bio-based insecticides in order to improve stratigies for pest control. Nanoparticle formulations provide protection for degradation-prone agents, denaturation in areas of intense pH, and further prolong the exposure time of a compound by increasing the retention of the formula through bio-adhesion (Prasad et al. 2019; Sahoo et al. 2007). Nanobiotechnology is the combination of engineering and molecular biology, which focuses on the new classification and recognition charge of the multifunctional devices and structure for organic and chemical assessment with higher sensitivity, specificity, and a greater charge of recognition. Nano-objects with essential analytical purposes consist of nanotubes, nanochannels, nanoparticles, nano-blocks, nanopores and nanofibers (Fortina et al. 2005).

Recent literature suggested that the particular sectors of nanobiotechnology, consisting of liposomes nanoparticles for drug delivery, emulsions, imaging, biomaterials, food, optical, electronics, pathogens, biosensors and in vitro diagnostics. The special bodily and chemical houses of nanomaterials (small size, multiplied reactivity, excessive surface-to-volume ratio), whilst are probably to supply fitness advantages can also additionally be related with deleterious outcomes on cells and tissues. Nanomaterials have dimensions comparable to organelles observed in the cell and have the plausibility to intrude into necessary cell functions, ensuing in conceivable toxicity (Zhang et al. 2012). Advances in nanomaterial modification enable for the attachment of remarkable biomolecules including microbes, pathogens, proteins and nucleic acids (Crean et al. 2011). The development of eco-friendly nano-formulations with efficient delivery system and small quantities of nano-pesticides will be in great demand in the future (Bhattacharyya et al. 2016; Gupta et al. 2018).

11.1.2 Vector-Borne Diseases

Vector-borne diseases cause major public health tribulations, and their control is accomplished mainly with the usage of synthetic chemical insecticides. Since ancient times, mosquitoes consider as disease causing agent o human. They serve as vectors for pathogens that trigger life-threatening human diseases (Chandra et al. 2008). In 124 countries they place at risk up to 55% of the world's population (Beatty et al. 2007). Nowadays the control of biological vectors are prime importance for controlling the vector borne diseases (Kovendan et al. 2012). In worldwide, various methods were developed to control the vector-borne diseases such as

dengue hemorrhagic fever, dengue syndrome, malaria, Japanese encephalitis, yellow fever, chikungunya fever and lymphatic filariasis (Ali et al. 1995). Amid the many diseases, filariasis and dengue are the eminent parasites to cause infections in tropical regions (Pandey et al. 2007). Mosquito-borne diseases can be controlled by targeting the causative parasites and pathogens (Hamaidia & Soltani 2014). There are different forms of mosquitoes and several of them are capable of spreading diseases, including *A. aegypti*, *Culex quinquefasciatus* and *Anopheles stephensi* (Diptera: Culicidae).

A. aegypti are arboviral vectors that are spreading tropical diseases and also becoming one of the greatest public health issues. They are the primary for the transmission of dengue, Chikungunya, Zika, Malaria, Filariasis, Japanese encephalitis, West Nile fever and yellow fever infection. Dengue is the most ubiquitous disease, with about 390 million infections per year (Bhatt et al. 2013). Chikungunya virus has caused over 2.5 million infections in the last decade and has more recently it spreads in the Americas (Staples and Fischer 2014) and emerging in Europe (Schaffner et al. 2013) Yellow fever has caused approximately 200,000 severe cases per year in Africa (Garske et al. 2014), Zika viruses have triggered about four million infections in America (Boeuf et al. 2016). Unfortunately, most mosquito-vectored arboviruses have no treatment accessible for dengue in particular.

Culex quinquefasciatus is the most prevalent type of mosquitoes in populated environments. It may also spread West Nile virus (WNV), SLEV (St. Louis Encephalitis Virus), Pathogenic Protozoa and Japanese Encephalitis virus (JEV) (Bhattacharya et al. 2016). Blood pathogens or the lymph system, muscles and connective tissues in the vertebrate hosts are source of filariasis. The WHO initiated its Global Lymphatic Filariasis Initiative in 2000 and reiterated the goal date by 2020 (WHO 2014).

Malaria is caused by plasmodium, a single-cell protozoan that is transmitted by the mosquito *Anopheles sp*. It mostly affected in developing region as resultant of millions of death occur by malaria (Khan et al. 2018, 2019). The WHO report of 2015 showed that nearly 438,000 people have died of malarial infection. Till now, more than 216 million people are affected per year. While the disease is prevalent, it spreads severely in tropical and subtropical regions (Ismail et al. 2018; Kolluri et al. 2018; Khan et al. 2019).

Various strategies for managing vector-borne diseases have been established worldwide (Baird 2000). Recently, there has been a resurgence in the onset of mosquito-borne diseases to improvements in public health policies and susceptibility changes in mosquitoes to pathogen transmission. Whilst the usage of chemical insecticides has been proven to control mosquitoes over decades, but the application of chemical pesticides in the long term causes a malevolent effect on human and environment. The usage of synthetic insecticide contributes to major pesticide health issues that range from stomach distress, nausea, vomiting, dizziness and depression to skin cancer, eye disorders and acquired defects (Lorenz 2007). Side effects from toxic insects, rodents, amphibians and fishes on the climate, to enhanced tolerance of mosquitoes (Denholm et al. 2002). Nature product such as plants has the potent active to control the mosquito. Still, they have various limitations such as

seasonal variation and unavailability among the years and effectiveness on multiple metabolites (Suryawanshi et al. 2015). Recently, nanomaterials have to arise as a promising novel method to control mosquito-borne diseases.

11.1.3 Nanotechnology in Mosquito Control

Nanotechnology is a revolutionary field in the various areas of research, including medicine, biology and agriculture. Formulation of nano-emulsion preparation of smart nano-pesticide using nanomaterials as active pesticide agents or nanocarriers for their delivery. It can also be determined as valuable as compared to the chemical insecticide for targeting delivery of pesticides for controlling the mosquitoes larva and adult (Ahmed et al. 2019). Extensive research on nanopesticides is expected to deal with the restrictions of the accessible strategies used for pest control and endowed with nano-based novel formulations that enter into the target (pest), remain steady and active in the environment, without impact on non-target organisms, using cost-effective formulation. Beside this, nanoparticles are used in the formulation of insect repellents and also for the rapid diagnosis as biosensors. Nanoparticles-coated pesticides are used for controlled release, which makes an impact on bioavailability and pesticides stability properties (Fig. 11.1). Chitosan nanoparticles play a vital insect component includes mosquitoes which has the part as well as in exoskeleton cuticle and most tissues such as foregut, midgut, hindgut and trachea. Biosynthesis of chitin is mostly reliant on the enzyme chitin synthetase

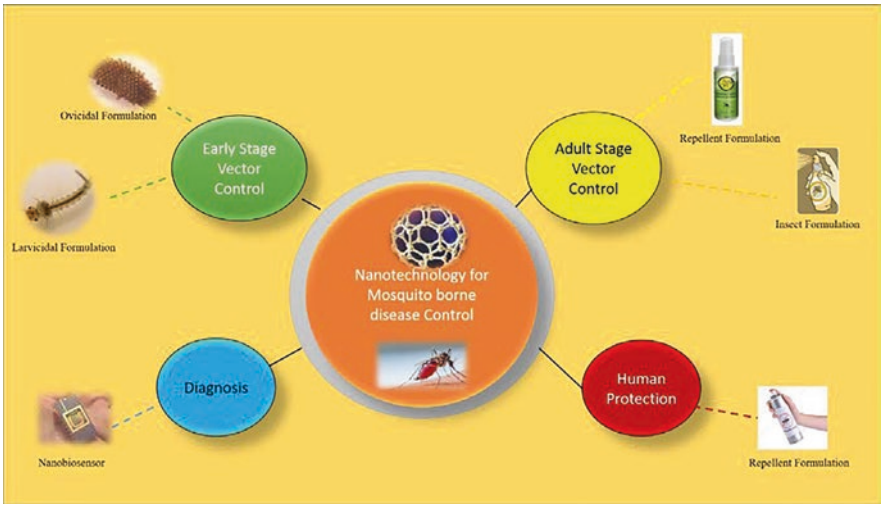

Fig. 11.1 Nanotechnology in Mosquito-Borne Disease Control. The usage of nanoparticles in many sectors in mosquito-borne disease control include, (i) Early-stage vector control, (ii) Adult-stage vector control, (iii) Diagnosis and (iv) Human protection

for the catalysing activity. In this process, they trigger the sugars for transmission to acceptors present in the mosquitoes. CHS A and CHS B are the chitin synthesis genes, where CHS A is present in cuticle and foregut, hindgut and trachea, and, CHS B is associated with the midgut of mosquitoes. The biosynthesis of epithelial cell chitin is linked to the peripheral matrix (PM) (Sen and Blau 2006; Kilama and Ntoumi 2009; Schwendener 2014).

Table 11.1 represents the key categories of nanoparticles used for the improvisation of potent actions that are conventionally done for the prevention of mosquito-borne diseases. It highlights the possible advantages of a variety of nanomaterials used, and some data have shown that they have been used thus far (encoded by accompanying references). Information of the various nanoparticles formed by the use of various nanoscale materials are provided in the following section.

11.2 Drug Delivery System of Nanoparticles for Mosquitoes Borne Diseases

Nanoparticles constitute versatile drug delivery system to control wide range of mosquiotes borne diseases. Nanoparticle mediated drug delivery systems are developed for the optimized release of sufficient and necessary amounts of drugs within a specific time, controlled and targeted delivery plays an important role in vector borne disease control. The large surface area also provides a high affinity to drug and tiny molecules, such as ligands or antibodies, which can be used for targeted and controlled release of therapeutic drugs. Possession of specific characteristics of nanoparticles, viz., high effective loading capacity, larger surface area, fast mass transfer to delivery drug, target delivery and the ability for easy attachment of various small therapeutic molecules, encouraged the use of NPs as nanocarriers. Nanoliposome also used to entrap anti-infectious drugs are active against infections due to facultative intracellular bacteria, parasites such as leishmania, protozoan, viruses such as the one causing mosquitoes borne diseases.The following types of nanocarriers have been used for the delivery of pesticides/drug such as, nanoliposomes, nanosuspension and polymer based nanoparticles.

11.2.1 Nanoliposomes

Liposomes are synthetic nano-sized vesicles comprising of phospholipids and the cholesterol layer surrounded by an aqueous core. Based on the number of layers and size of the nanoparticles, they are divided into three different types as small unilamellar, large unilamellar and multilamellar liposomes (Fig. 11.2). Affording to their physiochemical characterisation, the nanoparticles are either aqueously entrapped or might be inserted into the liposome layers (Shargh et al. 2012;

Table 11.1 Depiction the overview of types of nanoparticles used to control vector-borne diseases

S. No	Content	Types of Nanoparticles	Materials	Properties	References
1	Drug Delivery System of nanoparticles	Nanoliposomes	Lipids and micelles	Immunological Compatibility	Qiu et al. (2008), Fotoran et al. (2019), Shakeel et al. (2019)
		Nanosuspensions	Aqueous	Bioavailability and increase surface area	Omwoyo et al. (2014), Pessoa et al. (2018a)
		Polymer-Based Nanoparticles	Chitin and chitosan	Control drug release	Krishnaswamy and Orsat (2017), Tripathy et al. (2012), Ahmed and Aljaeid (2016)
2	Nanoparticle synthesis by biological methods	Green-based nanoparticle	Plant leaves, root, fruit and etc.,	Reduced size and the different shape and size of the particles	Parthiban et al. (2019), Murugan et al. (2016), Sowndarya et al. (2017), Mondal and Hajra (2016), Rajagopal et al. (2021)
		Microorganism-based nanoparticle	Bacteria and fungi	Unique nanostructures: bacterial nanocellulose, exopolysaccharides, bacterial nanowires, and biomineralised nanoscale materials	Soni and Prakash (2012), Salunkhe et al. (2011)

3	Nanotechnology for arbovirus detection and control	Biosensor	Nano-chips, nanowires and etc.,	Point-of-care (POC) and ASSURED (Affordable, Sensitive, Specific, User-friendly, Robust and rapid, Equipment-free, and Deliverable)	Campos et al. (2020), Pashchenko et al. (2018), Vinayagam et al. (2018)
		Insect Repellent	Insect formulation and Encapsulation	Drug Longevity, biocompatibility and biodegradability	Nogueira Barradas et al. (2016), Coelho et al. (2018), Gomes et al. (2019)

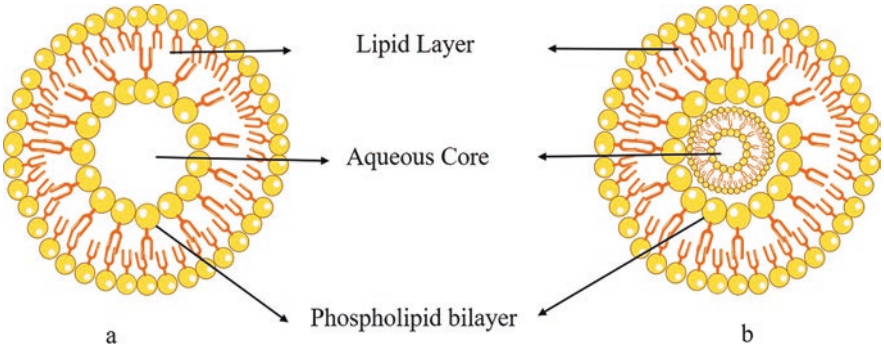

Fig. 11.2 Types of nanoliposomes synthesis. (**a**) Unilamellar liposomes, (**b**) Multilamellar liposomes

Firouzmand et al. 2013; Frezza et al. 2013; Eskandari et al. 2014; Kalat et al. 2014; Oliveira et al. 2014). These nanoliposomes compatability with immune system facilitated for targeted uptake by cells via receptor mediated endocytosis (Santos-Magalhães and Mosqueira 2010).

Nanoliposomes have been previously used for deliverying the drug or vaccine to control malaria. Despite that, the encapsulated therapeutic drug (Chloroquine) within the nanoliposomes shows potent activity by regulating the bioavailability and the dose-dependence inside the body. Pointedly, they reduce the toxic effect and also diminish the drug resistance risk (Qiu et al. 2008).

Recently, gel-core liposomes are used as a nanocarrier for the controlled delivery of the antimalarial drug. Gel core nanoliposomes are the composite of lipid-based carrier coated with the polymer for the controlled delivery of Pfs25 with immune-stimulatory adjuvant (CpGODN). In these gel-core liposomes, polymer integration into the liposomes interior aqueous core increases their stability, and they influence the controlled drug release via the slow release of the drug. The gradual diffusion enables the nanoliposome capability for long-lasting persistence of antigen without any need of stimulating (Baruah et al. 2017).

Lipid particles for drug delivery may be adjusted to form multi-layer vesicles with enhanced cargo interactions and stability. The in vitro treatment of *P. falciparum* NF54 with liposome encapsulated chloroquine. Lipids are capable of establishing hydrogen bonds rather than covalent connections and have been used to create stable vesicles-within-vesicles with a high capacity for entrapping antimalarial medicines such as chloroquine (hydrophilic) and artemisinin (hydrophilic) (lipophilic).While, vesicles deal with parasite-infected erythrocytes more directly than with normal red blood cells. A very interesting method for improved drug delivery is the hydrogen-bonded, multilamellar liposomes, since they are permissive not only to small compounds but also to bigger peptides (Fotoran et al. 2019).

Artemether and lumefantrine combination therapy has been well known for uncomplicated malaria treatment. Both drugs were formulated and freeze-dried with nanoliposomes. The initial bursting impact and the continued release trend

over a duration of 30 h has been observed in *in vitro* drug-release research. Due to tissue distribution, the combination therapy of ART+LUM-NL's intake in reticulo-endothelial system (RES) organs was high, particularly in liver and spleen. In vitro/in vivo toxicological examinations indicate that no erythrocytes are hemolyzed and that there is no indication of renal or hepatic damage in examined animals while treating the ART+LUM-NL's. It was predicted that nanoliposomes might increase the availability of artemether and lumefantrine by extending their in vivo retention. Thus, the nanocarriers are suitable candidate for controlling mosquitoes borne diseases. This type of formulation for malarial therapy does not show any symptoms of fibrosis, fats infiltration, core lobule necrosis and lymphocytic infiltration. (Shakeel et al. 2019).

For medicinal uses, liposomes are certified by the United States Food and Drug Administration. In the human and animal vaccine industries, vaccine components may be incorporated within the aquatic cavities of fibre recombinant vaccines. The liposome preparation laboratory and industrial techniques have been established and the possibility that they may be used in human vaccines is prospective (Adu-Bobie et al. 2003). A liposomal carrier's positive results are (1) their ability to ensure I antigen's protection and stability, including its native adherence, (2) enhanced allophycocyanin (APC) absorption by passive or active targeting and (3) strengthened or controlled antigen absorption.

11.2.2 Nanosuspensions

Nanosuspensions of drugs are nanosized, heterogeneous aqueous dispersions of insoluble drug particles stabilized by steric, electrostatic and surfactants. Thus, they prevent the agglomeration and confirming the stability of pharmaceutical nanosuspensions (Rabinow 2004). The preparation of nanosuspension is by the biphasic approach where the nanosized drug particles are dissolved in the aqueous solution via a top-down or bottom-up method to minimise the particle size (Fig. 11.3). The main advantage of nanosuspensions is the lowering of toxicity level by providing the bioavailability of the drug; besides, the diminished size increases the surface area.

Lumefantrine, a antimalarial drug, used to treat multi-drug resistance malaria. The mechanism of Lumefantrine is by converting the heme of *Plasmodium flaciparum* into hemozoin. The higher amount of accumulating toxic heme causes the death of the parasite and also control malarial infection. Nevertheless, Lumefantrine has a lesser water solubility and causes reduced bioavailability via oral and dietary way (Nakache et al. 2000; Baird and Hoffmann 2004). Nanosuspension-based drug delivery has the advantage to combat malarial infection. The enhanced mechanism of Lumefantrine-based nano-suspension shows a potent anti-malarial activity. In these methods, the size of the Lumefantrine may reduce from 72 μm to 0.251 μm via in vitro and in vivo experiments and tested against the *P. Yoelii nigeriensis* and *P. falciparum* (Omwoyo et al. 2014). In addition to these, the drug dihydro-

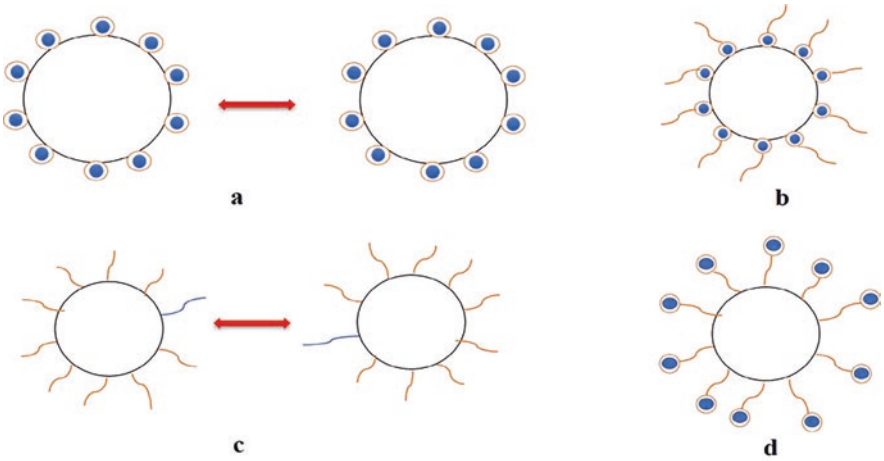

Fig. 11.3 Types of Nanosuspension. (**a**) Electrostatic stabilisation, (**b, d**) Electrosteric stabilisation, (**c**) Steric stabilisation

artemisinin (DHA) was also tested against *P. falciparum* in in vitro trials. The nanosuspension with the low amount of drug concentration reduced the risk of side effects rather than anti-malarial activity (Lee et al., 2014). Quercetin nanosuspension have been represented as a potential drug for controlling mosquitoes borne diseases (Pessoa et al. 2018).

Nanosuspensions are a distinctive and economically successful solution to addressing issues such as low solubility and poor bioavailability of hydrophobic medicines. Media milling and high-pressure homogenisation technologies have been successfully exploited for large-scale processing of nanosuspensions. The applications of nanosuspensions for different routes of administration have been extended by

11.2.3 Polymer-Based Nanoparticles

Polymeric nanoparticles are used as a carrier for the controlled release of drug in the pharmaceutical sectors. It may be used in two forms: nanocapsule and nanospheres (Fig. 11.4). The preparation of polymeric nanoparticles follows two strategies, namely top-down and bottom-up approach. In the top-down approach, a dispersion of polymer generates the polymer-based nanoparticles, while in the bottom-up approach, polymerisation of monomers forms the polymer-based nanoparticles. The main advantage of the polymer nanoparticles is biocompatibility and biodegradability, and their size vary from 1 to 1000 mm (Krishnaswamy and Orsat 2017; Prasad et al. 2017).

Primaquine (PQ) is a mostly used as anti-malarial drug against malarial parasite of *P. vivax* and *P. ovale*. Even though it has potent activity against the malarial parasites, it showed some side effect against the non-targeted organisms due to their

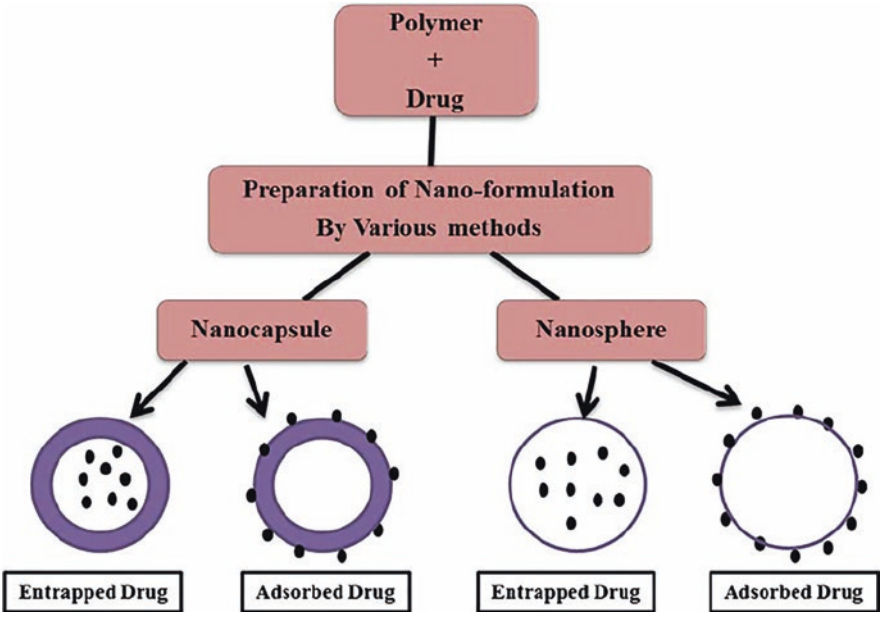

Fig. 11.4 Types of Polymer-based nanoparticles Preparation. (Source: Kumar et al. 2012)

short half-life and their lower bioavailability. The formation of PQ into a chitosan-based nanoparticle has a hope to overcome the risk of side-effects. Many researchers determine the PQ loaded solid lipid nanoparticles have the potential to reduce the multiplication of malarial parasite (Baird and Rieckmann 2003; Omwoyo et al. 2014; Dennis et al. 2015; Ahmed and Aljaeid 2016).

Chitin-based polymeric nanoparticles have more advantages owing to their lower toxicity, higher stability, water solubility, biocompatibility, biodegradability, sustainable release of the drug, quick fabrication and most importantly non-immunogenicity. All these make them an excellent agent for controlling mosquito-borne diseases (Baird and Rieckmann 2003; Dennis et al. 2015).

The encapsulation of Primaquine (PQ) with polymer-based nanoparticles are used for controlling malarial parasite (Moon et al. 2012; Bennet and Kim 2014). Scientists prepared nano-chloroquine (Nch) particles ranging from 150 to 300 nm in size, and they tested them against the spleen and the liver. The result shows reduction in the damage of spleen and liver (~37% and ~29%) as effective as conventional chloroquine (Tripathy et al. 2012).

Researchers have been exploring alternative delivery mechanisms in the last few decades to improve the effectiveness of multiple drugs. Nanotechnology is a promising novel field with aspirations of clinical science for developments in the wide range of applications in drug delivery. Polymeric nanoparticles provide a new path for recently developed disease site-specific drugs and current poorly soluble drugs to accomplish drug delivery and drug targeting. Overcoming the limitations in

traditional drug delivery systems, polymeric nanoparticles are expected for easier implementation and efficient drug distribution, and potentially can increase safety and patient compliance.

11.3 Nanoparticle Synthesis by Biological Methods

11.3.1 Green-Based Nanoparticle

Chemical pesticides are commonly used to control the mosquito population, but it shows the adverse effect of the nontarget community also. Mosquito develops the resistance against synthetic pesticide pollutes the environmental (Milam et al., 2000). The use of chemical insecticide shows a negative impact on the environment and human health and generates resistance via mutation in mosquito population (Lees et al., 2014). In the past, the crude extract of the plant can be used for the larvicidal activity (Senthil-Nathan, 2015). In higher plants, lots of works have been done based on their biologically active material with antilarval properties (Ali et al., 2013). The green synthesis of silver nanoparticles exhibits more advantage than chemical synthesis. It does not produce any hazard to the environment, and it also shows that cost-effective as compared to the conventional method (Parthiban et al., 2019; Tripathy et al., 2013). Recently, the researchers focused on the nanoparticles coated with the natural compounds for prevention of mosquito vector without showing much toxicity (Benelli, 2016a; Kayalvizhi et al., 2016). The green engineered silver nanohybrid showed enhanced mortality range against mosquito because the metallic silver nanomaterial quickly penetrates insect cell through cuticle and mortality was induced by disturbing the normal physiological process (Benelli, 2016b). The green synthesised nanoparticles are well suitable for their reducing and the capping activity. Thus, they employed their ideal activity associated with their reduced size and the different shape and size of the particles (Tripathy et al., 2013). Green Nanotechnology is described as an environmentally safe, clean, nontoxic method to prepare nanoparticles. Beside this, the synthesis method is easy and cheap and does not need high energy, pressure, temperature and a toxic chemicals (Jeong et al. 2005; Benelli and Govindarajan 2017; Prasad et al. 2018b; Sarma et al. 2021). Some widely used nanoparticles include silver, gold, copper, titanium, zinc, silica, selenium, and chitin nanoparticles. In a biological method, the synthesis of nanomaterials consists of plant exact, which includes the whole part of the plant (Saxena et al. 2010; Prasad 2014; Joshi et al. 2018) (Fig. 11.5). Especially, the use of different botanicals act as both reducing and capping agents for the synthesis of nanoparticles with different biophysical features and the toxicity against the pathogens, parasites and the vectors (Benelli et al. 2016; Buhroo et al. 2017) (Fig. 11.6).

Effective green synthesised metallic silver nanoparticles were also obtained from many plant extracts including *Dicranopteris linearis*, *Chenopodium ambrosioides*, *Aristolochia indica*, *Gracilaria edulis*, *Couroupita guianensis*, and *Phyllanthus*

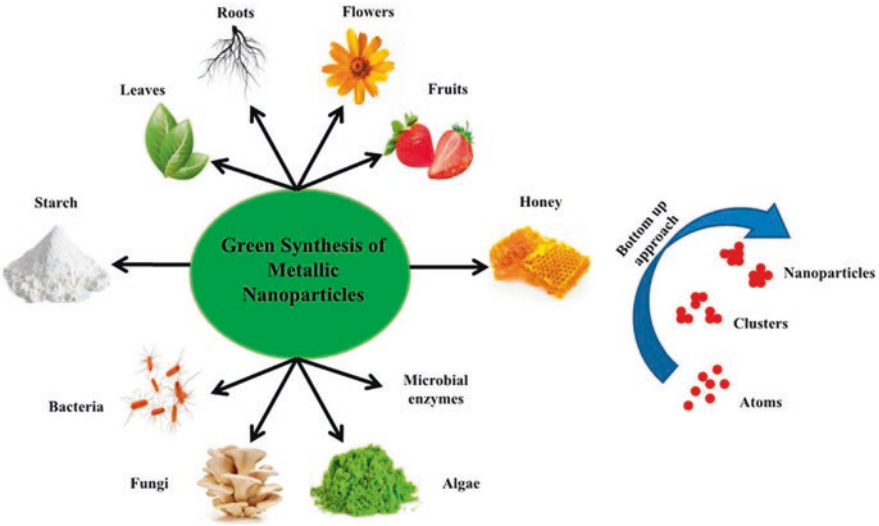

Fig. 11.5 Different types of green synthesis used for the preparation of metal nanoparticles. (Source: Kumar et al. 2020)

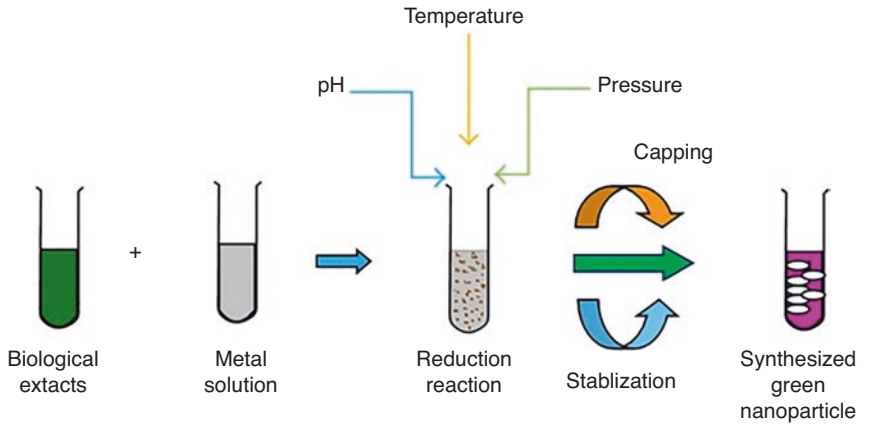

Fig. 11.6 Preparation of green synthesised nanoparticle. (Source: Patra and Baek 2014)

niruri, against mosquito vectors such as *Anopheles, Aedes* and *Culex spp*. They showed lethal concentration in the range between 1 and 30 µg/mL, and the whole abolition of the larval species was achieved within 72 h of the first treatment (Benelli 2016b; Benelli et al. 2018).

Green synthesised silver nanoparticles of *Sargassum muticum* and *D. linearis* are eradicating the 100% of egg hatchability of *A. aegypti* and the *Culex quinquefasciatus*. It showed potent activity within the range of 25 µg/mL and 20 µg/mL concentrations. Compared to *An. stephensi* and *Ae. aegypti*, *C. quinquefasciatus* showed

resistance towards larvicidal activity. Silver nanoparticles from the plant extract of *Rubus ellipticus* showed there is no hatchability of *An. stephensi*, *Culex quinquefasciatus* and *Ae. aegypti* at the dose of 75 µg/mL, 90 µg/mL and 60 µg/mL, respectively (Azarudeen et al. 2017). Likewise, many silver nanoparticles derived from the leaf-extracts of various plants showed adulticidal activity against mosquito species such as *Ae. aegypti*, *Ae. albopictus*, *C. quinquefasciatus* and *An. stephensi*. Unluckily, the exact mechanism of the ovicidal and the adulticidal activity of green-based nanoparticles are unknown (Benelli et al. 2018). However, it has been hypothesised that the nanoparticles penetrate into the exoskeleton and bind with larval DNA. Finally, it alters the DNA function, causes rapid degradation of proteins and importantly decreases in the membrane permeability of insect. These all lead to affect the cell function and induce the cell death with the enormous production of ROS in the mosquito (Benelli 2016b; Azarudeen et al. 2017).

In addition to these, some previous studies revealed that the exposure of nanoparticles against *An. stephensi* and *Ae. aegypti* shows longevity in adult emergence and the fecundity of the females. Some of the examples are green fabricated nanoparticles from the plant extract of *Hypnea musciformis* and *P. aquilinum*, which reduced the longevity of *Ae. aegypti* and *An. Stephensi* and also female fecundity (Alto and Juliano 2001; Panneerselvam et al. 2016). Thus, the green fabricated nanoparticles act as an excellent candidate to control vector-borne diseases efficiently.

The synthesis of metal nanoparticles from plant-derived compounds are effective and showed with excellent anti-plasmodial potential as well as mosquitocidal properties. More than 100 studies have demonstrated a highly efficient mosquito toxicity to plant-based polydisperse metal nanoparticles. The use of various botanicals as reducers and stabilisers leads to different size, type and toxic properties of metal nanoparticles against mosquito vectors (Benelli et al. 2017).

11.3.2 Microorganism-Based Nanoparticle

Nowadays, microbial-based nanoparticles synthesis has a novel approach to control mosquito-borne diseases. Notably, the integration of nanoparticles by using microbes is well studied based on their interaction with metals, and they are also commercially employed in biotechnological processes such as bioremediation and bioleaching. Microbes are well recognised to produce inorganic compounds via intracellular or extracellular metabolites. Both metabolites are used for the synthesis of nanoparticles. Extracellular metabolites synthesised nanoparticles process are cheap and time-consuming compared to intracellular biosynthesis. Extracellular biosynthesis nanoparticles have potent medical applications. Thus, most of the studies are focused on this method to produce microbial nanoparticle synthesis (Durán et al. 2005; Gericke and Pinches 2006; Prasad et al. 2016, 2019a, b; Srivastava et al. 2021).

Most microorganisms are used for producing the nanoparticles like chemical synthesised nanoparticles (Fig. 11.7). In addition to these, the nanoparticles are synthesised with controlled size and determine the nanoparticle composition by

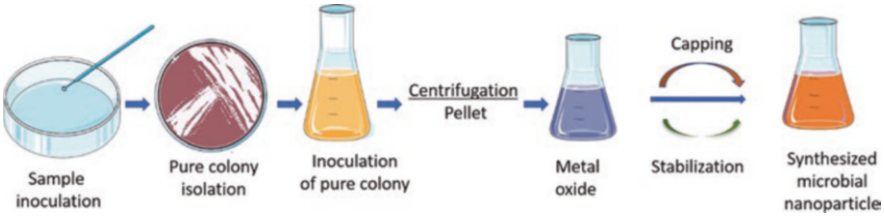

Fig. 11.7 Preparation of microbial synthesised nanoparticles. Metal nanoparticle mechanisms are revealed to be trapped on the surface of the cell membrane by metal nanoparticles. The trapped metal ions are then reduced to nanoparticles by reduction

microbial synthesis (Gericke and Pinches 2006). The mechanisms for toxicity of mosquito mortality have recently been studied in the treatment of nanoparticles. So, hypothetically suggested that the toxicity mechanism of nanoparticle aganist mosquito larva by the penetration of nanoparticle. In intracellular space, nanoparticles destroy enzymes and organelles resulting in loss of cell function and cell death (Selvan et al. 2018; Sowndarya et al. 2017).

The silver nanoparticles synthesised from the entomopathogenic bacteria *B. thuringiensis* (Bt) showed potent activity against *A. aegypti*, a dengue vector. The larvicidal activity of these nanomaterials showed potency at low concentration (Banu et al. 2014). This also reduces the xenobiotics chemical load in the environment (Banu and Balasubramanian 2014a, b). Likewise, other metals such as zinc, copper, selenium and gold are used to synthesise nanoparticles for controlling mosquito-borne diseases.

Fungi have numerous bioactive compounds compared to other microbial species. The filamentous fungi (Ascomycetes, *Fungi Imperfecti*, etc.) produced up to 6400 different compounds (Berdy 2005). Fungi are a promising source of secondary metabolites (Siddhardha et al. 2012). The types of fungi include *Cladosporium oxysporum*, *Cladosporium spherospermum*, *Gilmaniella subornata*, *Chaetomium indicum*, and *Penicillium purpurogenum* and their secondary metabolites are screened against the larvicidal activity (Siddhardha et al. 2012).

Fungal extracellular metabolite synthesised nanoparticles are stabilised by their proteins and they act as a reducing agent. Fungal proteins are associated with the nanoparticle synthesis (Prasad 2016, 2017; Prasad et al. 2018b; Abdel-Aziz et al. 2018). During synthesis, the strain produced specific NADH-dependent reductase (Kumar and McLendon 1997; Macdonald and Smith 1996).Synthesis of gold nanoparticles from the fungus *A. niger* are effective and eco-friendly approach against the mosquito (Soni and Prakash 2012). This group of researchers also reported that entomopathogenic fungi *Chrysosporium tropicum* acts against mosquitoes. They synthesised silver and gold nanoparticles from fungus *Chrysosporium tropicum* and studied for all the stages of larvae. Among these, the silver nanoparticles showed potent activity against the larvae of *C. quinquefasciatus*. While the gold nanoparticles were found to be very potent against *An. stephensi* (Soni and Prakash 2012, 2013).

The pathogenicity and nanoparticle synthesis ability of microbial isolates as *E. coli*, *A. bisporus*, *Pencillium* sp. and *Vibrio* sp. showed potent larvicidal activity within 24 h of post-treatment (Dhanasekaran and Thangaraj 2013). The synthesis of nanoparticle is large quantity for commercialization by this method. Then this particle is formulated and commercialised as the bio-larvicides for vector-borne disease and also for agriculture pest (Balasubramanian and Banu 2016).

11.4 Nanotechnology for Arbovirus Detection and Control

The development of nanotechnology-based biosensor is much attention for detection of arbovirus. On the other hand, there were under studied about the using nanotechnology to overcome the transmission of mosquito-borne diseases by preparing the formulation of larvicidal agent and the repellent (Campos et al. 2020).

11.4.1 Biosensor

In order to reduce and exhibit the further transmission of arbovirus causing diseases (Chikungunya, yellow fever, zika and dengue) the rapid detection method is a very effective tool (Patterson et al. 2016). Regarding this, the WHO has also accentuated the importance of developing point-of-care (POC) tests which are ASSURED (Affordable, Sensitive, Specific, User-friendly, Robust and rapid, Equipment-free, and Deliverable) (Pashchenko et al. 2018). A unique method for the detection of arboviruses must have those characteristics features and also facilitate the early diagnosis of diseases. For early diagnosis and protection from the mosquitoes borne diseases is major challenges in public health. There is a rapid and timely analysis plays a vital role at early confirming viral infection, therefore the affected candidate can be subsequently treated by clinically with the essential precautions (Rashid and Yusof 2018).

Biosensors are biological-based analytical devices, which are used to distinguish analysis in a complex sample matrix. They do not need a long sample treatment process. The main advantage of a biosensor is that the receptor specifically interacts with a diagnostic molecule. This interaction makes physicochemical changes including production of gases, mass, heat, ions, coloured moieties or light (Sethi 1994; Singh et al. 2020).

The multicoloured silver nanoplates are used to detect yellow fever and dengue, which was demonstrated by (Yen et al. 2015). Recently it was improved by using the LFA technology. The technology is associated with the nanotechnology tools of lab-on-a chip. The nanoparticle in the chip will change colour during aggregation. This technology improves the diagnosis selectivity and also sensitivity (Campos

et al. 2020). For diagnosing serotype-specific DENV, a triangular silver nanoparticle coated biosensor was employed, based on the pH reduction method. It differentiates the DENV serotype from other serotypes. In this biosensor, they are identified based on colour response (Fig. 11.8). The colour response was accomplished by the interaction of TAg-DNA probe and the dengue virus RNA. Yet, it was not tested by using real samples from the dengue infected people, but it is a promising diagnosis tool for clinical POC diagnostic testing (Vinayagam et al. 2018).

Nano biosensor has a potential for early detection of arbovirus-borne diseases in an effective manner. Because it has specificity, sensitivity and stable recognition in complex matrix in real time analysis. Even though, the improved techniques and various protocols are needed and also in tested to improve the efficiency and production of nanobiosensor. For accomplishing the highly equipped nanobiosensor, we need a narrow scientific boundary amid other disciplines includeing biology, chemistry, sociology and nanotechnology. Nanotechnology based diagnosis device enough small quantity of blood sample and it takes only 40 mins for detection (Fig. 11.9) (Priye et al. 2017; Rong et al. 2019). In spite of these advances, there is a need to improve the devices for proper and accurate use of nanobiosensors in hospitals to early detection and prevention of arbovirus borne diseases (Campos et al. 2020).

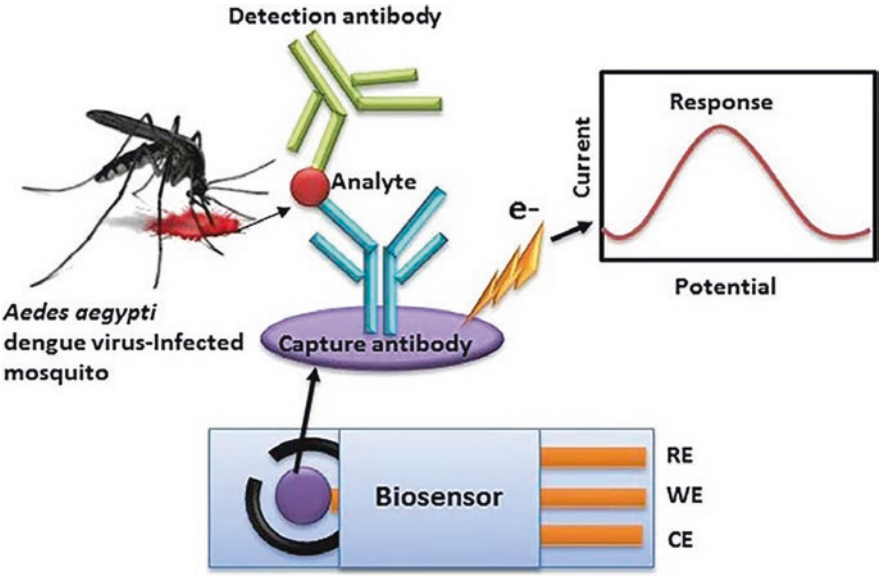

Fig. 11.8 Nanoparticles in Biosensor for detecting Dengue Fever. (Source: Anusha et al. 2019)

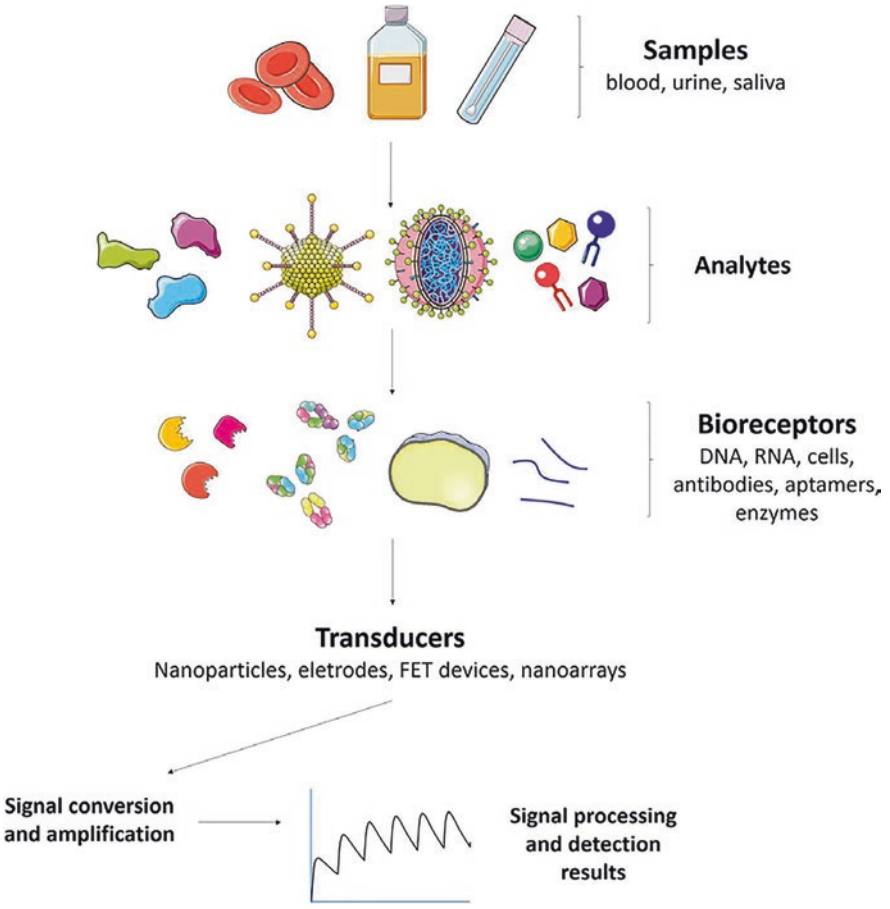

Fig. 11.9 The detection of NS1-anti-dengue and IgM antibodies, zika and/or chikungunya can involve different samples (blood, urine, saliva) In order to track arboviruses, analysts may communicate with bioreceptors. (Source: Campos et al. 2020)

11.4.2 Insect Repellents

The advancement of nanotechnology-based encapsulation of synthetic and natural repellent have an effective against the biological vectors. These constant releases of formulation deliver a controlled or slow release of potent agent to the environment. In addition to these, they increase the action duration and reduce the human exposure (for example, by permeation through the skin). Encapsulation also protects the active compound from premature degradation triggered by the effect of temperature, light, humidity and oxidation (Coelho et al. 2018). Various types of matrices including natural and synthetic are used for the preparation of carriers, for example, lipids, polysaccharides, proteins, polymers and others. Notably, the main

characteristic feature of those matrices are biocompatibility and biodegradability and most importantly low cost (Nogueira Barradas et al. 2016).

Encapsulated DEET, a polymeric nanosphere with an average size of 114 ± 37 nm has high stability and low polydisperse index. The continuous release of nano-encapsulated DEET provides repellent activity against biological vectors up to 9 h. As compared to using DEET, the nano-encapsulated DEET has a longer time activity. It showed that the release mechanism was temperature dependent, thus it has high potent activity (Gomes et al. 2019).

11.5 Conclusion

Recently, control of mosquito-borne diseases facing a critical challenge, which deals with the scarcity of potent agents or detection tools against malaria and arboviruses transmitted diseases such as zika virus, dengue, and chikungunya. On this background the synthesis of nanoparticles from the biological product and their drug delivery system make an impact to control the vector-borne diseases. In addition to this, the rapid detection might be used to control and to take safety measures against vector-borne-diseases. The synthesis of nanoparticles is more advantageous than chemical insecticides owing to its target-specific mechanism. From an entomological point of view, nanoparticles have a potent activity to reduce the mosquito population, and persuade the egg mortality and oviposition pre-emption. As a conclusion, it is important to learn about nanoparticles preparation and to appreciate the new and more effective tools involving nanomaterials against vector-borne-diseases.

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Chapter 12
Phytosynthesized Metal Nanomaterials as an Effective Mosquitocidal Agent

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12.1 Introduction

Mosquitoes are notable vectors of various diseases, including dengue, malaria, filariasis and yellow fever (Khater et al. 2019). According to the World Health Organization (WHO) in 2020, malaria is the most common parasitic infection transmitted by mosquitoes, which leads to 219 million cases globally, with more than 400,000 deaths, every year. Further, Dengue is a viral infection, which is transmitted by mosquitoes and affects 96 million symptomatic cases and 40,000 deaths globally, every year (WHO 2020). Thus, there is a quest to develop a novel and efficient mosquitocidal agent for a long time to eradicate the mosquito population. There are several conventional mosquito repellents or mosquitocidal agents, such as dichlorodiphenyltrichloroethane (DDT), lindane, malathion, fenitrothion, propoxur, chlorpyrifos-methyl, pirimiphos-methyl, bendiocarb, permethrin, cypermethrin, alpha-cypermethrin, cyfluthrin, deltamethrin, lambda-cyhalothrin, bifenthrin and etofenprox, that are synthesized via chemicals. These chemicals-based mosquitocidal agents have exhibited adverse toxicity towards humans and the environment with several limitations (Suresh et al. 2020). Thus, biological mosquitocides, such as plant extracts as mosquito repellents and mosquitocides, microbial mosquitocides, biological control agents, including fishes, sterile insect technique (SIT), boosted SIT, transgenic mosquitoes and symbiont-based methods with bacteria are used as alternatives to the chemical mosquitocides (Huang et al. 2017). However, the efficiency of these bio-mosquitocides are low, as compared to the chemical-based mosquitocidal agents (Benelli et al. 2016). Further, mosquitoes develop resistance towards most of the mosquitocidal agents, due to their ability to adapt to harsh environments and rapid evolution with less life cycle time (Senthil-Nathan 2019). Thus, there is a requirement for a novel mosquitocidal agent with high efficacy to inhibit the growth and development of mosquitoes and are safer for non-target organisms.

Nanotechnology is an emerging field of forefront innovation, which involves the contribution from various fields, including chemistry, physics, biology, material science and medicine (Quazi 2020). In recent times, nanomaterials are introduced as a potential alternative to conventional mosquitocidal chemicals and biological agents due to their high surface-to-volume ratio and ability to inhibit their growth at the cellular level (Borgheti-Cardoso et al. 2020). However, nanomaterials prepared via physical and chemical approaches are either costly or toxic to plants, animals, humans and the environment (Maroufpour et al. 2020; Sarma et al. 2021; Saglam et al. 2021). Thus, nanomaterials fabricated using plant extracts are widely used recently as an effective mosquitocidal agent (Rana et al. 2020). The synergistic mosquitocidal property of the phytochemicals from plants and nanomaterials is beneficial in inhibiting the population of mosquitoes by targeting their egg, pupa, larva and adult (Seetharaman et al. 2018). Moreover, the phytochemicals as surface functional groups in these nanomaterials are beneficial in reducing their adverse toxic effects (Rheder et al. 2018). Hence, this chapter is an overview of the various synthesis approaches to fabricate metal nanoparticles and the significance of

phytosynthesis approach. In addition, the mosquitocidal property of the metal nanoparticles and their mechanism of action are also discussed.

12.2 Synthesis Approaches of Metal Nanomaterials

The synthesis approaches are highly significant in the fabrication of nanomaterials to yield them with exclusive and desired properties for specific applications. Various synthesis approaches, such as physical, chemical and biological methods, are available for the formation of distinct nanomaterials as listed in Table 12.1 (Gudikandula and Charya Maringanti 2016).

Table 12.1 Size and morphology of metal nanoparticles synthesized via various approaches

Nanomaterial	Synthesis method	Size (nm)	Morphology	Reference
Gold	Laser ablation	11–5	Spherical	Naharuddin et al. (2020)
Gold	Sputtering	1.6–7.4	Spherical	Ishida et al. (2016)
Gold	Sonochemical	92.37–112.3	Spherical	Usman et al. (2019)
Silver	Laser ablation	26–21	Spherical	Sadrolhosseini et al. (2019c)
Silver	Sputtering	5.9, 5.4 and 3.8	Spherical, worm-like network	Asanithi et al. (2012)
Silver	Cryomilling	4–8	Spherical	Kumar et al. (2016)
Silver	Ball milling	1–30	Spherical	Rak et al. (2016)
Silver	Sonochemical	3–8	Spherical	Vinoth et al. (2017)
Platinum	Sonochemical	3.5	–	Jameel et al. (2020)
Platinum	Microwave-assisted synthesis	2–8	Spherical	Inwati et al. (2016)
Gold	Chemical reduction	15–30	Spherical	Dong et al. (2020)
Copper	Chemical reduction	28.3	Cubic	Khan et al. (2016)
Platinum	Pulsed laser ablation	4.7	Spherical	Mendivil Palma et al. (2016)
Gold	Microbial synthesis	106	Flower shaped	Singh et al. (2016a)
Gold, silver	Microbial synthesis	102, 92.4	Spherical	Singh et al. (2016b)
Silver	Microbial Synthesis	15–25	Spherical	Gudikandula et al. (2017)
Platinum	Microbial synthesis	28.96	Cubic, spherical, truncated	Gupta and Chundawat (2019)
Silver, copper	Green alga synthesis	40–100, 10–70	Cubic, spherical, truncated	Arya et al. (2018)
Gold	Brown alga synthesis	8.4	Spherical	González-Ballesteros et al. (2017)
Silver	Marine green alga synthesis	25	Spherical	Edison et al. (2016)

12.2.1 Physical Approach

Fabrication of nanomaterials through physical methods involves high electrical or thermal energy and mechanical pressure that can cause material abrasion, melting and evaporation, which eventually leads to generation of nanoparticles (NPs). The swift reaction time to yield the final product, high purity, uniform size and shape of nanoparticles are the major advantages of physical methods (Jeyaraj et al. 2019). Several physical methods, such as microwave, ball milling, vapor deposition, laser ablation, arc discharge, flame pyrolysis and sputter deposition are available for the production of NPs (Jeyaraj et al. 2019). Recently, Shah and Zhang (2019) synthesized novel hexagonal gold nanoparticles (AuNPs) by microwave-assisted synthesis method. The study reported for the first time that the hydrolyzed organosilane (3-mercaptopropyl) trimethoxysilane (MPTMS) can be used to reduce the Au^{+} ions under microwave irradiation. The results revealed that the hexagonal AuNPs were formed under different irradiation power, where the higher irradiation power can lead to the formation of larger amounts of AuNPs. In addition, the average size of the AuNPs was found to increase with an increment in the irradiation time, when the reaction was completed within 60s of the time period (Shah and Zheng 2019). In another study, Bayazit et al. (2016) combined microwave irradiation method with microflow chemistry to fabricate AuNPs with controllable size. The spherical AuNPs with the mean diameter between 4 and 15 nm were formed within 90s of irradiation time. Further, the modification ratio of citrate to Au were identified to be the influencing factor of the AuNPs morphology, which leads to the formation of Au nanowire-like structure with polygonal heads. The study explored that the fabrication of AuNPs with smaller particle size and size distribution is possible with ultrafast and effective microwave-assisted technique (Bayazit et al. 2016).

Recently, Rafique et al. (2019) utilized another novel physical approach to produce silver nanoparticles (AgNPs) via the laser ablation method using continuous wave (CW) diode laser and a pulsed neodymium-doped yttrium aluminium garnet (Nd:YAG) laser. The study revealed that utilization of two distinct laser types can produce spherical AgNPs with various sizes, which includes 20 and 9 nm, when using continuous wave (CW) laser and Nd:Yag laser, respectively. It can be noted that the clean and surface contaminant-free AgNPs were produced via simple laser ablation method. The advantage of this method is its simplicity, rapid reaction time, low cost and eco-friendliness to produce ultra-pure AgNPs, compared to other conventional methods (Rafique et al. 2019). Likewise, Nancy et al. (2018) synthesized AgNPs with controllable sizes in liquid medium via laser ablation for different laser energy densities. The results emphasized that nearly spherical-shaped AgNPs were produced. Further, the variation in the laser energy has been identified to produce AgNPs with various sizes. The smaller AgNPs with a size range of 5 nm were obtained with lower laser energy, whereas increment in the laser energy to high level has led to the growth of particle size to 35 nm (Nancy et al. 2018). Moreover, the mechanism of nanoparticle synthesis has been identified to involve the heat generated by the incidence of laser on the metal target followed by melting and

vaporization. Later, the metal plate releases the metal nanoparticles depending on the absorbed energy and plasma plume expands (Sadrolhosseini et al. 2019a).

In another physical approach, Yadav and Vasu (2016) studied the synthesis of copper nanoparticles (CuNPs) by a wet milling process using a planetary ball milling equipment. The ball milling process involves the mechanical co-grinding of metal powders in a cylindrical container with metallic balls. The study revealed that an increment in the milling time will lead to decrement in the crystal size. Further, it is reported that the average crystal size of the milled CuNPs is 21 nm, after 40 h of milling time (Yadav and Vasu 2016). Furthermore, Ramesh et al. (2020) used waste copper chip material to produce CuNPs via high-energy ball milling process (HEBM). After 72 h of milling, hollow sphere-shaped CuNPs were obtained with the size range of 50 nm. This study demonstrated that ball milling can be an effective and economical method to produce CuNPs (Ramesh et al. 2020). Moreover, Wang et al. (2017) synthesized novel platinum nanoparticles (PtNPs) using atomic layer deposition (ALD) method. In this study, the effect of reaction temperature, number of ALD cycles and the type of substrate for the formation of PtNPs were studied. The results revealed that the growth orientation of Pt and its shape can be altered via various substrates. In addition, the particle size and density vary according to the type of ALD methods, number of cycles and reaction temperatures. The study demonstrated that the performance of PtNPs can be changed by varying the fabrication parameters of the ALD process (Wang et al. 2017). In another study, Sadrolhosseini et al. (2019b) synthesized PtNPs via novel laser ablation technique in graphene oxide solution. The study revealed the formation of platinum-graphene oxide nanocomposite with the size range of 12 to 22 nm, where the particle size further decreased with an increment in the concentration of PtNPs and ablation time (Sadrolhosseini et al. 2019b). Even though physical approaches are highly beneficial in yielding smaller sized nanoparticles with high purity, the cost of equipment required is high, which remains as a limitation of physical synthesis, compared to the other nanoparticle synthesis approaches (Jeevanandam et al. 2016).

12.2.2 Chemical Approach

Chemical synthesis approaches can be used to synthesize nanoparticles with desired size and shape. The significant factor to control the size and shape of nanoparticles is the nucleation and growth kinetics of the particle formation in a solution (Nikam et al. 2018). The main advantage of this method is its simplicity and easy scalability, under regular environmental conditions. It has been reported that even the minute changes in the reaction parameters, such as precursors, reducing agents, capping agents, solvent and pH, can lead to a substantial modification in the size, shape, distribution and self-assembly patterns of the nanoparticles (Iravani et al. 2014). The mechanism involved in chemical synthesis is the formation of atomic groups that are accomplished by the chemical reactions under mild reaction condition. Thus, the resultant atomic groups can undergo nucleation followed by growth process, which

can lead to the formation of nanoparticles with a definite shape and size (Yu et al. 2008). Tyagi et al. (2016) synthesized citrate reduced gold nanoparticles (AuNPs) via the simplified chemical reduction method to yield fairly monodispersed gold nanoparticles. The study discussed the role of pH and the ratio of reactant concentration to explore the size control of AuNPs. The results demonstrated that the nanoparticles were uniform in morphology and monodispersed at optimal pH, whereas the particles were of non-uniform size and shape with a change in the optimal pH (Tyagi et al. 2016). In another study, Abkenar and Naderi (2016) synthesized AuNPs by the chemical reduction method using copper anode slime as a gold precursor with 0.1% of Au, which is an insoluble product that is deposited during the electrorefining of copper at the bottom of the electrorefining tank. The extraction of gold from the anode slime was performed using thiourea solution and the resultant cationic complex of gold-thiourea was used as gold solution. The reducing agents such as VenMet solution and sodium citrate were used to synthesize gold nanoparticles directly from the gold-thiourea solution. The results revealed that the reduction of gold-thiourea using two different reducing agents can yield various sizes and shapes of gold nanoparticles, including cubical and spherical nanoparticles with an average size range of 15–190 nm and 190–500 nm for VenMat solution and sodium citrate, respectively. This study suggested that the variation in the reducing agent and other synthesis parameters can lead to nanoparticles with distinct morphology (Abkenar and Naderi 2016). Therefore, chemical reduction is the simple and economical method to produce nanoparticles with a diverse range of size and shape.

Recently, Cheng et al. (2016) synthesized novel silver nanoparticles (AgNPs) with controllable size and morphology. The silver reduction was combined with citrate as reducing agent and tannic acid as both auxiliary reducing agent and stabilizer. It is worthy to note that the alteration of the reaction parameters and concentration of tannic acid in the reaction mixture has resulted in various AgNPs morphologies. Further, it has been revealed that the larger sized AgNPs will be yielded upon increasing the concentration of tannic acid. In addition, the reaction condition at 60 °C has led to the formation of particles with diverse shapes, such as spherical, rod-like, triangle and polygon NPs, with an increment in the tannic acid concentration (Cheng et al. 2016). Likewise, Gurusamy et al. (2017) synthesized multi-coloured silver nanoparticles of various sizes by varying the concentration precursor, capping and reducing agent, such as silver nitrate, poly-(N-vinylpyrrolidone) and hydrazine hydrate, respectively. The results strongly suggested that the variation in the morphology of AgNPs is dependent on both capping and reducing agents. Their findings also indicated that the successful synthesis of AgNPs with various sizes and shapes can be obtained by a simple and economical chemical reduction method (Gurusamy et al. 2017). In the same way, the copper nanoparticles were synthesized by several chemical methods and the most popular method is the chemical reduction method that utilizes exclusive reducing agents to reduce copper from its salts. As an evidence, Begletsova et al. (2017) produced copper nanoparticles via cetylpyridinium chloride as stabilizing agent and hydrazine hydrate (HH) as reducing agent by the simple chemical reduction method. The study demonstrated that the alterations in the volume of HH and pH can yield stable CuNPs with a size range of 40 to 80 nm under optimal reaction conditions

(Begletsova et al. 2017). In another study, novel platinum nanoparticles (PtNPs) were synthesized by Nagao et al. (2017) (Nagao et al. 2017) by utilizing sodium borohydride to reduce Pt ions and polyethyleneimine (PEI) as a protective agent. The results revealed that cubic and tetrahedral PtNPs are synthesized at lower pH, whereas spherical PtNPs were obtained at higher pH of the PEI solution. It is evident from this study that the one pot chemical synthesis approach possesses ability to yield PtNPs with narrow size distribution by simply adjusting the pH of the PEI. Even though, chemical approaches are simple and requires less cost, compared to physical methods, the utilization of toxic chemicals is a major limitation for utilizing these nanoparticles in biomedical applications (Jeevanandam et al. 2016).

12.2.3 Biological Approach

Nature consists of several organisms, both macroscopic and microscopic, such as bacteria, fungi, algae, yeast and plants. These organisms contain natural biomolecules which have been identified to be significant in the production of nanoparticles with distinct morphologies. They can act as a green fuel for the formation of safe and environment-friendly nanoparticles (Sharma et al. 2019). The use of nanoparticles in the field of biomedical and agriculture application has led to a need for producing nanoparticles with eco-friendly and reliable methods. The best option to achieve this goal is to utilize biological entities to reduce the metal ions to metal nanoparticles (Kaur 2018). Thus, the synthesis of metallic nanoparticles (AuNPs) via biological entities, such as microbes and plants, has gained the focus of researchers due to the current interest to produce green nanoparticles with unique properties, compared to their bulk counterparts (Sehgal et al. 2018). Camas et al. (2019) developed a novel biogenic approach for the synthesis of AuNPs using marine bacterial strains. This study is the first to report the use of actinobacterial strain (K1D109), which belongs to the *Cittricoccus sp.* isolated from *Petrosia ficiformis* sponge, to reduce the Au ions to AuNPs. The study showed that the optimum reaction conditions, such as 35 °C and reaction time of 24 h can lead to the formation of spherical AuNPs with the size range of 24–65 nm (Camas et al. 2019). In another study, Molnar et al. (2018) synthesized 6 to 40 nm-sized AuNPs using 29 thermophilic filamentous fungi. The results revealed that two steps were involved in the formation of fungi mediated AuNPs, such as reduction of Au^{3+} to Au^{0} and stabilization of core AuNPs by proteins as capping ligands (Molnár et al. 2018). The mechanism involved in the formation of nanoparticles includes entrapment of metal ions inside or on the surface of the microbial cells, through the electrostatic attraction between the ions and the negatively charged cell wall as well as the reduction in the presence of enzymes (Li et al. 2011).

Other than gold nanoparticles, AgNPs are the most common nanoparticles that are used in various applications, such as solar fuel cell efficiency improvement, radio sensitizers and as antimicrobial agents. Shu et al. (2020) synthesized green AgNPs using yeast extract as reducing agent. The experimental results revealed that the yeast extracts reduced Ag ions and obtained well dispersed and uniform

spherical-shaped AgNPs with an average size of 13.8 nm. Further, the study emphasized that the biomolecules of amino acids, alpha-linolenic acid and carbohydrates present in the yeast extract have an active role in the formation of AuNPs (Shu et al. 2020). In another study, Saravanan et al. (2017) synthesized AgNPs using *Leuconostoc lactis* bacterial strains that produce exopolysaccharide (EPS), which are isolated from idli batter. The EPS was precipitated through centrifugation, dissolved in Milli Q water and dialyzed at 4 °C for 48 h for purification. The extracted EPS from *Leuconostoc lactis* bacterial strain was used to reduce the Ag ions under constant stirring for 24 h. The results revealed that the bacterial EPS can act as reducing and stabilizing agent to yield 35 nm-sized spherical AgNPs (Saravanan et al. 2017). Recently, Arya et al. (2018) used green alga *Botryococcus braunii* to synthesize copper and silver nanoparticles. The green alga was isolated by the serial dilution method and incubated for three weeks and the algal biomass was used to reduce the Cu and Ag ions. The results revealed that the green algae can be successfully used to synthesize cubical morphology with an average size of copper and silver nanoparticles found to be 10–70 nm and 40–100 nm, respectively (Arya et al. 2018). Likewise, Gupta et al. (2019) used the biological approach to synthesize platinum nanoparticles via the fungus *Fusarium oxysporum.* The results revealed that the fungus-mediated green synthesis approach can produce cubical, spherical and truncated triangular-shaped platinum nanoparticles with an average size of 28.96 nm. The study stated that the presence of proteins, long chain fatty acids, amides and polysaccharides in the fungal extract as reducing and capping agents is responsible for the formation of PtNPs (Gupta and Chundawat 2019). Even though, microbial synthesis approaches of nanoparticles are less- or nontoxic to humans and the environment, the stability of the nanoparticle and the longer reaction time are the specific limitations which hurdle their large-scale synthesis, compared to conventional (physical and chemical) synthesis approaches. Thus, researchers prefer a hybrid synthesis approach to combine conventional and biosynthesis approaches for the fabrication of stable, monodispersed and less-toxic nanoparticles (Jeevanandam et al. 2016).

12.3 Limitations of Physicochemical Approach Compared to Biosynthesis Approaches

The production of toxic chemicals, salts and stabilizing agents as byproducts is enormous in physicochemical nanoparticle synthesis approaches, compared to green synthesis or biogenic techniques (Das et al. 2017). Both physical and chemical synthesis require high power consumption, high radiation, highly concentrated reducing and stabilizing agents as well as sophisticated apparatus, which will lead to higher costs than green synthesis methods. Further, the byproducts and the nanoparticles from the physical and chemical synthesis methods are often a great threat for the environment and the human health as it can lead to acute or chronic toxicity. Hence, green synthesis approach is highly recommended to synthesized

nanoparticles in recent times, as it requires less energy and is eco-friendly in nature (Parveen et al. 2016a; Soshnikova et al. 2018a; Prasad 2019a, b).

12.3.1 Advantages and Disadvantages of Biological Approach

The most significant advantage of biological method is its ability to yield nanoparticles in a single-step bio-reduction process (Parveen et al. 2016b) without or less energy consumption. In addition, the nanoparticles from biogenic approaches are highly reproducible, polydisperse, non-toxic and eco-friendly with less health risk and are widely suggested to be beneficial in biomedical and clinical applications (Das et al. 2017; Aziz et al. 2016, 2019; Prasad et al. 2016).

12.3.1.1 Bacteria

Advantages Bacterial strains are cheap to procure, grow rapidly, easy to cultivate, compared to other biological systems, and can lead to high production of nanoparticles. Conditions such as oxygenation, temperature and incubation time can be controlled to modify the morphology of nanoparticles. The deftness of bacterial extracts in the manipulation of nanoparticle morphology provides supremacy over other biological organisms.

Disadvantages Intracellular synthesis of biogenic nanoparticles can yield nanoparticles slowly, after several hours or days, compared to physical and chemical methods. Further, the nanoparticles synthesized by microorganisms are prone to disintegration or agglomeration and deteriorate over a time period (Jamkhande et al. 2019).

12.3.1.2 Fungi

Advantages Fungi have high forbearance to metals and are easy to handle. The nanoparticles extracted from fungi are highly beneficial in agricultural pest control, due to their less toxicity towards plants and specific biomolecules as surface functional groups. Fungi produce several proteins, which eventually helps to increase the rate of nanoparticle synthesis (Pantidos and Horsfall 2014; Prasad 2016, 2017; Prasad et al. 2016, 2018a, b; Abdel-Aziz et al. 2018).

Disadvantages Most of the fungal species, that are utilized for nanoparticle synthesis, are highly toxic to humans or plants, which is a major obstacle for large scale production (Vahabi et al. 2011). Further, the fungal synthesized nanoparticles are unstable, polydispersed and are not pure, due to the presence of several biomolecules as surface functional groups (Rai et al. 2015).

12.3.1.3 Algae

Advantages Algae-synthesized nanoparticles are highly effective as anti-fungal agents, anti-bacterial agents, anti-biofilms and biosensors to detect diseases, such as cancer and diabetes (Aziz et al. 2014, 2015). Further, the synthesis requires less temperature, compared to other biosynthesis approaches, and are less toxic and eco-friendly in nature.

Disadvantages Nanoparticles synthesized are pernicious to eukaryotic cells (LewisOscar et al. 2016).

12.3.1.4 Virus

Advantages The virus-mediated nanoparticle synthesis or virus-like nanoparticles can be synthesized in large quantities in a short span. They are robust, polyvalent and dynamic. The viral nanoparticles obtained from plant viruses and bacteriophages are more beneficial in nature, as they are safe to humans with less side effects. Further, VNPs are beneficial in targeted cancer imaging and therapy (Steinmetz 2010).

Disadvantages The engineered viral nanoparticles may lead to mutations, which may cross-infect other species (Jeevanandam et al. 2018).

12.4 Phytosynthesis of Metal Nanomaterials

The limitations in the microbe-mediated nanoparticle fabrication have led to the emergence of phytosynthesis approaches, where biomolecules named phytochemicals extracted from plants are utilized as reducing and stabilizing agents for nanoparticle synthesis. Recently, the attraction towards phytosynthesis from plant biomass or extracts in increasing, due its eco-friendliness, affordability, rapidity, cost-effectiveness, non-toxicity and its ability to produce an abundance of nanoparticles. The phenomenon of phytosynthesis is simpler as it avoids multistep processes, such as cultivation and maintenance of microbes, preparation and extraction of enzymes (Prasad 2014; Andra et al. 2019). Further, synthesis of nanoparticles via plant extracts is rapid, compared to microbial synthesis approach, as plants serve as a natural source of metabolites, which can act as reducing, capping and stabilizing agents (Bamoharram et al. 2012). Moreover, the production of nanoparticles from plants is more stable with low contamination level. In recent times, the use of green synthesis with plant extracts is widely under research due to its essential requirement in various fields, especially biomedical and environmental applications (Zhu et al. 2019). Additionally, phytosynthesis of plant extract produces nanoparticles

that can be used to increase the biomass in agriculture and improve fruit taste and crop yield of edible plants, such as carrot, radish, watermelon and tomato (Husen and Siddiqi 2014; Singhal et al. 2017).

12.4.1 Phytosynthesis of Common Metallic Nanoparticles

Nature provides an enormous amount of plant species, in which most of them can be utilized for the synthesis of novel nanoparticles. The phenomenon in which green plants are used for nanoparticle synthesis is termed as green route or phytosynthesis approach, which is a subclass of biosynthesis methods. Green chemistry or green route approach plays a major role in producing distinct types of metals from different parts of the plant. Recently, it has been reported that the common metal nanoparticles, such as gold, silver, palladium, platinum, copper and ferric iron can be synthesized via phytosynthesis approach (Kuppusamy et al. 2016).

12.4.1.1 Gold Nanoparticles

Gold is the most common metal to be synthesized via phytosynthesis, due to its wide applications in several fields ranging from biomedical to electronics. Patil et al. (2017) extracted phytochemicals from the galls of *Rhus chinensis* plant for the synthesis of spherical- and oval-shaped, 20–40 nm-sized gold nanoparticles. The study showed that the hydroxyl groups, ether and ester in gallotannins, tannins and polyphenols, are responsible for the gold nanoparticle formation. The resultant Au nanoparticles are demonstrated to possess dose-dependent cytotoxicity towards various types of cancer cell lines, such as human gastric adenocarcinoma (MKN-28), human liver (Hep-3B) and human bone osteosarcoma (MB-63) (Patil et al. 2017). Likewise, Soshnikova et al. (2018b) synthesized 5–15 nm-sized, spherical Au nanoparticles using distinct varieties of dried *Fructus Amomi* (cardamom) fruits, such as *Amomum villosum* and *Elettaria cardamomum*. This study also revealed that the existence of phenols with hydroxyl groups, tannins with precipitated alkaloids and proteins, and terpenoids with several isoprene units in the plant extract served as a reducing and capping agent for the nanoparticle formation (Soshnikova et al. 2018b). Similarly, Gupta et al. (2019) fabricated 10–25 nm-sized, spherical Au nanoparticles via the phytochemicals extracted from the medicinal plant named *Ocimum gratissimum* Linn. The Fourier transform infrared (FTIR) spectra revealed the presence of terpenoids, which have been identified as the prime reducing and capping agents to form gold nanoparticles (Gupta et al. 2019). Further, Balamurugan et al. (2016) synthesized 5–50 nm-sized, spherical gold nanoparticles via flower extracts of *Peltophorum pterocarpum* as capping and reducing agent. The reducing sugars, sterols, carbohydrates, glycosides and flavonoids present in the flower extract are proposed to be responsible for nanoparticle formation (Balamurugan et al. 2016).

12.4.1.2 Silver Nanoparticles

Silver is another metal that is phytosynthesized as nanosized particles, which has gained applicational importance in the field of biomedical and pharmaceuticals, next to gold nanoparticles, due to its excellent antimicrobial property (Srikar et al. 2016). Murugan et al. (2016) utilized aquatic plants, such as sponge-weed named *Codium tomentosum*, extract for the synthesis of 20–40 nm-sized, irregular-shaped silver nanoparticles. The FTIR results revealed that the presence of peptide linkages, polyphenols, proteins, enzymes or polysaccharides, flavones and terpenoids in the aqueous extract is the deciding factor in the formation of silver nanoparticles (Murugan et al. 2016). Further, Pilaquinga et al. (2019) fabricated 10–14 nm-sized, spherical-shaped silver nanoparticles via the fruit extract of *Solanum mammosum*. The presence of alkaloids, such as indol-alkaloids, alpha-chaconine, alpha-tomatine, alpha-solanine, pirrolizidin, tropane and glycoalkaloids are identified to be crucial for silver nanoparticle formation as well as their mosquitocidal property (Pilaquinga et al. 2019). Furthermore, Arjunan et al. (2012) extracted phytochemicals from *Annona squamosa* and used them for the synthesis of irregular-shaped silver nanoparticles, where the FTIR spectra indicated that the carbonyl groups in the amino acid residues play a crucial role in the nanoparticle formation. The study also showed that these phytosynthesized nanoparticles possess enhanced mosquitocidal property against *Anopheles stephensi*, *Aedes aegypti* and *Culex quinquefasciatus* to combat diseases such as filariasis, malaria and dengue (Arjunan et al. 2012). Moreover, Dinesh et al. (2015) utilized *Aloe vera* leaf extract for the synthesis of 35–55 nm-sized silver nanoparticles of spherical and cubical morphology. The study emphasized that the existence of carbonyl groups from polyphenols, such as epigallocatechin gallate, catechin gallate, theaflavin, epigallocatechin, epicatechin gallate and gallocatechin gallate, in the leaf extract leads to the formation of nanoparticles (Dinesh et al. 2015). Besides, Velmurugan et al. (2015) used the leaf extract of *Prunus* x *yedoensis* for the synthesis of 20–70 nm-sized, oval- and spherical-shaped silver nanoparticles. The FTIR spectra revealed that the existence of alkaloids, phytosterol, amino acids, flavonoids and triterpenoids as the surface functional biomolecules in plant extracts are responsible for the effective nanoparticle synthesis (Velmurugan et al. 2015).

12.4.1.3 Copper Nanoparticles

Copper nanoparticles are also widely used in biomedical applications (Yadav et al. 2017) and phytosynthesized CuNPs will be highly beneficial to enhance its biological properties. Tahvilian et al. (2019) fabricated 45–50 nm-sized, spherical-shaped CuNPs using the aqueous leaf extract of *Allium saralicum*. It has been identified from the FTIR spectra that the carbonyl and sp-2 carbon groups present in the leaf extract play a critical role in the synthesis of nanoparticles and reduce their cytotoxicity (Tahvilian et al. 2019). Similarly, Rajesh et al. (2018) fabricated ~15 nm-sized, monodispersed, spherical CuNPs with the help of bud extract from *Syzygium*

aromaticum. The FTIR spectra revealed that the proteins along with carotenoids, tannins, alkaloids and flavonoids in the extract act as reducing and stabilizing agents for the nanoparticle formation (Rajesh et al. 2018). Likewise, Kuppusamy et al. (2017) synthesized 45–100 nm-sized, spherical-shaped CuNPs using aqueous *Commelina nudiflora* extract. The flavonoids, proteins, alkaloids and reducing sugars present in the plant extract are identified to be the reducing and capping agents that are responsible for the fabrication of nanoparticles (Kuppusamy et al. 2017). Moreover, Harne et al. (2012) utilized the aqueous latex extract of *Calotropis procera* for the fabrication of 5–30 nm-sized, spherical and monodispersed CuNPs. The study emphasized via FTIR spectra that the secondary amine, carboxylic acid, amide II, amide III, alcohol and C-N stretching of amines along with proteins act as a surface functional group for the nanoparticle formation (Harne et al. 2012).

12.4.1.4 Other Metal Nanoparticles

Recently, several metal nanoparticles have been synthesized via phytosynthesis approach. Pan et al. (2020) utilized the skin extract of red peanut named *Arachis hypogea* for the synthesis of iron nanoparticles. Biomolecules, such as flavonols, epicatechin, phenolic compounds and anthocyanins, present in the skin extract are responsible for the nanoparticle formation (Pan et al. 2020). Further, Cui et al. (2020) used polysaccharide from *Ginkgo biloba* leaves for synthesizing palladium nanoparticles and stabilizing them to form spherical, monodispersed and 7–14 nm sized nanoparticles (Cui et al. 2020). Furthermore, Sahin et al. (2020) synthesized 22 nm-sized, monodispersed and spherical-shaped palladium nanoparticles from the peel extract of *Punica granatum* (Pomegranate). This study showed that the presence of tannins, phenolics and flavonoids in the peel extract is responsible for the nanoparticle formation (Şahin Ün et al. 2020). Moreover, 1–6 nm-sized, spherical-shaped platinum nanoparticles were synthesized recently with the help of black cumin seed (*Nigella sativa*) extract. The synergistic effect of biomolecules present in the seed extract has been identified to be the responsible factor for the nanoparticle formation (Aygun et al. 2020). It can be noted from all these studies that the phytosynthesis approach predominantly yields spherical nanoparticles, and their shapes can be modified via alterations in the synthesis parameters (Jeevanandam et al. 2019).

12.5 Mosquitocidal Activity of Metal Nanomaterials

Mosquito vectors that belongs to the order *Diptera* and genera *Anopheles*, *Aedes* and *Culex* possess the ability to transmit various diseases, such as dngue, malaria, chikungunya, filariasis, Japanese encephalitis, yellow fever and Zika. These mosquito-borne diseases are responsible for millions of deaths every year, globally. In recent times, several nanomaterials are used to inhibit the growth and development of mosquitoes in all their life stages. In addition, the mosquitocidal activities

of metal nanoparticles such as gold, silver or platinum are proven to be enhanced by phytosynthesis approaches, compared to physicochemical methods (Soni and Prakash 2012; Syed and Ahmad 2012; Castro et al. 2015; Lalitha et al. 2020; Suresh et al. 2020).

12.5.1 Gold Nanoparticles

In recent studies, broth extracts of *Cacumen platycladi, Coleus amboinicus*, *Artemisia nilagirica, Terminalia arjuna, Salicornia brachiata, Zingiber officinale* and *Phoenix dactylifera* have been used to synthesize gold nanoparticles. Hence, gold nanoparticles (AuNPs) that are biosynthesized using distinct plants, bacteria, algae, lichens, and fungi have been reported to be potent and successful insecticides against mosquito larvae even at less dosages (Murugan et al. 2015). Recent reports stated that the research on gold nanoparticles to demonstrate their insecticidal ability is insufficient, compared to that on AgNPs. The biosynthesized AuNPs from *Jatropha curcas* latex are reported to possess inhibitory effect against serum trypsin in different species of insects, including *A. Aegypti* (Patil et al. 2016). In another study, AuNPs are proven to disrupt the reproduction and development in German cockroaches named *Blattella germanica* (L.). Further, the larvicidal effects of AuNPs synthesized from the zein biopolymer (Ze-AuNPs) were also tested against *A. aegypti* vector. Histopathological results showed remarkable physiological changes, such as complete abdominal disintegration (midgut and caeca), caudal hair loss in antenna, lower, lateral, and upper head (Benelli 2018). Thus, AuNPs can be utilized as a potential insecticidal agent to inhibit the growth of a wide range of insects. A similar study of AuNPs synthesized from the leaf extracts of *Artemisia vulgaris L.* was found to exhibit a larvicidal effect against third and fourth instars of *A. aegypti.* This study also showed that the nanoparticle can lead to physiological damage in epithelial cells, cortex, and midgut along with AuNPs deposition in the midgut region (Saranya et al. 2020).

A recent study reported that the AuNPs synthesized using the aqueous extracts of lichens named *Parmelia sulcata* possess exclusive mosquitocidal property. The results revealed the inhibition of *A. stephensi and A. aegypti* larvae (I–IV instar), pupae and adult, and even affected the hatching of eggs, depending on the concentration of nanoparticles. Further, the comparative study showed that the nanoparticle inhibited *A. stephensi* more than *A. aegypti*, even at low concentration (Gandhi et al. 2019). Similarly, Murugan et al. (2015) emphasized the synthesis of AuNPs using *Cymbopogon citratus* to inhibit the growth of *A. stephensi* and *A. aegypti.* The study showed that the nanoparticles can lead to acute toxicity in the mosquito with a lethal concentration (LC50) of 18.8 to 41.5 parts per million (ppm) and boosted the predation efficiency of copepods named *Mesocyclops apsericornis* (Murugan et al. 2015). In another study, low doses of biosynthesized

gold nanoparticles using *Couroupita guianensis* also showed high toxicity against *A. stephensi* (Subramaniam et al. 2016).

12.5.2 Silver Nanoparticles

Silver is the most common mosquitocidal agent among the metal nanoparticles. Khader et al. (2018) compared the larvicidal potential of several selected medicinal plants with phytosynthesized silver nanoparticles against third instar larvae of *A. aegypti* and *Culex tritaeniorhynchus*. In this study, alcoholic extracts of *Annona squamosa*, *Phyllanthus amarus*, *Eclipta prostrata* and *Cocconia grandis* are used for the synthesis of spherical-shaped, less than one-micron-sized silver nanoparticles. This study showed that the phytosynthesized silver nanoparticles are highly efficient in inhibiting the growth of mosquito larvae, compared to the alcoholic plant extracts (Khader et al. 2018). Likewise, Parthiban et al. (2019) recently fabricated AgNPs using the aqueous leaf extract of *Annona reticulata* and investigated its potential larvicidal activity against *A. aegypti* mosquito. The resultant nanoparticles were spherical in shape with sizes ranging from 7–8 nm and functional groups, such as amide groups and aromatic rings from triterpenoids, polyphenols and flavonoids. The study revealed that these phytosynthesized AgNPs are highly effective in inhibiting the growth of fourth instar larvae of *A. aegypti* mosquito with LC50 value of 4.43 µg/mL (Parthiban et al. 2019). Similarly, Shelar et al. (2019) synthesized silver nanoparticles via *Momordica charantia* plant and investigated its larvicidal and helminthicidal property. The study showed that the flavonoids, polyphenols and terpenoids present in the aqueous fruit peel extract is responsible for the formation of silver nanoparticles below 100 nm in size. These nanoparticles were also identified to possess the ability of inhibiting 85% of *A. albopictus* and *A. aegypti* larvae at 20 ppm of concentration (Shelar et al. 2019). Further, Kovendan et al. (2016) fabricated cubical and spherical shaped, 40–60 nm sized silver nanoparticles via leaf extract of *Psychotria nilgiriensis*. The study emphasized the nanoparticle formation is due to the presence of amine, carboxyl and hydroxyl groups in the leaf extract. These nanoparticles were identified to possess inhibitory effect against larva and pupa of *A. aegypti* mosquito at even low doses (3 ppm) (Kovendan et al. 2016). Furthermore, the essential oils extracted from *Curcuma zedoaria* were used to fabricate globular-shaped, ~100 nm-sized silver nanoparticles and their larvicidal activity against insecticide-susceptible and resistant *Culex quinquefasciatus* strains were evaluated. The study showed that the existence of eucalyptol, beta-tumerone, beta-sesquiphellandrene and alpha-zingiberene in the essential oils was responsible for nanoparticle formation. The resultant nanoparticles were identified to possess complete inhibitory activity against susceptible and resistant mosquito strain after 24 h of exposure with LC50 of 0.57 and 0.64 ppm, respectively (Sutthanont et al. 2019). It is evident from all these studies that the phytosynthesized silver nanoparticles are highly beneficial in inhibiting the growth of mosquitoes in all its life stages.

12.5.3 Copper Nanoparticles

Among metal nanoparticles, nanosized copper nanoparticles were also reported to be highly beneficial as a potential mosquitocidal agent. Abd El Hafiz Hassanain et al. (2019) utilized leaf extracts of *Lantana camara* to synthesize 11–17.8 nm-sized, spherical-shaped copper nanoparticles. These nanoparticles were identified to possess effective larvicidal activity against fourth instar larvae of *Anopholes multicolor*, that can cause malaria in humans, with LC50 value of 12.6 ppm at lower dose of 20 ppm (Abd El Hafiz Hassanain et al. 2019). Further, asymmetrical, dispersed and aggregated copper nanoparticles of ~100 nm in size were synthesized via aqueous leaf extract of *Artocarpus heterophyllus*, which contains phenolic and flavonoid compounds as the stabilization agent to form nanoparticles. The study also showed that 10 mg/litre of these nanoparticles can lead to 100% mortality against first to fourth instar larvae of *A. aegypti* mosquito (Sharon et al. 2018). Furthermore, Mondal and Hajra (2016) extracted the phytochemicals with alcoholic and phenolic groups from the petals of *Tagetes* species (Marigold) and *Helianthus* species (sunflower) and utilized them for the synthesis of spherical-shaped, 5–20 nm-sized copper nanoparticles. The resultant nanoparticles at 10 mg per litre of dose, possess 15% of enhanced larvicidal activity against *C. quinquifasciatus* after 24 h of incubation (Mondal and Hajra 2016). Moreover, Angajala et al. (2014) synthesized spherical, 50–100 nm sized copper nanoparticles using the aqueous leaf extract of *Aegle marmelos* correa, which contains phytochemicals, such as beta-sitosterol as reducing agent along with other phytocompounds for the nanoparticle formation. The study further emphasized the larvicidal efficacy of phytosynthesized copper nanoparticles against *Anopheles stephensi*, *Aedes aegypti* and *Culex quinquefasciatus*, with better LC50 of 500.06 ppm against *A. stephensi*, compared to the standard Temephos larvicide and crude plant extract (Angajala et al. 2014). Recently, Shehu et al. (2020) synthesized a novel copper-cobalt bimetallic nanoparticles via the fruit extract of the Palmyra palm with the majority of terpenoids as reducing agent to convert the precursors into nanosized particles. These nanoparticles are proven to possess moderate larvicidal activity against first, second and third instar larvae of *C. quinquefasciatus* with LC50 value of 12, 14.7 and 16 ppm (Shehu et al. 2020).

12.5.4 Other Metal Nanoparticles

Apart from gold, silver and copper, few other novel metal nanoparticles were also identified to possess enhanced mosquitocidal property. Sowndarya et al. (2017) synthesized novel 46–79 nm-sized selenium nanoparticles via the leaf extracts of *Clausena dentata*. The study showed that the formation of selenium nanoparticles is due to the conversion of the aldehyde group to carboxylic acid in the metal ion by terpenoids in the plant extract. Further, the study demonstrated that the phytosynthesized selenium nanoparticle possess a high mortality rate against the fourth instar

larvae of *Aedes aegypti*, *Anopheles stephensi* and *Culex quinquefasciatus* at a low concentration of 104.13, 240.71 and 99.60 mg/L, respectively (Sowndarya et al. 2017). Furthermore, Elemike et al. (2017) fabricated silver nanocomposite using the aqueous leaf extract of *Achyranthes aspera*. The results revealed that the spherical and polydispersed nanoparticles of silver were embedded on the phytochemical extracts as a matrix. These nanocomposites were identified to possess enhanced larvicidal activity against *Aedes aegypti* mosquito without causing any toxic effect against non-toxic organisms, such as *Daphnia magna*, *Gambusia affinis* and *Moina macrocopa* (Sharma et al. 2020). Similar nanocomposite of silver with aggregated spherical morphology and size lower than 30 nm was synthesized via aqueous leaf extract of *Rubus ellipticus* and was investigated for their toxicity and oviposition deterrent activity against mosquito vectors, which can lead to malaria, filariasis and Zika virus. The FTIR spectral results emphasized that the terpenoids and flavonoids present in the leaf extract is responsible for nanoparticle formation and conjugate with them to form as bio-nanocomposite. These nanocomposites were identified to possess enhanced toxicity against the eggs, larvae and adults of *A. aegypti*, *A. stephensi* and *C. quinquefasciatus* with zero hatchability, reduced egg laying capability by gravid females and effective adulticidal potential. Besides, these nanocomposites were also found to be safer for non-target organisms, such as *Diplonychus indicus*, *Anisops bouvieri* and *Gambusia affinis* (AlQahtani et al. 2017). Furthermore, Elemike et al. (2017) stated that a novel silver-silver oxide nanoparticles with spherical morphology and average particle size of 23.6 nm can be synthesized using the aqueous *Eupatorium odoratum* leaf extract. The resultant nanoparticles were identified to possess enhanced inhibitory activity against the third and fourth instar larvae of *C. quinquefasciatus* after 12 h of exposure with LC50 value of 461.6 and 553.4 ppm (Elemike et al. 2017). Recently, Rajkumar et al. (2019) fabricated a novel chitosan-derived silver nanocomposites with 30–60 nm in size and spherical morphology using the aqueous leaf extract of *Carmona retusa* (Vahl) Masam. These bio-nanocomposites were also identified to possess enhanced larvicidal activity against *A. aegypti*, *A. stephensi* and *C. quinquefasciatus* at low LC50 and LC90 values (Rajkumar et al. 2019) (Table 12.2).

12.6 Mosquitocidal Mechanism of Phytosynthesized Metal Nanoparticles

In general, several works in the literature reported that the phytochemicals extracted from the plants possess enhanced mosquitocidal property (Senthil-Nathan 2019). The nanoparticles prepared with the help of plant extracts will possess these phytochemicals, which eventually increases the mosquitocidal property of the nanoparticles, compared to the crude phytochemicals via the synergistic effect (Gupta 2020). Figure 12.1 shows the probable mosquitocidal mechanism of the phytosynthesized metal nanoparticles. The metal nanoparticles synthesized via plant extracts

Table 12.2 Mosquitocidal activity of various phytosynthesized metal nanoparticles

Metal nanoparticle	Plant extract	Mosquitocidal activity	Reference
Gold	*Jatropha curcas* latex	*A. aegypti*	Patil et al. (2016)
Gold	*Artemisia vulgaris*	Third and fourth instars of *A. aegypti*	Saranya et al. (2020)
Gold	*Parmelia sulcate*	I-IV instar larvae of *A. stephensi* and *A. aegypti*	Gandhi et al. (2019)
Gold	*Cymbopogon citratus*	*A. stephensi* and *A. aegypti*	Murugan et al. (2015)
Gold	*Couroupita guianensis*	*A. stephensi*	Subramaniam et al. (2016)
Silver	*Annona squamosa*, *Phyllanthus amarus*, *Eclipta prostrata* and *Cocconia grandis*	*A. aegypti* and *Culex tritaeniorhynchus* third instar larvae	Khader et al. (2018)
Silver	*Annona reticulata*	*A. aegypti*	Parthiban et al. (2019)
Silver	*Momordica charantia*	*A. albopictus* and *A. aegypti*	Shelar et al. (2019)
Silver	*Psychotria nilgiriensis*	Larva and pupa of *A. aegypti*	Kovendan et al. (2016)
Silver	*Curcuma zedoaria* essential oil	Insecticide-susceptible and resistance *Culex quinquefasciatus*	Sutthanont et al. (2019)
Copper	*Lantana camara*	Fourth instar larvae of *Anopholes multicolor*	Abd El Hafiz Hassanain et al. (2019)
Copper	*Artocarpus heterophyllus*	Fourth instar larvae of *A. aegypti*	Sharon et al. (2018)
Copper	Marigold and sunflower	*C. quinquifasciatus* larvae	Mondal and Hajra (2016)
Copper	*Aegle marmelos* correa	*Anopheles stephensi, Aedes aegypti* and *Culex quinquefasciatus* larva	Angajala et al. (2014)
Copper-cobalt bimetallic	Palmyra palm fruit	I-III instar larvae of *C. quinquifasciatus*	Shehu et al. (2020)
Selenium	*Clausena dentata*	*Aedes aegypti, Anopheles stephensi* and *Culex quinquefasciatus*	Sowndarya et al. (2017)
Silver nanocomposite	*Achyranthes aspera*	*Aedes aegypti* larvae	Sharma et al. (2020)
Silver nanocomposite	*Rubus ellipticus*	*Eggs, larvae* and *adults of A. aegypti, A. stephensi* and *C. quinquefasciatus*	AlQahtani et al. (2017)
Silver-silver oxide	*Eupatorium odoratum*	Third and fourth instar larvae of *C. quinquefasciatus*	Elemike et al. (2017)

(continued)

Table 12.2 (continued)

Metal nanoparticle	Plant extract	Mosquitocidal activity	Reference
Chitosan-silver nanocomposite	*Carmona retusa*	*A. aegypti*, *A. stephensi* and *C. quinquefasciatus* larva	Rajkumar et al. (2019)

are usually suspended in the mixture of water and phytochemicals (Rana et al. 2020). These aqueous nanoparticles must be sprayed on the water surface, where the life stages of mosquito, such as eggs, larvae and adult, will grow and develop (Lourthuraj et al. 2020). The nanoparticles will slowly disintegrate into their ions, where they will either enter into the mosquito cells (egg, larvae or adult) or attach to the surface of the cell. In both these cases, the nanoparticles will lead to an increase in the cell membrane potential, produce reactive oxygen species and elevate lipid peroxidation (Buhroo et al. 2017; Suresh et al. 2020). Further, these toxic reactions of the nanoparticles will be synergistically supported by the phytochemicals that are toxic to the mosquitoes (Foko et al. 2019). Furthermore, the main significance of phytochemical-assisted metal nanoparticle is their ability to reduce the toxicity of nanoparticles towards other non-target organisms, compared to metal nanoparticles synthesized via chemical approaches (Lalitha et al. 2020). These toxic reactions of phytosynthesized metal nanoparticles will lead to the inhibition of the mosquito life stages, affect their growth and development, and mitigate their population.

12.7 Future Perspective and Conclusion

It is evident from the literature as mentioned in the previous sections that the phytosynthesized metal nanoparticles are highly beneficial as potential mosquitocidal agents, compared to the conventional physical and chemical synthesized nanosized metal particles (Barabadi et al. 2019). The high production cost in physical methods and the toxicity towards non-target organisms via chemical synthesized nanoparticles are the major limitations of conventional synthesis approaches (Shanmuganathan et al. 2019). These limitations can be addressed via phytosynthesis approach, where the plants are available in large quantities, which eventually reduces the production costs and the biomolecules in the plant extracts reduces the potential toxicity of nanoparticles towards non-target organisms (Ramanathan and Aqra 2019). However, it is not possible to attain nanoparticles with high stability via phytosynthesis approach, compared to physical and chemical methods (Granata et al. 2016). The challenge of stability in phytosynthesis can be overcome by using a biopolymer as a template or matrix (Jeevanandam et al. 2020). In future, there is a possibility of biopiracy to utilize several traditional or plants belong to keystone species for the large-scale fabrication of metal nanoparticles with mosquitocidal property (Dwivedy et al. n.d.). Thus, it is necessary to gain clarity on the actual mechanism of nanoparticle formation via phytochemicals. Further, it will be possible in the future that the

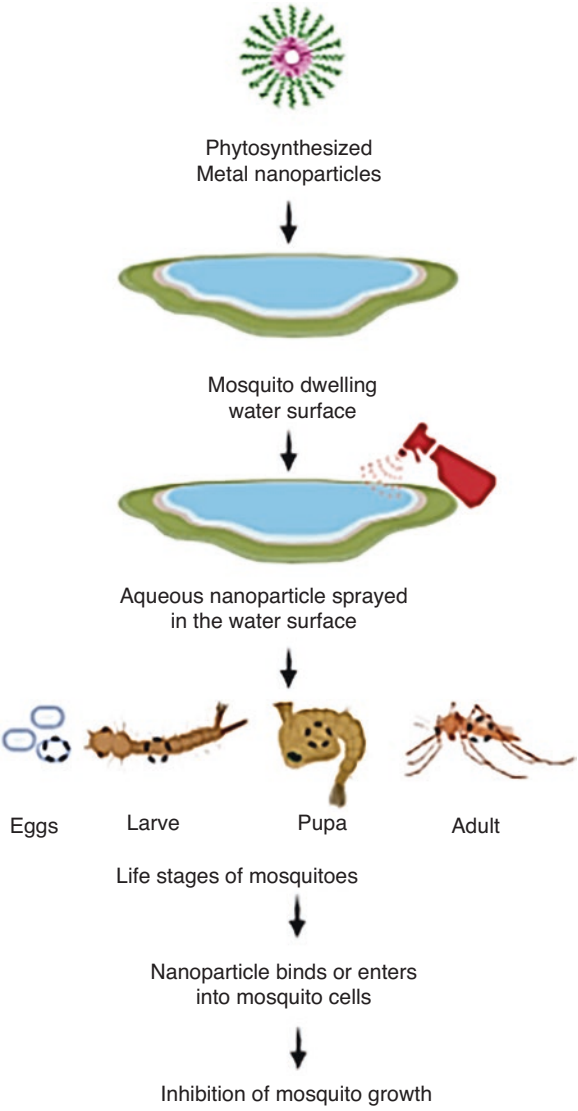

Fig. 12.1 Mosquitocidal mechanism of phytosynthesized metal nanoparticles

phytochemicals responsible for nanoparticle formation as well as with enhanced mosquitocidal property can be made to be expressed in the plants via genetic engineering and grow them via plant tissue culture approach (Shkryl et al. 2018). The incorporation of genetic engineering and tissue culture in the production and extraction of nanoparticles will reduce the biopiracy issues and can be utilized for the large-scale, commercial production of phytosynthesized metal nanoparticles with effective mosquitocidal property. Hence, phytosynthesized metal nanoparticles or nanocomposites can be a potential mosquitocidal agent to mitigate the population of mosquitoes in the future.

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Chapter 13
Perspectives of Metals and Metal Oxide Nanoparticles for Antimicrobial Consequence – An Overview

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13.1 Introduction

13.1.1 What Are Nanostructures?

A nanoparticle that typically possesses 0.2–100 nm scale. On the other hand, it can be in the form of very fine particles, nanoclusters, and nanocrystals.

The emergence of multidrug-resistance microbes has turned into a global medical challenge, which prompted researchers towards the search for alternatives for the effective antimicrobial treatment for infection (Beyth et al. 2015). With the beginning of nanotechnology in biomedical research, scientists have attempted to use nanoparticles because of their unique physicochemical characters, including, smaller size with greater surface area, enhanced catalytic, magnetic and optical property, and their biocompatibility (Gao et al. 2014). The proposed mechanism of nanoparticles against microbes involves (i) free metal ion mediated toxicity released as of nanoparticle surface and (b) oxidative stress-mediated apoptosis due to the release of reactive oxygen species (Seil and Webster 2012; Prasad et al. 2016). Morphological and physicochemical properties of nanoparticles have great influence in the antimicrobial activities of nanoparticles. Nanoparticles with smaller size and positive charge exhibit enhanced bactericidal activity due to their stability, water-solubility, targeting capability of drugs, and bioavailability (Kumar et al. 2015; Prasad et al. 2019, 2020).

Nanoparticles have a remarkable potential to control disease-causing pathogens, especially multidrug-resistant microbes, through efficient release of the drug molecule (Sampath Kumar et al. 2015). Hence, nano-based treatment, including nanomedicine or nano-drug, are showing promising therapeutic efficiency to combat microbial diseases (Kumar et al. 2014). Figure 13.1 highlighs various general applications of nanoparticles. This chapter focuses on recent advancements in the

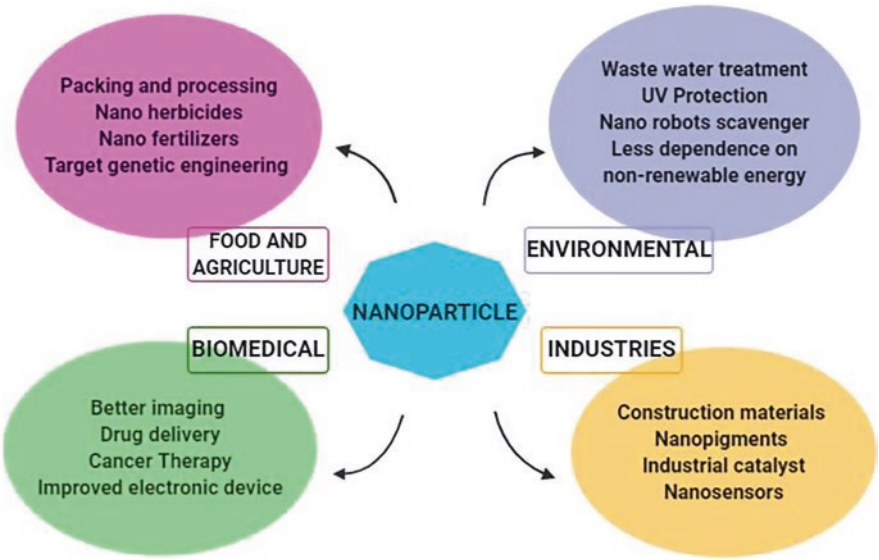

Fig. 13.1 Applications of nanoparticles in various industries

antimicrobial property and activity of the nanoparticles, with their mechanism of action and possibilities to reduce the nanoparticle-mediated toxicity.

13.2 Metal Nanoparticles as Antimicrobial Agents

Metals have been widely used as antimicrobial agents from the ancient times, around 1500 BP, where the Indians, Romans, Egyptians, and Greeks utilized silver and copper utensils to store food and water as a preservative and disinfectant (Galib et al. 2011). However, the medical applications of metals came to a standstill position after the discovery of antibiotics as early as 1920. In recent times, antimicrobial resistance or multidrug-resistance due to its biofilm-forming ability has turned into an epidemic problem globally, which might cause more than ten million deaths by 2050. Hence, researchers have turned their attention to alternative antimicrobial therapy (Prasad et al. 2020).

Metal has the ability to discriminate between bacterial and mammalian cells and interact with bacteria, interfering with the metabolic pathways leading to cellular death even in multidrug-resistant bacteria (Shenmchuk et al. 2010). The advancement in nanotechnology has increased the utilization of metal nanoparticles in the biomedicine field specifically as an antimicrobial agent because of their distinctive properties, including nano size and high surface-to-volume ratio with enhanced surface reactivity (Pelgrift and Friedman 2013).

13.2.1 Mode of Action of Metal and Metal Oxide Nanoparticles

Metals and metal oxide nanoparticles exhibit antimicrobial properties through three different mechanisms as mentioned below and the general mechanism is represented in Fig. 13.2.

13.2.1.1 Nanoparticle Interaction with Cell Membrane

The entry of the metal-based nanomaterials into the cell is based on the interaction with the transmembrane system via van der Waals forces, electrostatic attraction, and hydrophobic and receptor–ligand interactions. The bacterial cell wall acts as a defensive barrier which prevents entry of foreign particles (Dizaj et al. 2014). Cellular components differ between Gram-positive and Gram-negative bacteria. The Gram-negative bacteria have a rich source of lipopolysaccharides, which are

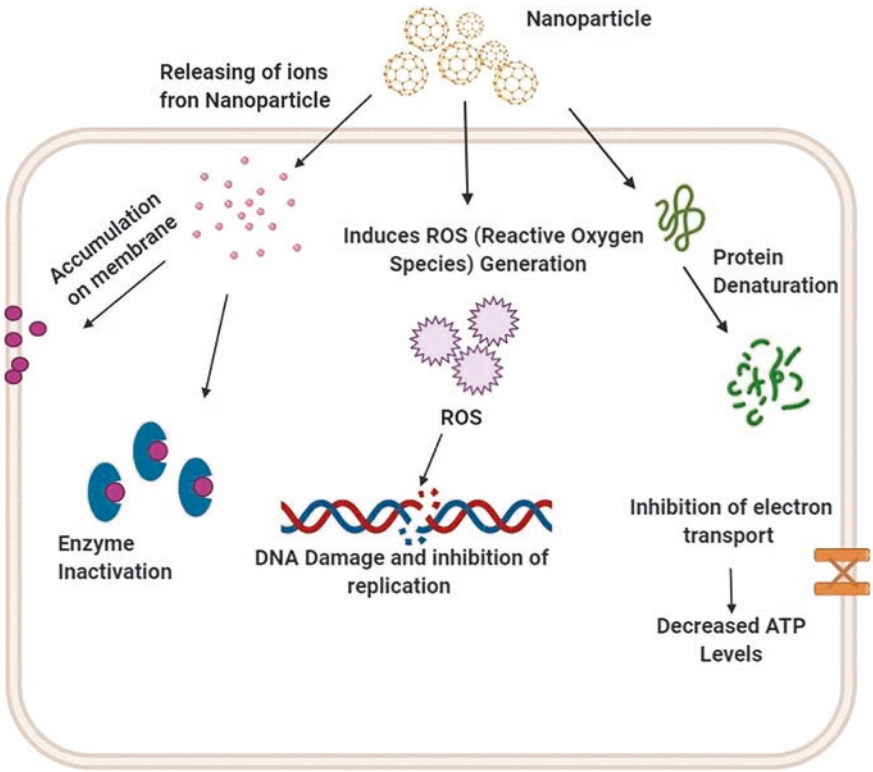

Fig. 13.2 Mechanism of action of antimicrobial activity of nanoparticles

negatively charged and interact quickly with positively charged nanoparticles based on the electrostatic force of attraction.

However, Gram-positive bacteria are composed of teichoic acid in which nanoparticles are distributed along with the phosphate group, which prevents its aggregation. Despite the charge, penetration of nanoparticles is quicker in Gram-positive bacteria, since the cell wall is thin, which is formed by peptidoglycan with abundant pores, while the thick lipopolysaccharides in Gram-negative bacteria act as a barrier to the entry of nanoparticles. Interaction of nanoparticles with the cell membrane alters the structural integrity of the membrane, disrupting cell membrane and leading to the efflux of water into the cytosol, which is compensated by the bacterial protein efflux pump and electron transport creating ionic imbalance (Shaikh et al. 2019). The penetrated nanoparticles interact with the components of the cell, including protein, DNA, enzymes, and lysosome, leading to oxidative stress, protein deactivation, enzyme inhibition, electrolyte imbalance, impaired respiration and disruption in energy transduction, ultimately leading to cell death (Prasad and Swamy 2013, Swamy and Prasad 2012; Prasad et al. 2011, 2012; Joshi et al. 2018; Gupta et al. 2018).

The shape, size, and charge of the nanoparticles influence the penetration into the cell membrane. Most of the metal nanoparticles such as gold (Au), silver (Ag), zinc oxide (ZnO), magnesium oxide (MgO), and titanium oxide (TiO_2) exhibit similar action (Gao et al. 2014).

13.2.1.2 Oxidative Stress-Mediated Cell Death

Nanoparticles induce the formation of reactive oxygen species, which includes hydrogen peroxide (H_2O_2), hydroxyl radicals (OH^-) or superoxide anions (O_2^-), and singlet oxygen, which interact with the cell membrane in the lipid core, leading to lipid peroxidation disrupting cell membrane, protein oxidation, inhibition of enzymes, and damage to DNA and RNA. Reactive oxygen species also inhibit the transcription and translation machinery and electron transport chain, leading to the death of the bacteria (Li et al. 2012).

13.2.1.3 Interaction of Dissolved Metal Ions with Protein and DNA

The metal ions released from nanoparticles are quickly absorbed into the cell through the cell membrane via ion transportors, which interact directly with the functional group of proteins and nucleic acids, like mercapto (–SH), carboxyl (–COOH), and amino (–NH) groups, inducing oxidative damage inhibiting its enzymatic activity affecting the normal physiological process culminating to death (Leung et al. 2014).

13.3 Antimicrobial Action of Nanoparticles

Scientific evidence on the antimicrobial activity of both the metal and metal oxide nanoparticles are highlighted in Table 13.1.

13.3.1 Silver Nanoparticles (Ag NPs)

Ag NPs are often used in biomedical devices and also widely employed in antimicrobial therapy (Durán et al. 2016; Zhu et al. 2015). Scientific studies have revealed that Ag NPs exhibit antibacterial activity by inducing pits and gaps in the cell membrane of bacteria leading to the destruction of the cell. Penetrated Ag NPs also interact with –SH groups of the enzymes, which may lead to the disruption of metabolic processes and causes cell death (Lok et al. 2007; Prasad and Swamy 2013; Prasad 2014; Aziz et al. 2014, 2015, 2016, 2019). Jo et al. (Jo et al. 2009) observed the antimicrobial potential of Ag NPs against foodborne fungi, which rarely produce spore. Ag NPs have also been reported for their antifungal property against plant pathogens, which controls the spore-forming ability and it was observed to be less toxic than synthetic fungicides.

Antimicrobial activities of Ag NPs have increased the attention towards nanoparticles in the food, pharmaceutical, and biomedical industries (Prasad 2014). The enhanced bactericidal activity of Ag NPs against *Streptococcus mutans*, when compared to other nanoparticles, suggests its application for treating dental caries, which is caused by *S. mutans* (Hernández-Sierra et al. 2008). Nanocomposite of Ag and ZnO NPs exhibit bactericidal activity against *L. plantarum* in orange juice indicating that Ag NPs can be used in food packaging industries (Emamifar et al. 2011). The possible antibacterial activity of the nanoparticles is represented in Fig. 13.3.

Mounting evidence on antibacterial potentials of Ag NPs against foodborne pathogens like *L. monocytogenes, S. typhimurium, E. coli*, and *V. parahaemolyticus* illustrated that Ag NPs may be used as an alternative cleansing and disinfectant agent on surfaces related to food environments (Zarei et al. 2014). The size and shape of Ag NPs influence their antimicrobial property. A small size with truncated triangular morphology showed high antibacterial activity due to its high-atom-density surfaces and ease penetration into the bacterial cell wall. Ag NPs exhibit antiviral properties by interrupting viral replication, inhibiting viral entry into host cells by attenuating fusion, infectivity, and CD-4-dependant virion binding, and also acts as a virucidal agent (Lara et al. 2010). Ag NPs also inhibit the post-entry stages of the life cycle in HIV-1 and Herpes Simplex Virus Type 1. Ag NPs encapsulated with mercaptoethane sulfonate compete with binding to the cellular heparan sulfate through its sulfonate end groups inhibiting its entry into the cell with no cytotoxic effect in mammalian cells (Baram-Pinto et al. 2009; Elechiguerra et al. 2005). Other studies also revealed the antiviral properties of Ag NPs against Hepatitis B virus, monkey-pox virus, and respiratory syncytial virus (Lu et al. 2008).

Table 13.1 Antimicrobial property of metal nanoparticles and their mode of action

Nanoparticles	Size (nm)	Pathogen	Mode of action	References
Ag Nps	20–30	*Bacillus* and *M. tuberculosis*	By interacting with the cell wall and the lysis of the cell	Zhou et al. (2012)
	25	Methicillin-resistant *S. aureus*	By interacting with the cell wall and the lysis of the cell	Panáček et al. (2006)
	20–30	*V. cholera*	By modifying the permeability of the cell membrane and the respiration	Krishnaraj et al. (2010)
Gold	25–30	*K. pneumoniae*	By changing the structure of the outer membrane and death of the cell	Murugan et al. (2015)
	43–79	*K. pneumoniae*	Not yet identified	Madhiyazhagan et al. (2015)
Copper Zinc oxide	43–79	*S. typhi*	By affecting the integrity of the cell membrane	Murugan et al. (2015)
Selenium nanoparticles	30–100	*B. anthracis*	Not yet identified	Singh et al. (2015)
Titanium Oxide nanoparticles	120	Drug-resistant *N. gonorrhoeae*	By affecting the integrity of the cell membrane	Li et al. (2013)
	5–15	*L. monocytogenes*	By separating the cytoplasmic membrane from the cell wall and changes in morphology of the cell	Tamayo et al. (2014)
	55	*E.coli* O157:H7	By interacting with the cell wall and the lysis of the cell	Paredes et al. (2014)
	20–30	BCG	By interacting with the cell wall and the lysis of the cell	Zhou et al. (2012)
	9–22	*K. pneumoniae*	By changing the structure of the outer membrane and death of the cell	Prema and Thangapandiyan (2013)
	—	Drug-resistant *N. gonorrhoeae*	By disrupting the cell and the leakage of intracellular contents	Addae et al. (2014)
	20–30	*S. typhi*	By affecting the cell wall of the bacteria may lead to cell death	Yallappa et al. (2015)
	5	*L. monocytogenes*	By separating the cytoplasmic membrane from the cell wall and changes in morphology of the cell	Jin et al. (2009)
	30–200	*Aspergillus fumigates*	Antifungal activity	Shakibaie et al. (2015)
	62–74	*Prevotella intermedia*	Photocatalytic activity	Vargas-Reus et al. (2012)

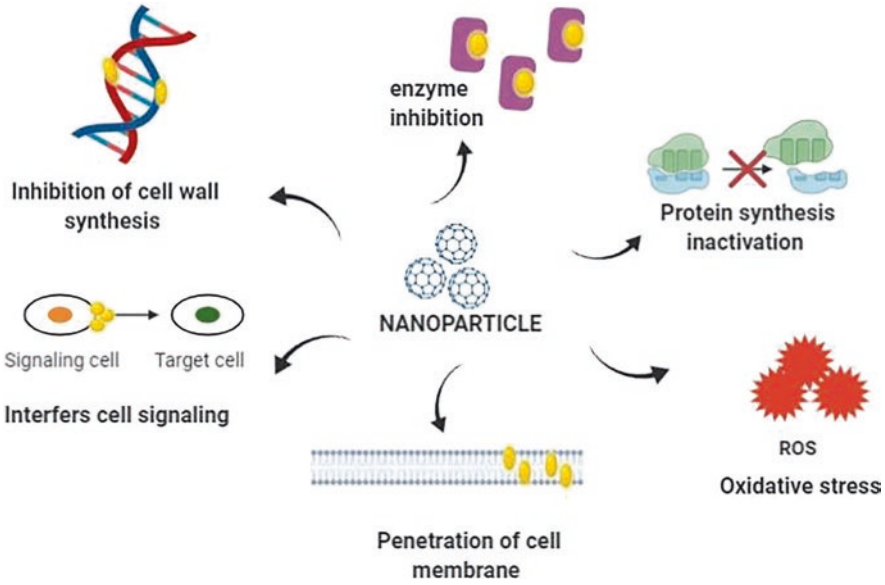

Fig. 13.3 Mechanism of action of antibacterial activity of nanoparticles

Fungus pathogenic species *Candida albicans* has been shown to cause severe bloodstream infection in humans. *C. albicans* has the potential for transformation between yeast and hyphal morphologies that tend to build up biofilm and also reflect its pathogenic factor. Ag NPs (1 nm) have been developed in order to fight against *C. albicans* biofilm. The results showed that Ag NPs greatly inhibit or reduce the biofilm formation (Lara et al. 2015).

13.3.2 Selenium Nanoparticles (Se NPs)

Se NPs showed potent antifungal activity upon *C. albicans* and *A. Fumigates*. Cerium oxide NPs significantly reduced the inflammatory response related to peritonitis, indicating the new therapeutic avenue for the management intra-abdominal infection (Shakibaie et al. 2015; Manne et al. 2015).

13.3.3 Magnesium Oxide Nanoparticles (MgO NPs)

MgO NPs revealed their potent antiviral properties against hand, foot and mouth disease-causing virus. It is reported that 250 μg/mL concentrations of MgO NPs did not cause any abnormality in Razi Bovine kidney cell line (Rafiei et al. 2015).

13.3.4 Zinc Oxide Nanoparticles (ZnO_NPs)

ZnO NPs possess an antioxidant and anticoccidial effect on *Eimeria papillata*-triggered infection in the jejunum (Dkhil et al. 2015). Besides, ZnO NPs have also been shown to possess antimicrobial properties against an array of pathogens such as *S. typhimurium*, *C. jejuni*, and other foodborne microbes such as *E. coli*, *Listeria monocytogenes*, *V. cholera*, *K. pneumoniae*, and *N. gonorrhea* (Tayel et al. 2011; Xie et al. 2011; Liu et al. 2009; Jin et al. 2009; Salem et al. 2015; Nagarajan and Kuppusamy 2013; Bhuyan et al. 2015). Khan et al. (Khan et al. 2015) highlighted that ZnO NPs are valuable nanoparticles in order to maintain and keep the hygiene of the oral cavity therein minimizing the bacterial colonies.

Approximately 550 tons of ZnO NPs have been produced annually, employed in a profit-making product and it is also showing a reduced amount of toxic as compared to CuO and Ag NPs to humans (Keller et al. 2013; Bondarenko et al. 2013). The antimicrobial property of ZnO NPs is nearly similar to Ag NPs (Adams et al. 2014).

13.3.5 Gold Nanoparticles (Au NPs)

Au NPs have many beneficial properties including their easy preparation, fluorescence, scattering effect, and biocompatibility which are widely used in the field of biomedicine (Huang et al. 2007). Au nanosphere could be made by reduction of auric acid in the presence of sodium citrate and the size of the Au NPs is also varied by the addition of different concentrations of reducing agent (Turkevich et al. 1951). Au NPs are stable and can interact (covalently and noncovalently) with appropriate ligands such as peptides, antibodies, and DNA (Han et al. 2007; Paciotti et al. 2006). Au NPs possess light-absorbing ability, and hence can conjugate with antibodies that may act against selected pathogens, *Staphylococcus aureus*, to kill them photothermally or hyperthermally (Zharov 2006; Norman et al. 2008).

13.3.6 Titanium Oxide Nanoparticles (TiO_2 NPs)

TiO_2 NPs are largely used in the food products such as candy and chewing gums. An adult human is exposed about 1 mg/kg B.WT/day of titanium (Weir et al. 2012). It is one of the most abundant nanoparticles in terms of production throughout the world, approximately 3000 tons/year (Keller et al. 2013). TiO_2 NPs have shown promising antimicrobial properties upon various microbes such as *E. coli, S. aureus, P. aeruginosa, E. faecium, B. subtilis*, and *K. pneumoniae* (Rajakumar et al. 2012). The nanoparticles (62–74 nm) with minimal inhibitory concentration value were tested for the above mentioned bacteria ranges between 40 and 80 μg/mL.

Similarly, another study showed the TiO_2 NPs' minimal inhibitory concentration value to be 1187.5 µg/mL on biofilm-forming bacteria *P. gingivalis, F. nucleatum, A. actinomycetemcomitans*, and *Prevotella intermedia* (Vargas-Reus et al. 2012). TiO_2 NPs has a unique characteristic that is photocatalytic activity, when exposed to photoactivation it notably increased the antimicrobial property on a number of species *P. aeruginosa, B. fragilis, E. hire, B. fragilis, S. aureus,* and *S. Typhimurium* (Maness et al. 1999).

13.3.7 Calcium Carbonate and Magnesium Oxide composites ($CaCO_3$ and MgO)

The $CaCO_3$ NPs' antimicrobial potential has been assessed on *S. typhimurium, S. aureusi E. coli,* and *B. subtilis*, it reveals the better antimicrobial activity of CaO on an aforementioned bacterial species. On the other hand, $CaCO_3$/MgO nanocomposites showed greater antibacterial potential on *E. coli* and *S. aureus*. The mechanism of antibacterial potential of CaO and MgO is generating the superoxide anion on their surface and besides augmenting in pH value because of the hydration of CaO and MgO (Yamamoto et al. 2010).

13.3.8 Aluminium Oxide Nanoparticles (Al_2O_3 NPs)

Aluminum oxide NPs (Al_2O_3 NPs) possesses several uses in industrial and home care products. It also evaluated for the antimicrobial property on *E. coli*, higher concentration of nanoparticles showed a moderate growth inhibitory effect when tested against bacteria. This attribution of the Al NPs is due to the surface charge interactions between the cell membrane and cell wall with nanoparticles, and also infiltration within the cells of the bacteria (Sadiq et al. 2009).

Basically, Al NPs are thermodynamically stable (Martınez-Flores et al. 2003). They possess close to neutral pH, which holds a + ve charge on their surface. The positively charged Al NPs tend to interact with negatively charged bacterial cells', *E. coli*, surface (Li and Logan 2004). This is due to the electrostatic force between bacteria and nanoparticle surface, in association with hydrophobic interactions and polymer cross-link. This antimicrobial activity of the nanoparticles produce reactive oxygen species that disrupt the cell wall as well as membrane, subsequently causing cell death (Ruparelia et al. 2008). Al NPs save the cells from death due to oxidative stress, thereby, act as free radical scavengers. Their action is based on nanostructure (Mohammad et al. 2008).

13.3.9 Copper and Copper Oxide Nanoparticles (Cu & CuO NPs)

Cu & CuO NPs revealed microbicidal activity against a variety of disease-causing bacterial species. For example, CuO NPs (50–100 nm) produced in a green chemistry manner pronounced a considerable antimicrobial activity upon various disease-causing species such as *Shigella dysenteriae, V. cholera*, and *K. pneumoniae* (Sutradhar et al. 2014). One more study showed that CuO NPs (20–95 nm) have antimicrobial activity on methicillin-resistant *S. aureus* and *E. coli* (Ren et al. 2009).

Oral pathogens *P. gingivalis, S. mutans,* and *F. nuceatum* could be inhibited in the range of minimal inhibitory concentration values 250–500 μg/mL of CuO NPs (10–50 nm). CuO NPs (23 nm) showed their antimicrobial activity on *Enterococcus faecalis*; however, they do not show antimicrobial activity on *K. pneumoniae* (Ahamed et al. 2014). The antimicrobial activity is based on the shape and size of the nanoparticles (Azam et al. 2012). It has been reported that Cu^{2+} ion release from the nanoparticles could trigger mutation in DNA and consequently produce the reactive oxygen species (Pan et al. 2010).

On the other hand, another study opposes that the release of Cu^{2+} ions from the nanoform is insignificant, so the less antimicrobial activity of the nanoparticles. Indeed, reactive oxygen species production is not because of the Cu^{2+} ions, but its nanoform. In the same manner, nanoparticles enter into the bacterial cell membrane and produce the reactive oxygen species, therein causing cell death (Applerot et al. 2012;Yadav et al. 2017). CuO NPs shows bactericidal activity via inhibiting *E. coli's* cellular respiration and also interacting with various biomolecules (Wahab et al. 2013). Ren et al. (Ren et al. 2009) reported that *B. subtilis* has an attraction towards amines and carboxylic groups present on the cell membrane. The nanoparticles may have the potential to inhibit the enzyme or degrade the protein through interaction with protein-SH group (Schrand et al. 2010). CuO tagged with linoleic acid inactivates certain enzymes (Das et al. 2010).

13.4 Nanoantibiotics: An Option to Fight Against Antibiotic Resistance

Frequent antibiotic treatment is commonly known to augment the resistance that develops in multidrug-resistant organisms, an increased dose of antibiotics also causes adverse side effects. So, an alternative is needed to overcome these problems; metallic nanoparticles are well characterized and possess antimicrobial properties. The functions of nanoparticles are structured in Fig. 13.4. Nanoparticles could be conjugated with antibiotics that can gradually reduce the dosage, toxicity and improve the antimicrobial activity against multidrug-resistant and great bioavailability (Allahverdiyev et al. 2011). Nanoantibiotics showed promising antimicrobial activity and also have a safe delivery of antibiotics (Abeylath and Turos

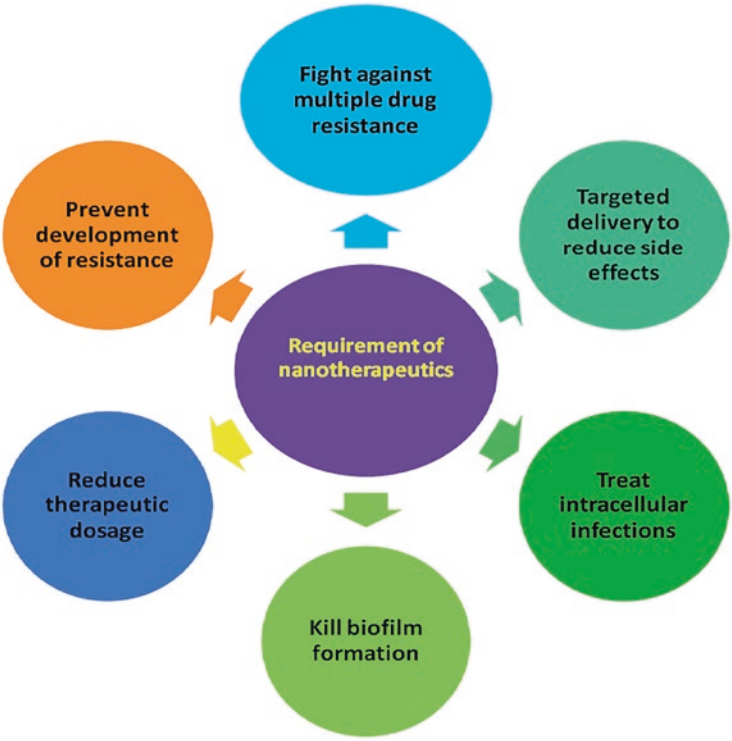

Fig. 13.4 Function of nanostructures in antimicrobial treatment

2008; Huh and Kwon 2011). A recent study revealed that nanomaterials could reduce the development of drug-resistant bacteria (Mühling et al. 2009).

13.4.1 Silica Nanoparticles (SiO_2 NPs)

The SiO_2 has antimicrobial activity at the nano-scale level because of the surface area enhancement (Dhapte et al. 2014). The Si NPs also inhibit the adherence of bacteria on an oral biofilm (Cousins et al. 2007). The combination treatment for antibacterial activities of Cu/SiO_2 properties had been studied well by disk diffusion method. Results demonstrated that the antibacterial (*C. albicans, P. citrinum, E. cloacae, E. coli,* and *S. aureus*) properties of Cu-SiO_2 nanocomposite were noticeably identified against bacteria (both Gram-positive and Gram-negative) and fungi because Cu NPs of Cu-SiO_2 were formed on the surface of SiO_2 NP (Kim et al. 2007).

Another combination of Ag-Si nanocomposite was also analyzed against various microbes and the results were compared with the conventional methods, including silver nitrate and silver zeolite. The Ag-Si nanocomposite showed improved

antimicrobial activities (Egger et al. 2009). To determine the minimal inhibitory concentration and minimal bactericidal concentration the Ag-SiO_2 particles were tested against *S. aureus* and *E. coli* using the standard serial dilution method. The findings of the result suggest that Ag-SiO_2 NPs have greater antibacterial property (Xu et al. 2009). Literature showed that Si nanowires combined with the living cells and bacteria disrupted the functions of cell-like cell differentiation, adhesion and spreading. The Ag NPs Si nanowires revealed the antibacterial properties and also showed biocompatibility with epithelial cells of the lung adenocarcinoma (Li and Logan 2004). These results showed that the combination of Si with Ag and/or nanocomposites has the antimicrobial potential and usefulness in the biomedical field.

13.4.1.1 Silica–Antibiotics Combination

Gentamicin-Loaded Silica Nanoparticles

Gentamicin-loaded with silica xerogel is showed potential antimicrobial against *Salmonella, Mycobacterium* species, and *Brucella* which severely causes chronic infections and also a big challenge to eradicate. Silica nanoparticles could effectively deliver the antibiotic with minimizing the dosage, increasing longevity and reducing the toxicity level of the antibiotic (Seleem et al. 2009).

Silica NPs Conjugated with Tetracycline Antibiotic

The antibiotic tetracycline encapsulated with silica NPs was demonstrated by Capeletti et al. (Capeletti et al. 2014). The prepared nanostructures were tested against vulnerable *E. coli* and the results were compared to pristine tetracycline alone and a mixture of tetracycline + ampicillin for its antimicrobial efficiency. The Si-based NPs have interacted with the lipopolysaccharides of the peptidoglycan layer of the outer membrane of the bacteria.

The formation of the hydrogen bond between the saccharides and hydroxyl groups is identified on the silica surface. This complex can weaken the peptidoglycan layer and it may lead to the disruption of the cells. It is also noted that there is no toxicity effect in the mammalian cells. The antibiotics can disrupt the cell wall of the bacteria, and also they do not affect the mammalian cells. This is because of the differences in the structure of the bacterial cell walls and mammals. It is also evident that the bactericidal actions of encapsulated tetracycline may be due to the hydrolyzing effect of nanoantibiotic on sugar molecules of peptidoglycan.

13.5 Nanoparticle and Biofilm Interaction

Biofilm is the key factor which makes the microbes resistant to antibiotics and the immune system. Scientific reports revealed that nanoparticles disrupt the structural integrity of biofilm by attaching with exopolysacharides. Ag NPs inhibits the production of exopolysacharides, which might be due to the mechanism of antibiofilm property of Ag NPs against *Klebsiella pneumoniae* and *E. coli* (Su et al. 2009).

Nanoparticles influence the rate of biofilm formation and bacterial adhesion, whose mechanism of action is not yet completely elucidated. MgO NPs adhere and diffuse into biofilms leading to the disruption of the membrane potential, promote lipid peroxidation and binds with DNA and disrupts its function, altering the normal functioning of bacteria inhibiting its ability to form biofilm (Lellouche et al. 2012). Potassium ion channels play a vital role in long-distance electrical signal conduction within the bacterial biofilm and also influences the metabolic activity of bacteria (Lundberg et al. 2013). Most of the nanoparticles like Ag NPs and ZnO NPs have been identified to interrupt the ion channels and inhibit the metabolic activity thereby attenuating the biofilm formation.

13.6 Application of Metallic Nanoparticles

The general applications of metallic nanoparticles are highlighted in Fig. 13.5.

13.6.1 Dental Materials

Bacteria accumulate in the plaque and spreads over the mouth, which causes damage to teeth. The groups coated with CuO and ZnO NPs have the possibility to restrain the growth of *S. mutans* (Ramazanzadeh et al. 2015). Addition of titanium dioxide NPs (TiO_2 NPs) showed the antibacterial effects following light exposure (Aboelzahab et al. 2012).

13.6.2 Antitumor Properties

Although medicines are available in plenty, many people die from cancer. Chemotherapeutic drugs are often associated with severe side effects. Hence, NP-based drugs recently grab great interest in terms of nano-size, efficient delivery, biocompatibility, site targeting, and fewer side effects (Tourinho et al. 2012). Various types of nano-carriers have been reported so far, including polymeric micelles, dendrimers, liposomes, and inorganic in anti-cancer treatment in order to

Fig. 13.5 Applications of metallic nanoparticles

reduce the side effects (Liang et al. 2020). Inorganic nanomaterials such as metal, including silver, gold, and nickel as well as metal oxides of iron, zinc, and titanium show potential influence in medicine, including cancer therapy, cell imaging, and gene or drug delivery (Sunderam et al. 2019).

13.6.3 Textile Industry

Recently, the blending of nanoparticles with textiles during fabrication has improved greatly. Ag NPs are employed widely for the improvement of properties such as antibacterial, self-cleaning, and UV blocking of finished fabrics (Fouda et al. 2017). Besides, ZnO-NPs are included in textile manufacturing in order to increase UV locking and for the antibacterial properties (Mohamed et al. 2019). Inorganic nanoparticles are preferred over organic nanoparticles in the textile industry as UV blockers (Riva et al. 2006).

13.6.4 Food Management

The nanotechnology is a useful tool in two main areas in the food industry including food packaging and food additives/ingredients (Sharaf et al. 2019; Chausal et al. 2021). Nanoparticles are used in the food industry in a variety of applications such as nano-particulate delivery systems, wrapping, and food safety (Prasad et al. 2017).

Nanometal oxides, ZnO NPs, are employed in polymeric materials in the production of packing tissue to enhance the antimicrobial properties (Espitia et al. 2012).

13.6.5 Wastewater Management

Industries are one of the major causes of water pollution. The effluents released by the industries contain several hazardous chemicals. Nanotechnology has offered a novel approach in the treatment of wastewater in terms of removing toxic metals and disinfection (Prasad and Thirugnanasanbandham 2019; Uddandarao et al. 2019). The photocatalytic activity of Palladium with ZnO NPs allows the elimination of disease-causing microbes from the wastewater (Mishra et al. 2020). An array of metals in nanoscales, including Ag, ZnO, CuO, TiO_2, and carbon nanotubes, has high potential disinfection properties in the polluted water (Rafique et al. 2020).

13.7 Conclusion

In an epoch of increasing multidrug resistance where the microbes are developing resistance against several antibiotics, treatment against infectious disease has turned into a serious global issue due to increased mortality and morbidity. The emergence of nanotechnology has introduced nanoparticles as a *via*ble alternative to antibiotics specifically against multidrug-resistance bacteria, through their multifaceted activity such as cell wall penetration, oxidative stress-mediated damage to biomolecules altering the gene regulation and metabolism thereby blocking the bacteria defence and survival. Despite several reports on the antimicrobial efficiency of nanoparticles, their toxicity in mammalian cells still remains a debate. Hence, future research should focus on understanding the molecular mechanism behind the antibacterial activity of nanoparticles and fabrication of biocompatible engineered nanocomposite to attenuate human and environmental toxicity.

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Chapter 14
Advancement in Nanomaterial Synthesis and its Biomedical Applications

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Contents

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14.1 Introduction

Health has been the most important criteria to measure the development of a country. Health indices have always been dwindling throughout the world due to various factors that emerged time to time. It was infectious diseases that claimed the lives of millions during the initial stages of human settlement (Dobson and Carper 1996). With the discovery of antibiotics and the advancement of health care, we have succeeded in overcoming infections to a greater extent initially. Then came an era of non-communicable diseases with a steep rise in the death rate among different countries. The determinants of health have been redefined in the light of escalating rates of diseases like coronary artery disease, stroke, cancers etc. At the dawn of the twenty-first century we were facing a grave situation of highly prevalent non-communicable diseases with a soaring rate of infectious diseases contributed by newly emerging pandemics (Heinrich et al. 2020) of Ebola, SARS-CoV-2 etc. Making the matters more complicated is the resurgence of bacterial strains that are resistant to multiple antibiotics. The situation is warranting to shift the concentration from developing newer antibiotics to adopt newer strategies to make the available antibiotics more efficacious. For this, medical sciences embraced the newly emerged science of nanotechnology. The application of nanoscience in medical sciences have already developed different speciality streams like nanovaccines, nanodiagnostics, nanopharmaceutics so on and so forth (Islan et al. 2017; Saglam et al. 2021). In this chapter we discuss about the research and developments in the field of nanomedicine in controlling infections and other diseases.

14.2 Historical Development of Nanomaterials in Relevance to Biology and Medicine

Evolution of nanoscience can be traced back to oldest civilizations that existed on earth. In the fifth century B.C. philosophers debated on the continuity of matter and ascertained that any matter can be divided into infinitesimally smaller subunits culminating in indivisible and invisible matter (Bayda et al. 2020). This smallest subunit of matter is equivalent to the modern entity of ‘atom’, and can be considered as a recognition and acceptance of materials in micro- and nanoscales in those days. In the fourth century AD Romans created the Lycurgus cup, a dichroic glass cup which appears green on direct light and reddish purple in transmitted light, is considered as the oldest manmade nanomaterial. The dichroic property of Lycurgus cup was

established in 1990 through transmission electron microscopy. It is due to the presence of silver-gold alloy nanoparticles in 7:3 proportion of 50–100 nm size containing dispersed copper of about 10% (Elsner 2013). The vast array of ceramic glazes used by the Islamic world and Europe contained silver and copper nanoparticles (Padovani et al. 2003; Barber and Freestone 1990). They were extensively used from the ninth to seventeenth centuries. Later Italians utilized similar nanoparticles during the Renaissance period for pottery making. They were influenced by the Ottoman techniques prevalent from the thirteenth to eighteenth centuries using 'Damascus' saber blades, cementite nanowires and carbon nanotubes which provided strength, resilience and keen edges respectively to produce 'Damascus' saber blades strength, made from cementite nanowires for resilience and carbon nanotubes for keen edges (Sciau 2012). Michael Faraday studied colloidal gold in suspension, its optical and electronic properties and demonstrated how the gold nanoparticles changed their colour in solutions under specific lighting conditions (Lin et al. 1986). The ancient Indian treatment systems like Ayurveda and Siddha also utilized metals and minerals in the nanoscale for the treatment of various ailments. Detailed procedures of calcining the metals and minerals into "Bhasma' of nano-proportions were utilized in the treatment of various ailments at small doses. The science detailing these methods of purification and reduction along with their modes of use in the treatment branch termed 'Rasasastra' had enormous patronage from Buddhism (Ranade and Acharya 2015). The famous Indian Alchemy principles also lay hidden in these scriptures. Calcined gold, silver, copper, lead, tin, antimony, sulphur, arsenic etc. were utilized for the treatment of various ailments with the aid of appropriate vehicles. Even biological materials like amber, stag horn, conch shell and elephant tusk were also calcined and used as medicine in the form of nanoparticles. The qualities of certain metals like silver and gold were known to prevent infections from the tenth to thirteenth centuries. This knowledge was inculcated while making confectionaries prepared in India and its adjoining provinces by covering with finely thin silver or gold foils beaten up for several days to make them reach nano-proportions, which were called 'Chandi ka warq' and 'Sone ka warq' respectively. This practice is still in vogue in parts of Indian subcontinent.

The modern evolution of nanotechnology took place in 1959 when Richard Feynman, Nobel laureate and famous American physicist introduced it conceptually with the famous lecture "*There's Plenty of Room at the Bottom*" given at California Institute of Technology (Richard 1960). The concept laid by Feynman helped in constructing machines of molecular proportions for performing humongous task of handling large volumes of data in a tiniest of space. The materialization of the concepts laid down by Feynman during the latter half of the twentieth century earned him the title 'Father of modern nanotechnology'. The spark created by Feynman was carried forward by many other eminent personalities like Norio Taniguchi from Japan who coined the term "nanotechnology" in 1974 (Taniguchi 1974).

Towards the end of the twentieth century several more scientists were attracted to the opportunities hidden in the field of nanotechnology and came up with increased momentum of research activities. Several opportunities were suggested

for the synthesis of nanomaterials and broadly they were classified as two categories: top-down and bottom-up approaches (Khan et al. 2011).

The breaking down of a material into nano-sized particles from a relatively large material by the use of precision engineering and lithography is termed top-down approach (Madou 2011). Majority of micro-electronics industry utilizes top-down approach with precision engineering while lithography utilizes patterning of surfaces through deposition of materials or through exposure ions, electrons or light (Biswas et al. 2012).Bottom-up approach on the other hand utilizes self-assembly of atoms or molecules by physical or chemical interactions to form materials in nanoscale range (1–100 nm) (Luby et al. 2015).

The first published book on nanotechnology was by K. Eric Drexler in the year 1986 entitled "Engines of Creation: The Coming Era of Nanotechnology", which introduced the term 'Molecular engineering' (Bayda et al. 2020; Drexler 1981). He described the build-up of complex machines from self-assembly of individual atoms to form nanostructures. Later in 1991 he associated with Peterson and Pergamit to publish yet another milestone publication titled "Unbounding the Future: The Nanotechnology Revolution" in which they introduced terms like 'nanobots' or 'assemblers' for medical applications, and the term 'nanomedicine' was introduced henceforth (Drexler et al. 1991). The evolution of nanotechnology is subdivided into four distinct generations and as per Mihail Roco, we are presently in the fourth generation of nanotechnology era (Roco 2007) (Fig. 14.1). Nanomaterials and their uses in the field of medicine are presented in Table 14.1.

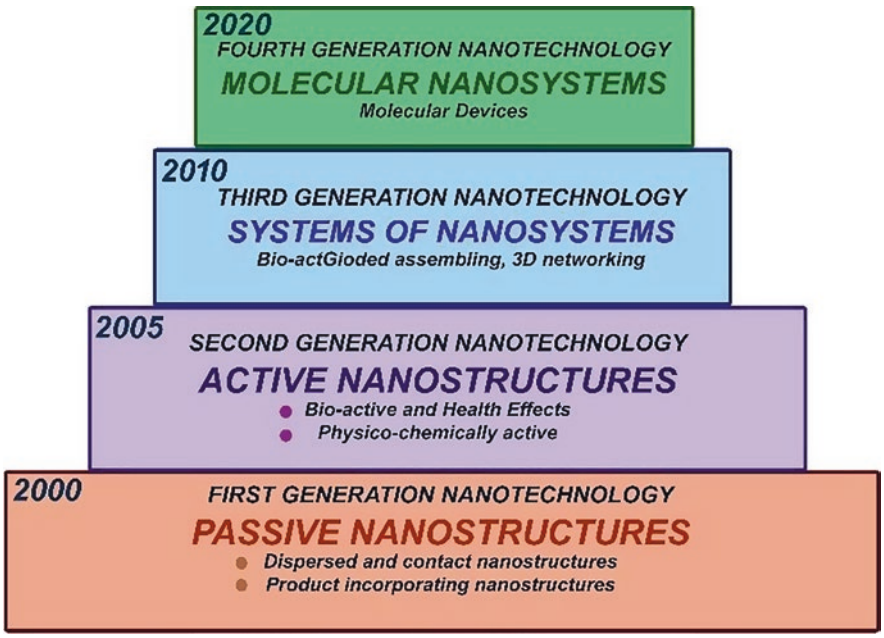

Fig. 14.1 Generations of Nanotechnology

Table 14.1 Nanomaterials used in Medicine

Nanomaterials	Description	Uses
Liposomes	Small spherical artificial vesicles produced from natural nontoxic phospholipids and cholesterol	Gene therapy, drug delivery, Targeted therapy
Nanoparticles	Colloidal particles ranging from 10 to 100 nm size which are biocompatible and biodegradable	Gene delivery, protein delivery, drug delivery, gene expression vector, gene transfection
Dendrimers	Macromolecular compounds with a central core with radiating branches of less than 10 nm	Gene delivery, intravascular drug delivery, intrabronchial drug delivery,
Carbon nano tubes	0.5–3 nm diameter tubes with 200–1000 nm length	Detection of DNA mutation, detection of disease biomarkers
Nano crystals	2–9.5 nm size materials smaller than 100 nm composed of atoms in a polycrystalline arrangement	Carrier for poorly soluble drugs, labelling of cancer markers in diagnostics
Nano shells	Spherical nanoparticle consisting of a dielectric core covered by a thin metallic shell	Tumour-specific imaging, deep tissue thermal ablation
Nano wires	Tiny wires of nanoscale dimensions	Disease protein biomarker detection, DNA mutation detection, gene expression detection
Quantum dots	2–9.5 nm semiconductor crystal having optical and electrical properties	Optical detection of genes, detection of proteins in cell assays, tumour and lymph node visualization

14.2.1 History of Nanobiology

The history of use of nanotechnology in the fields of biology and medicine extends from diagnosis, drug delivery to molecular imaging. Biological systems including the human body are an assembly of nanoscaled structures undergoing self-assembly and self-organization to form higher-order structure of biological units and organisms ranging from micro-, meso- and macroscale. Life processes involving elementary biological units like cell-membrane, DNA, proteins or lipids are of nano-dimensions (Fig. 14.2). These biological units and their functions are better comprehended, guided and manipulated with the help of nanotechnology (Logothetidis 2006). The application of nanoscience in the field of biology is henceforth called bio-nanotechnology. Miniaturization is the essential feature of nanomedicine wherein the nanometer scale is similar in size to the macromolecules like enzymes, receptors, and carrier proteins. The nanoscale devices in the range of 20–50 nm can easily enter cells as well as exit the vascular circulation and enter tissues swiftly. The birth of a new stream of nanotechnology called "nano-pharmaceuticals" developed and marketed products using nanotechnology for drug delivery of regenerative medicine, nanoparticles with antimicrobial activities and nanochips, nanoelectrodes and nano-biosensors for the detection of biomarkers. In medicine, nanotechnology coupled with Biotechnology, Information technology

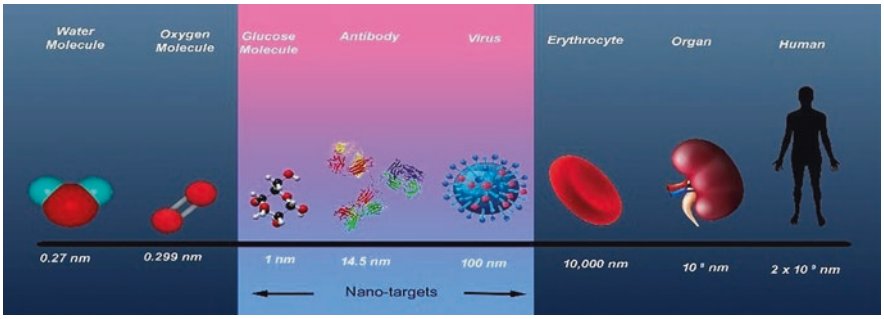

Fig. 14.2 Biological systems in Nanoscale

and Cognitive science (NBIC developments) are thought to contribute immensely in the fields of in vitro detection, in vivo diagnosis, multimodal imaging, chemotherapy, phototherapy, gene therapy, immunotherapy, theranostics and their clinical translation (Logothetidis 2006; McGinn 2012).

Profound advancements are made in the field of nano-oncology to improve the efficacy of traditional chemotherapy by incorporating nanomaterials to target the tumour site (Kumar et al. 2016a, b; Palazzolo et al. 2019a, b). Researches are advancing in using nanomaterials to modulate essential biological process for cancer therapy like autophagy, quenching of oxidative stress and to exert cytotoxic activity against the cancer cells (Sharma et al. 2019). Other than cancers, diabetes mellitus, neurodegenerative diseases as well as detecting and curing bacteria, fungi and viruses associated with infections are also being investigated with the help of nanotechnology. Another instrumental advancement in the field of bio-nanotechnology is the development of "Scaffolded DNA origami" by Paul Rothemund in 2006 by self-assembling DNA nanostructures in a "one-pot" reaction (Rothemund 2006). This forms the first application of DNA nanotechnology, which was conceptualized by Nadrian Seeman way back in 1982 (Seeman 1982). DNA nanotechnology is the hot seat of interdisciplinary research presently with inputs from physics, chemistry, materials science, computer science and medicine. Nano-informatics incorporating the vast opportunities of computer science is another field which is not being used to its fullest potential in the field of medicine (Sharma et al. 2019). Predictive analysis of nanocarriers by employing powerful machine-learning algorithms predicts their cellular uptake, activity and cytotoxicity. Nano-informatics can utilize powerful tools like data mining, network analysis, quantitative structure-property relationship (QSPR), quantitative structure-activity relationship (QSAR) and ADMET (absorption, distribution, metabolism, excretion, and toxicity) for predictions. The opportunities and possibilities for nanoscience are many and they are being utilized elaborately during the twenty-first century and hence we aptly termed as the "next industrial revolution".

The following properties of nanomaterials created tremendous attraction for them to be utilized as nanomedicine. (1) Biomolecules with nano-size dimensions are capable of regulating cellular biochemical pathways and in turn cellular

homoeostasis. Properly engineered nanoparticles can interfere with the biomolecules at any stage in the molecular processes giving us the capability to hinder or promote any biochemical process in the system biology of humans. (2) Nanomaterials have fairly good solubility due to the advantage of their size, and this can be further enhanced by modifying their surface properties. (3) Owing to their higher surface-to-volume ratio and greater surface area, they are capable of carrying a higher therapeutic payload to their target site. (4) Due to their property of selective targeting, nanoparticles can deliver therapeutic dosages to their specific target, reducing the untoward effects on the nearby healthy tissues. (5) Nanoparticles can now be utilized for personalized diagnosis and therapy (Bisht and Rayamajhi 2016).

14.3 Infection and Their Treatment – Current Knowledge

Infectious diseases posed the greatest threat to the establishment of human race on earth. The human population of present day is to a greater extent due to the victory over infectious diseases that started with the discovery of antibiotics. From the discovery of penicillin in 1928 by Alexander Fleming, the number of antibiotics in treatment have increased at a sudden pace, now reaching to a sizeable population amounting to hundreds. Antibiotic resistance also emerged simultaneously leading to the development of 'superbugs' which pose a real challenge to researchers. Antibiotic resistance has provided an evolutionary advantage to the microbes to survive the newly emerging antibiotics. Methicillin-resistant *Staphylococcus aureus*, fluoroquinolone-resistant *S. aureus*, erythromycin-resistant *Streptococcus pyogenes* and *S. pneumoniae* and vancomycin-resistant enterococci are few of the resistant strains that gain medical attention on a public health purview recently (Kapoor et al. 2017).

Antibiotics evolved after 1928 are classified and dealt based on their mechanism of action (Fig. 14.3);

14.3.1 Antibiotics Targeting Cell Wall

Gram-positive bacteria are protected by an outer cell wall which is tough, rigid and mesh-like. Meanwhile, the Gram-negative bacteria is covered by a thin cell wall surrounded by a second outer membrane. The space enclosed between the cell wall and the outer membrane is termed periplasm. The outer membrane is an additional protective layer which protects the bacteria from the entry of external substances. However, they are provided with channels called porins. which allow the entry of molecules into the cell (Hauser 2015). The tough cell wall helps in maintaining their shape and protects them from the osmotic and mechanical stressors. The cytoplasmic membrane prevents the entry and exit of ions and maintains the cytoplasmic components.

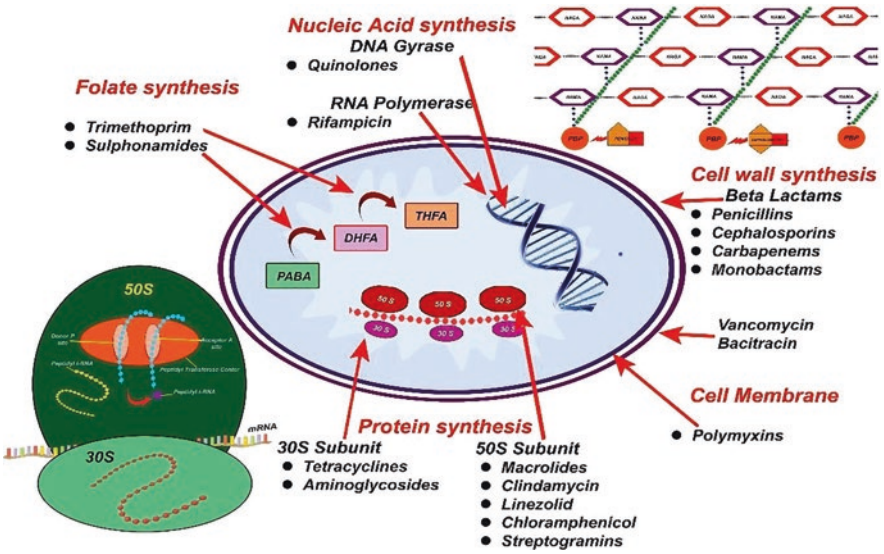

Fig. 14.3 Site of action of antibiotics in bacteria

Bacterial cell wall is made up of peptidoglycan, which is a polysaccharide layer cross-linked to glycan strands facilitated by the action of transglycosidases. The cross-linking extends from the sugars in the polymers to the peptides on the other strand. Precisely, the D-alanyl-alanine portion of peptide chain is cross-linked by glycine in the presence of penicillin binding proteins (PBPs). This cross-linking makes the cell walls stronger, and this biochemical pathway is targeted by a group of antibiotics like β-lactams and glycopeptides (Kahne et al. 2005; Reynolds 1989; Strohl 1997; Benton et al. 2007; Leach et al. 2007).

14.3.1.1 Beta-Lactam Antibiotics

They are the oldest and a broad class of antibiotics with a β-lactam ring in their molecular structure. They irreversibly inhibit the enzyme transpeptidase, an enzyme required for bacterial cell wall synthesis. The final step in transpeptidation in the synthesis of cell wall is facilitated by a transpeptidase called penicillin binding protein (PBP). PBP binds to D-alanyl-D-alanine attached at the end of the peptidoglycan precursors, muropeptides, to cross link the peptidoglycan. β-lactam antibiotics target the PBPs, as the β-lactam ring mimics the D-alanyl D-alanine portion of the peptide chain (Džidić et al. 2008). As the PBP links to the β-lactam ring, they will not be available to cross-link the peptidoglycan and the synthesis of the new cell wall abruptly ends. The disruption of peptidoglycan layer damages the permeability barrier of the bacterium. Penicillin derivatives, cephalosporins, monobactams and carbapenems belong to β-lactam antibiotics. In spite of escalating antimicrobial

resistance, these antibiotics are still clinically important due to their short $t_{1/2}$, low volume of distribution with significant kidney tubular secretion (MacDougall 2017).

14.3.1.2 Glycopeptides

Glycopeptides are cyclic or polycyclic glycosylated non-ribosomal peptides produced by filamentous actinomycetes belonging to various groups. The glycopeptides inhibit the cross-linking of the peptidoglycan by binding on to the D-alanyl D-alanine portion of peptide side chain. They in turn cross-link peptides within and between peptidoglycan on the surface of the cytoplasmic membrane. Vancomycin, a glycopeptide antibiotic prevents the binding of PBP with the D-alanyl subunit and binds noncovalently with the terminal carbohydrate, thus inhibiting the formation of cell wall (Grundmann et al. 2006).

14.3.2 Inhibition of Protein Biosynthesis

The genetic information in the bacterial DNA is first transcripted on to the m-RNA followed by translation of the triplet codons on the m-RNA by the ribosomes. The entire process of protein synthesis is catalysed by ribosomes and myriads of cytoplasmic factors. The bacterial 70S ribosomes are consisting of two sub-units, the 30S and 50S subunits which are integral to the functioning of the ribosomes (Yoneyama and Katsumata 2006; Vannuffel and Cocito 1996; Johnston et al. 2002). Antimicrobials target either the 30S or 50S sub-units of the bacterial ribosomes.

14.3.2.1 Inhibitors of 30S Subunits

Aminoglycosides

Aminoglycosides (AG) are positively charged molecules attaching on to the negatively charged outer membrane of the bacterial cell. This process leads to the formation of large pores, which allow the penetration of the antibiotic into the bacterial cell. The passage of the antibiotic through the cell membrane requires activation of energy-dependent transport channels which requires oxygen and an active proton motive force. Due to this peculiar requirement, AG are less active against anaerobic organisms, but they are synergistic to cell wall disrupting antibiotics like β-lactams and glycopeptides as they provide easier access to the AG into the cell. On their entry, AGs form hydrogen bonds with the conserved portions in 16S r-RNA of the 30S subunit near the A site, causing misreading and abrupt termination of translation of m-RNA. Tetracycline, chlortetracycline, doxycycline and minocycline exhibit antimicrobial effect following this mechanism (Wise 1999).

14.3.2.2 Inhibition of 50S Subunits

Chloramphenicol

Chloramphenicol is a broad-spectrumantibiotic isolated from *Salmonella venezuelae*. It is characterised by the presence of a nitrobenzene moiety derived from dichloroacetic acid. This antibiotic binds with the conserved sequences of the 23S r-RNA of the 50S subunit at the *peptidyl transferase* cavity and prevents the binding of t-RNA to the A site of the ribosome (Yoneyama and Katsumata 2006; Vannuffel and Cocito 1996).

Macrolides

Macrolides contain macrocyclic lactone ring and hence the name. Almost all members of this group are isolated from Streptomyces, and erythromycin is the best-known member of this group. Macrolides interferes with the early stage of protein synthesis, translocation, by targeting the conserved sequences of 23S r-RNA of 50S subunit and binds within the nascent peptide exit tunnel (NPET) adjacent to the peptidyl transferase centre and results in premature detachment of the newly formed incomplete peptide chains (Strohl 1997; Leach et al. 2007). Along with macrolides, linocosamides and streptogramins B also exhibit similar mechanism (Yoneyama and Katsumata 2006; Wise 1999).

Oxazolidinones

Oxazolidinones are compounds containing 2-oxazolidine, exhibiting good activity against Gram-positive bacteria. Oxazolidinones are a relatively newer group of antibiotics which are completely synthetic and act by interfering with protein synthesis at multiple stages like binding to 23S r-RNA of the 50S subunit and suppressing 70S inhibition and interact with peptidyl-t-RNA (Lambert 2005; Bozdogan and Appelbaum 2004; Strohl 1997; Leach et al. 2007).

14.3.3 Inhibitors of DNA Replication

14.3.3.1 Quinolones

Fluoroquinolones (FQ) inhibit DNA gyrase, the enzyme that nicks the double-stranded DNA, and introduces negative supercoils and reseals the nicked ends. They thus prevent the positive supercoiling essential for the transcription or replication of the strands. DNA gyrase enzyme consists of four chains – two A subunits and two B subunits. The A subunit is responsible for creating the nick in the DNA strand,

while B subunit adds the negative supercoils and the other A subunit reseal the strands. FQs have high affinity to A subunit and perform strand cutting and resealing. In Gram-positive bacteria, topoisomerase IV is the enzyme responsible for nicking the DNA strands, and it shows high affinity towards FQs. Hence, FQs have more potency against Gram-positive bacteria. In mammals, the homologous enzyme for DNA gyrase is topoisomerase II, which has very low affinity for FQ (Yoneyama and Katsumata 2006; Wise 1999; Higgins et al. 2003; Strohl 1997).

14.3.4 Folic Acid Metabolism Inhibitors

14.3.4.1 Sulfonamides and Trimethoprim

These antibiotics interfere with the folic acid metabolism pathways. Sulpha drugs and trimethoprim act on the folic acid metabolic pathway at two different steps. Sulphonamides have high affinity towards dihydropteroate synthase and inhibit it competitively compared to its natural substrate p-amino benzoic acid. Trimethoprim on the other hand inhibits dihydrofolate reductase, which catalyses a step much farther to that of dihydropteroate synthase (Yoneyama and Katsumata 2006; Tenover 2006; Straus and Hancock 2006).

14.4 Mechanisms of Antimicrobial Resistance

14.4.1 Prevention of Accumulation of Antimicrobials

This is achieved by either decreasing the uptake of the drug or increasing the efflux from the cell by changing the permeability of the outer membrane. Bacterial cells uptake materials from the outside by diffusion through porins, diffusion through the plasma membrane or by self-uptake. Porins are located on the outer membrane of Gram-negative bacteria and admit small hydrophilic molecules to pass through it. As the number of porins on the outer membrane decreases, the organism develops resistance against antibiotics that gain entry into the cell through them. β -lactam antibiotics and FQ resistance to Gram-negative bacteria is due to this process (Fig. 14.4).

14.4.1.1 Efflux Pumps

Efflux pumps are the membrane proteins that export the antibiotics from the interior of the cell to outside. The resistance of the organism against an antibiotic is determined by the efficiency of the efflux pumps (Džidić et al. 2008). Some resistant strains have developed speedy efflux pumps, which pump out the antibiotics at the

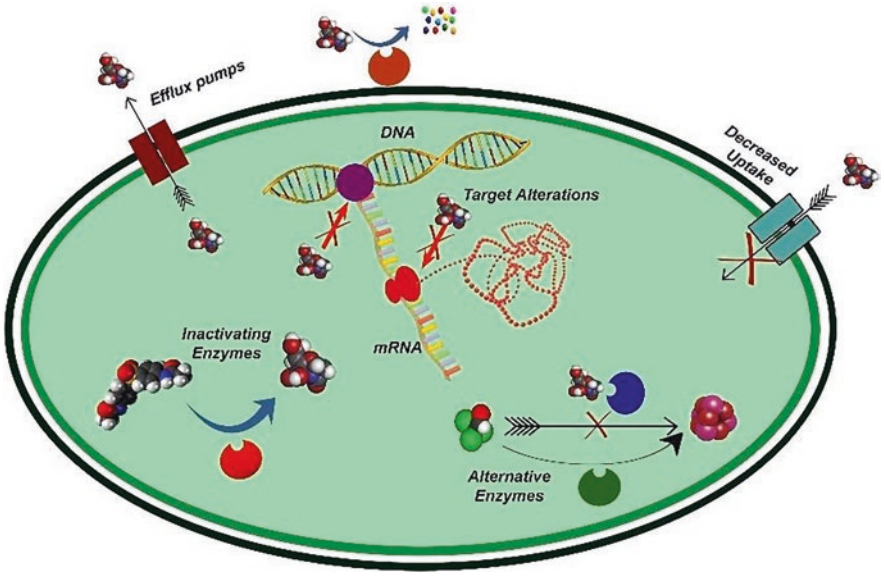

Fig. 14.4 Mechanism of antibiotic resistance in bacteria

same rate as they enter the cells and prevent the drugs from reaching their targets (Nikaido 1994; Kumar and Schweizer 2005). These pumps are located on the cytoplasmic membrane as compared to porins which are present on the outer membrane. Efflux pumps can be specific to a particular antibiotic, but most of them are multidrug transporters capable of pumping out wide range of unrelated antibiotics (Nikaido and Zgurskaya 1999; Webber and Piddock 2003).

14.4.1.2 Modification of Target Molecule

The binding of the antibiotic molecule to its target site is governed by the symmetry and dynamics of the interaction. Any natural or acquired change in the target molecule could hamper the effective drug interaction. A bacterium can acquire the change in target molecule through mutations in bacterial genes. Alterations in the 30S and 50S subunits can lead to resistance to antibiotics that affect protein synthesis like macrolides, chloramphenicol etc. Modification of PBP is another mechanism for resistance favoured by Gram-positive bacteria. It creates decreased affinity of the β -lactam antibiotics to the PBP (Mobashery and Azucena 1999; Lambert 2005). β -lactamase production is the complementary mechanism adopted by Gram-negative microbes for resistance. *E. faecium* resistance to ampicillin, Streptococcus pneumoniae resistance to penicillin etc., are mediated through this mechanism. Cell wall precursors are changed by mutations by certain bacteria. Antibiotics that inhibit cell wall synthesis are performed by binding to the D-alanyl-D-alanine moieties of peptidoglycan. Changing the D-alanyl-D-alanine to D-alanyl-lactate prevents

glycopeptides cross linking (Džidić et al. 2008; Grundmann et al. 2006). *E.faecium* and *E. faecalis* develop resistance through this mechanism. Mutation to DNA gyrase and topoisomerase IV genes produces defective enzymes that leads to replication failure and prevents antibiotics like FQ to bind. Ribosomal protection mechanisms and RNA polymerase mutations also impart resistance to bacterial strains (Kapoor et al. 2017).

14.4.1.3 Antibiotic Inactivation

Chiefly there are three enzymes that inactivate antibiotics – β-lactamases, aminoglycoside-modifying enzymes and chloramphenicol acetyltransferases (Alekshun and Levy 2007). β-lactamases hydrolyse β-lactam ring containing ester and amide bond like penicillin, cephalosporins, monobactams etc. Aminoglycoside modifying enzymes like phosphoryl-transferases, nucleotidyl-transferases and adenylyl-transferases reduce affinity to bind to 30S ribosomal subunit and generate resistance to multiple organisms (Maurice et al. 2008; Strateva and Yordanov 2009). Chloramphenicol-acetyl-transferases is another mechanism to build resistance to the antibiotic chloramphenicol (Tolmasky 2000). These enzymes present in some Gram-positive and some Gram-negative organisms along with few *Haemophilus influenza* strains acetylates hydroxyl groups of chloramphenicol making them unable to bind to the 50S subunits of ribosomes.

WHO has warned that several of the infectious diseases will become incurable due to resistance.For overcoming these several other treatment strategies have been scientifically developed. Here we list the major classes of alternatives for antibiotic treatment through non-antibiotic treatments to control infections.

14.5 Non-antibiotic Treatments for Infections

- Phage therapy
- Bacteriocins
- Killing factors in microbes
- Antibacterial activities of non-antibiotic drugs
- Quorum quenching

14.5.1 Phage Therapy

Phages are a group of viruses that have the capability to infect and kill bacteria. The first mentioning on phages was done by Ernest Hankin in 1896 and later the name bacteriophage was coined by Felix d'Herelle. Among all the different methods of

non-antibiotic treatment of infections above, phage therapy is the only treatment that entered clinical trials and was produced in large scale for the purpose of treatment during the 1940s. Humans are administered with phages orally, rectally, locally, parenterally as intravenous injections or through respiratory passages as aerosols or intrapleural injections (Sulakvelidze et al. 2001). Today, phage therapy is not considered as an armamentarium against bacterial infections in almost all parts of the world. One reason for its declined used is attributed to the early introduction of phage therapy before understanding its purpose. The advent of stronger and newer antibiotics pushed phage therapy to the verge of extinction (Kutter et al. 2010).

Bacteriophages replicate inside the bacterial cells following two major pathways:

1. Lytic module
   Lytic pathway involves the following steps:
   (a) Attachment of the phage on to the bacterial wall
   (b) Injection of its DNA inside the host cell
   (c) Termination of the synthesis of bacterial cell components
   (d) Phage DNA replication and formation of new phage capsids
   (e) Assembly and release of phage components by lysis of the host cell.
2. Lysogenic module

In this pathway the initial steps of attachment and inoculation of the phage DNA into the bacterial host cell are similar to that of the lytic pathway. In the third step, the phage DNA will anneal on to the host chromosome and gets integrated (lysogenization), and the replication of the phage DNA occurs along with the replication of bacterial DNA for subsequent several multiplications (Prophage). The prophages after several cycles of multiplication free themselves from the bacterial genome and induce the bacterial genome to synthesize phage components, which are released after the lysis of the bacterial cell. Phages inhibit bacterial restriction enzyme through genome modification (Andriashvili et al. 1986). As this infection cycle can go on for several lifecycles, lysogenic phages are not ideally used for phage therapy (Lorch 1999).

Phage therapy had not been successful in combating bacterial infections as the scientists were more concerned with the application of the phages while the clinical data pertaining to their use were completely ignored. As the phages replicates inside the bacterium host, they exhibit the interesting phenomena of self-dosing. Phages are highly specific about their host and due to this reason, its usage was relatively safe as the friendly micro flora of the body is spared from the attack of the phages. But this also has a disadvantage that the causative agent of the disease needs to be identified properly before dosing. This specificity is lacking in the case of antibiotics and they became more popular than the phage therapy in the years that followed. The most feared complication from phage therapy is the release of endotoxins by the bacteria lysed by the phages. Even though phage therapy took up gradually crossing many geographical restrictions, none of its advocates recognized the role bacterial immunity. The bacterial immune responses are of two kinds – the innate

and adaptive responses. The distinction between and the self and non-self-DNA through the restriction modification forms the innate response. This is achieved on the basis of the DNA methylation pattern and on the lack of phage replication machinery. The adaptive immunity in bacteria was discovered with the identification of CRISPR (Clustered regularly interspaced short palindromic repeats) sequences. CRISPR-mediated immune response involves complex processes like gene silencing mechanism (Brouns et al. 2008; Barrangou et al. 2007; Hale et al. 2009).

14.5.2 Bacteriocins

Bacteriocins are peptides which are bactericidal, produced by bacteria belonging to several groups which is evolved for eliminating competition from other strains. *E. coli* strain V produces a dialyzable and heat-stable compound called colicin V that inhibits the growth of coliphages (*E. coliφ*) at very low concentration. The use of bacteriocins is not extensive in clinical infections but limited to food preservation (Cleveland et al. 2001; O'sullivan et al. 2002). Application of bacteriocins are seen in food industry, where the probiotic microorganisms used in packaged foods secretes bacteriocins and prevents the growth of harmful bacteria. Bacteriocins are of four major types; Class I (antibiotics) are <5 kDa small heat-resistant peptides; class II are <15 kDa small heat-stable, membrane-active and unmodified peptides; class III consists of heat-labile proteins with size >15 kDa and class IV bacteriocins are lipid or carbohydrate moieties bound to it (Sablon et al. 2000; Garneau et al. 2002; Klaenhammer 1993). Bacteriocins exert inhibitory action mainly on Gram positive bacteria than Gram-negative, as they possess an outer membrane made mainly out of lipopolysaccharides (LPS). This outer membrane provides an evolutionary advantage of preventing free diffusion of molecules heavier than 0.6 kDa. The smallest known bacteriocin is of about 3 kDa size. Bacteriocins act by binding to the cell membrane and alter their osmotic stability leading to cell death (Cotter et al. 2013). Even though Gram-negative bacteria evades the action of bacteriocins, some of them gain entry to the cell interior through specific receptors over the outer membrane like OmpF, FhuA or over the inner membrane like SbmA, YejABEF and TonB. Absence of the outer protective LPS layer makes Gram-negative bacteria more susceptible to bacteriocins leading to cell death (Stevens et al. 1991). The mode of mechanism of bacteriocin is doubtful yet it is postulated that they bind to the lipid-II, which is essential for the transport of peptidoglycan subunit from cytoplasm to cell wall, thus interrupting the synthesis of cell wall leading to cell death. Several other mechanisms have also been postulated regarding the mode of action of bacteriocins; they include pore formation in cell wall using lipid-II as a docking molecule, de-energizing membrane and dissipating proton motive force, preventing uptake of amino acids and triggering their release from the cell, excluding potassium ions, depolarizing cytoplasmic membrane, hydrolysis and partial efflux of cellular ATP (Cotter et al. 2005; Abee et al. 1994). The advantage of bacteriocin use is

that they do not harm the beneficial microbiota of the body, but they are effective only against a small group of bacteria. Bacteriocins are short-acting than antibiotics, due to action of proteolytic enzymes on them which easily converts them to non-toxic amino acids. This can be overcome by the using dendrimers that prevent their degradation and deliver them at the site of infection (Tam et al. 2002; Bracci et al. 2003). Resistance development is another negative aspect of bacteriocin that limits its activity. Bacteriocin resistance is acquired through the immunity gene present in bacterial strain or through alteration in gene expression.

14.5.3 Killing Factors

Killing factors are the factors released by bacterial cells to kill sibling cells during starvation. This phenomenon was noticed in *B. subtilis* and is named as "cannibalism". "Cannibalism" is exhibited through a set of genes that induce lysis of their sister cells in their milieu during nutrient scarcity (Nandy et al. 2007). The lysed cells provide the nutrients for the killer cells for their survival and spore formation. *B. subtilis* exhibits predation rather than cannibalism, that is, it lyses the bacterial cells of other species. The feature of cannibalism is due to two peptides – sporulation delaying protein and sporulation killing factor. Killer *B. subtilis* cells preferentially target non-*B. subtilis* cells. This shows the antibiotic action of killer peptides (Burbulys et al. 1991).

14.5.4 Antibacterial Activities of Non-antibiotic Drugs

The drugs that are developed to treat non-infectious diseases but having antimicrobial activities are called non-antibiotics (Williams 1995; Lind and Kristiansen et al. 1990). They are effective against some Gram-negative bacteria, Gram positive bacteria, viruses, fungi, protozoa etc. (Jones 1996). Barbiturates, diuretic drugs, beta-adrenergic receptor antagonists, antihistamines, mucolytic agents, non-steroid anti-inflammatory drugs, proton pump inhibitors and psychotherapeutic drugs are studied in this regard. Alteration of cell permeability is considered as their mode of action in this regard. Alternative mechanisms like affection of efflux pump of microbes, cross-membrane ion transport, cell energy transport and activity of membrane-bound enzymes are also studied (Cederlund and Mårdh 1993). The concentration at which these drugs produce their activity is much higher than the physiologically observed dose. The combination of nonantibiotic drug with antibiotics may make the resistant bacteria susceptible to the non-effective drug. The combination of beta-lactam with phenothiazines when administered to beta-lactam-resistant microorganisms like MRSA makes them sensitive (Amaral and Kristiansen 2000). The advantage of such an approach is that the physiological impacts of the drugs involved are well established.

14.5.5 Quorum Quenching

Quorum quenching is the process of communication between bacterial cells through messenger molecules. It is established that such communication plays a significant part in the beginning of virulence mechanism. Two mechanisms in this regard have been recognized and analyzed (Nigam et al. 2014). First type involves recognition of signal by means of cytosolic transcription factor while in the second type it is facilitatedvia an auto inducing recognized through a membrane receptor. Any microbe can own either type of quorum sensing system or both. The former form of quorum sensing is facilitated by derivatives of acyl homoserine lactone while the auto inducing system involves peptides. It is assumed that if this signalling is weakened, the virulence of microbes can be controlled without selection pressure. It is known that selection pressure leads to the development of new drug-resistant microbes. Therefore, this method that hinders the spread of microbes without imposing selection pressure may be crucial to prevent evolution of drug-resistant microbes. Quorum quenching is achieved either through mimicking of quorum sensing molecules that compete with analogous quorum sensing molecules or through inhibiting enzymes involved in synthesis of quorum sensing molecules. The report of Triclosan as an anti-bacterial agent inhibiting enoyl-ACP reductase which produces an important intermediate in AHL biosynthesissupport this mechanism (Hoang and Schweizer 1999). The important advantages of quorum sensing inhibitors are that it limits evolution of new drug-resistant forms as well as virulence and bio-film formation (Czajkowski and Jafra 2009).

14.6 Mechanisms of Antibacterial Activity of Nanoparticles

Mainly three mechanisms have been identified as the modes of action of nanoparticles in killing the microbes. They are as follows: (1) due to direct intake of nanoparticles, (2) reactive oxygen species (ROS) production and (3) disruption of cell wall by nanoparticles.

14.6.1 Direct Absorption of Nanoparticles

Studies have shown that nanoparticles of silver (AgNPs) leach out silver ions when it comes in contact with the body fluids due to variation in the pH. These silver ions have high affinity towards enzymes containing thiol group rich amino acids like Cysteine. Thus, they have high affinity towards respiratory (NADH dehydrogenase) and electron transport group of enzymes (Prasad and Swamy 2013; Swamy and Prasad 2012). This interaction results in the uncoupling of the ATP molecule from the respiratory chain. They create a phosphate deficient environment inside the

bacterial cell by actively efflux phosphate ions and at the same time reduces their reuptake. They reduce proton motive force resulting from the loss of protons due to the binding of silver ions to the various transport proteins. They are also shown to increase the frequency of DNA mutations during the translation process and in leakage of intracellular contents from cytoplasm retrenchment and cell membrane degradation.

14.6.2 Reactive Oxygen Species (ROS) Production

ROS are formed as by-products of all metabolic pathways inside the cells of all respiring organisms. There are several inbuilt mechanisms in organisms to tackle this life-threatening escalation of ROS. Antioxidant defence mechanisms like glutathione, glutathione disulphide, reduced glutathione, glutathione peroxidases and peroxiredoxins play an important role in quenching the surge in oxidative stress. Excessive production of ROS brings in damages to the lipid bilayer of membranes, dysfunction of mitochondria and DNA damage. Metals in general and silver ions in particular catalyses ROS generation in the presence of oxygen dissolved in milieu. The generation of ROS is done either by inactivating the respiratory chain enzymes or the superoxide dismutase which scavenge the superoxide radicals or by a combined mechanism of both. Thiol group binding and inactivating metal ions thus provide significant antibacterial effect.

14.6.3 Cell Wall Damage

The low size of the metal ions and their electrostatic attraction to the negatively charged cell membrane allows them to easily adhere to them and penetrate to create pits by releasing lipopolysaccharides and proteins from them. This varies the permeability of the membrane by releasing muramic acid by binding to the N-acetylmuramic acid and N-acetylglucosamine of the peptidoglycan strands (Feng et al. 2000; Sondi and Salopek-Sondi 2004; Morones et al. 2005; Song et al. 2006).

14.7 Nanomaterials in Controlling Infections

Reducing the size of the particles to nanoscale has the advantage of easily surpassing the natural biological barriers inside living systems owing to their high surface-to-volume ratio. Nanosize of particles having high surface-to-volume ratio permits them to surpass the barriers to biological systems and molecules. Molecular interactions could be enhanced by manipulating the size, shape and chemical characteristics of the nanomaterials (Kim et al. 2010) and can be utilized as therapeutic and

diagnostic agents in the form of vehicles. Nanotechnology could be used to overcome the bacterial resistance by creating new and improved antimicrobial agents. The use of nanomaterials in infectious diseases can be discussed under the following headings (Blecher et al. 2011);

- Drug delivery systems
- Drug infused nanoparticles
- Immunomodulation

14.7.1 Nanotechnology-Based Drug Delivery Systems

14.7.1.1 Chitosan

Chitosan is a biopolymer made of natural polysaccharide exhibiting polycationic interactions with negatively charged microbial cell wall and other cytoplasmic membranes leading to the disruption of the cell membrane and subsequent leakage of intracellular elements from deranged osmotic stability.They also have the capability to enter the nucleus of the bacterial cell and other microorganisms like fungi and bind to the DNA and thus inhibits the mRNA and protein synthesis (Ma et al. 2008; Qi et al. 2004). Chitosan molecules have high affinity towards bacteria and fungi due to their relatively higher surface-to-charge ratio and surface charge density. Hence, they exhibit greater antimicrobial activity against Gram-positive as well as Gram-negative organisms. Thus, they exhibit antimicrobial activity against the most notorious pathogens like *E. coli* and *Staphylococcus aureus*. (Banerjee et al. 2010; Sanpui et al. 2008). Chitosan is derived from a natural substance, chitin, which is the structural ingredient of the exoskeleton of crustaceans. Studies have shown that the chitosan nanoparticles are more efficacious than chitosan alone or antibiotics like doxycycline. Its polycationic characteristic and high affinity towards metals are utilized in engaging it along with several other nanoparticles like metallic NPs (copper and silver), nitric oxide releasing nanoparticles and drug containing NPs used for targeted drug delivery and as carriers (Qi et al. 2004). Chitosan also escalates the antimicrobial property of these nanomaterials. In experimental models, silver nanoparticles-embedded membranes increased their zone of inhibition when incorporated with 70% of chitosan. Similarly, incorporation of chitosan in silver nanoparticles decreased the mean inhibitory concentration (MIC) against *S. aureus* (Ma et al. 2008).

14.7.1.2 Metallic Nanoparticles

Silver

Silver is traditionally used as an antimicrobial agent in treating conditions like burns and wounds. It is believed that silver ions on gaining entry into the bacterial cell wall and membranes target the DNA, respiratory enzymes and other proteins

containing sulphur or thiol groups resulting in loss of capability to replicate and finally cell death results (Aziz et al. 2014, 2015, 2016, 2019). Silver nanoparticles (Ag-NP) are attributed with small size and large surface area, and this makes them capable of easily penetrating the bacterial cell wall and other biological membranes (Rai et al. 2009; Pal et al. 2007; Ruparelia et al. 2008; Prasad 2014). Thus, the nanoparticle size is proportionated with its antimicrobial activity; smaller the size, greater the effect. Shape of the nanoparticles also influences its activity. Small triangular and truncated nanoparticles are more efficacious than round or rod-shaped particles. Hence, small and triangular nanoparticles (<10 nm) exhibit more antimicrobial efficacy than large round or rod-shaped nanoparticles (Pal et al. 2007). Ag-NPs thus exhibit a very varied antimicrobial property against viruses, bacteria and fungi due to their surface interaction. Several bacterial species belonging to both Gram-negative and Gram-positive strains succumb to them. This wide range of activity is achieved at relatively lower concentration of Ag-NPs than the conventional silver preparations. This paves way to lower dosing and lesser toxicity from silver. These conclusions are relatively theoretical and studies pertaining to the toxicity of Ag-NPs are yet to be unravelled. Ag-NPs also exhibit synergism with other antibiotics. This is another area of interest in Ag-NP research. Activities of penicillin G, amoxicillin, erythromycin, clindamycin and vancomycin increased against organisms like *S.aureus* and *E. coli*. Among these agents, erythromycin showed the greatest inhibition. As Ag-NPs exhibit wide range of targets, microorganisms should develop multiple, simultaneous compensatory mutations to develop resistance. Hence, Ag-NPs can overcome bacterial resistance against antibiotics and at the same time enhance their efficacy (Sanpui et al. 2008). Owing to these qualities Ag-NPs find its application in medical devises that constantly come in contact with body fluids and poses a threat to infection by serving as acoatings on them to prevent microbial colonization, in wound dressings and in enhancing the potency of antibiotics.

Copper

Copper has been less engaged as an antimicrobial agent when compared to silver. Yet its use as an antifungal agent is well documented in history as early as the nineteenth century (Cioffi et al. 2005). Copper oxide as a nanomaterial has recently gained importance due to its cost effectiveness and compatibility with other polymers. Yet copper oxide nanoparticles (CuO-NPs) are inferior to Ag-NP in their antimicrobial property against *E. coli* as well as methicillin-resistant *S.aureus* (MRSA) (Ruparelia et al. 2008; Ren et al. 2009). But they are found to be more efficacious against *B. subtilis*, which is attributed to the copper's affinity to amine and carboxyl groups on the cell surface of these pathogens (Ruparelia et al. 2008; Yadav et al. 2017). Compared to Ag-NPs, CuO-NP exhibit a broader range of activity, especially against fungi. Copper loaded nanoparticle laden polymer thin films demonstrated significant antifungal activity against *S. cervisiae* yeast, moulds and bacteria including *E. coli, S. aureus* and *Listeria monocytogenes*. They significantly reduced the

number of colony forming units (CFUs) especially in *S. cervisiae*, where no CFUs were noted (Cioffi et al. 2005). These results project out the biostatic property of CuO-NPs. On comparison with silver, CuO-NPs exhibit broader range of antimicrobial activity and weaker activity against most of the bacteria, they are strong antifungal agents and are capable of preventing surface microbial colonization especially on medical instruments.

Titanium

Titanium dioxide (TiO_2) has gained importance as a nanomaterial recently due to its activation on exposure to ultraviolet light forming active oxygen species, a process termed as photocatalysis. The family of active oxygen species generated includes hydrogen peroxide and hydroxyl radicals. They are responsible for obliterating the bacterial cell membranes resulting in cell death (Kim et al. 2003). This property of TiO_2 nanoparticles (TiO_2-NP) has been engaged in water and air purification and their activity against pathogenic opportunistic microorganisms (Martinez-Gutierrez et al. 2010). TiO_2-NP infused thin film composite membranes has been recently shown to have significant antimicrobial activity and prevents bacterial attachment to membrane surface and formation of *E. coli* biofilm on medical instruments by disrupting the bacterial cell membrane (Martinez-Gutierrez et al. 2010). Researches has been conducted by coupling TiO_2-NP with Ag-NP for their antimicrobial property. Even though TiO_2-AgNPs proved less efficacious than TiO_2 alone or Ag-NP alone, against their activities against Gram-positive bacteria, Gram-negative bacteria and various fungi responsible for opportunistic infections and colonization of medical devices, they showed more pronounced activity against several strains of fungi of medical importance. These results highlight that it might be more beneficial to combine metal nanoparticles to augment the antimicrobial activity.

Magnesium

Several non-metals like chlorine, bromine and iodine has been traditionally used as antibacterial agents, but their toxicities limit their use especially in medical conditions. Their antimicrobial property is due to the formation of covalent metal-halogen complexes that interact with specific cellular enzymes or through oxidative stress leading to lipid peroxidation ending in the leakage of intracellular contents culminating in cell death (Lellouche et al. 2009). Magnesium- halogen nanoparticle also exhibit antimicrobial activity through the same pathway. Magnesium oxide has a unique place among them as they easily adsorb and retain halogens and at nanoparticle level, these activities increase fivefold. Other advantages of this compound are that, as they bind with halogens, the compound gets converted to powder form which helps in easy handling. Magnesium – halogen nanoparticles are found to be more effective against endospores of different bacterial strains like *E. coli*, *B.*

megaterium and *B. subtilis*. Among them *E. coli* and *B. megaterium* are highly susceptible to MgO-halogen nanoparticle with complete destruction of entire endospores in less than 20 minutes. Several combinations of Mg-halogen combinations have been investigated for their antimicrobial activity. MgF_2-NPs also showed similar antibacterial effect comparable to MgO-halogen nanoparticles. MgF_2 – NPs exhibited dose-dependent inhibition of growth of *E. coli* and *S. aureus* and also inhibited biofilm formation on medical devices.

Zinc

Zinc oxide (ZnO) is another compound of interest in the field of antibacterial effect. It is the compound which is approved by FDA with respect to its antibacterial as well as safety profiles. Zinc oxide nanoparticles (ZnO-NPs) are demonstrated to be effective against major food-borne pathogens like *E. coli* O157:H7, *Listeria monocytogenes* and *Salmonella* spp. (Jin et al. 2009). ZnO-NPs are found to inhibit the growth of *E. coli* O157:H7 in a dose-dependent manner (Liu et al. 2009). Their antimicrobial action is attributed to membrane binding leading to lipid and protein destruction on membranes. This leads to altered membrane permeability and leakage of intracellular contents. These pathological changes are initiated by the generation of reactive oxygen species (Bhuyan et al. 2015).

14.7.1.3 Nitric Oxide – Releasing Nanoparticles

Nitric oxide (NO) has been identified as a molecule with varied physiological functions in the body. Several phagocytic cells like macrophages enhances the production and release of NO on stimulation through the transcription of inducible nitric oxide synthase (iNOS) (Englander and Friedman 2010). The NO thus released demonstrate antimicrobial activity by either of the several mechanisms identified like direct microbial DNA damage through generation of peroxynitrite, inactivation of zinc metalloproteins and interfering cellular respiration or by stimulating innate antimicrobial pathways that enhances host immune response. Also, there are research reports on the activity of NO as a wound healing agent. Considering these properties, a nanomaterial system has been created that donates or delivers NO to the site. NO – releasing nanoparticles (NO-NPs) entraps NO in a dry matrix and releases gaseous NO free radicals on exposure to moisture. This is utilized as a topical agent for promoting wound healing and preventing infections. NO–NPs can easily be applied on skin and ensures sustained delivery to the affected areas over prolonged period of time. These nanomaterials have been tested against *S. aureus*, *Acinetobacter* and MRSA – infected wounds and showed accelerated wound closure and decreased microbe burden (Martinez et al. 2009).

14.7.1.4 Drug – Infused Nanoparticles

Intracellular infections from organisms like *Salmonella*, *Listeria* and *M. tuberculosis* are difficult to eliminate due to the advantage they achieved from highly evolved evolutionary mechanisms like escaping phagosomes, phagosome–lysosome fusion inhibition and their ability to stay dormant (Pinto-Alphandary et al. 2000). These mechanisms downregulate several drug targets. Complicating the scenario is the fact that several antibiotics cannot penetrate intracellularly to act on these microorganisms. In such conditions, nanoparticles and liposomes are devised as potential drug carriers as they get endocytosed into phagocytic cells carrying intracellular pathogens. Several antibiotic-encapsulated liposomes are developed to deliver antibiotics like β-lactams like penicillin, ampicillin and cephalosporins, macrolides, aminoglycosides and fluoroquinolones for enhanced bacterial killing. Ampicillin-encapsulated liposomes against *Salmonella*, liposome-encapsulated tobramycin against *P. aeruginosa* and amphotericin B-encapsulated liposome against moulds and yeasts have been studied (Fattal et al. 1991). In spite of their success as a promising drug delivery system, there are limiting factors that impede their application in medicine. Some of the highly discussed limitations are their size, charge, purity, solubility of contents, stability, antigenicity, biocompatibility etc. There are two ways to deliver the drug to its target site by the nanocarriers – passive and active targeting. In passive targeting, nanocarriers are transported through the inter-endothelial cell spaces on the neovascularized vessels of the tumour mass or through the fenestrations on the vessels at the sites of inflammation. Passive transport is dependent on the plasma permeability and their time of retention. In the case of active targeting, nanocarriers are transported based on the receptor–ligand interaction, and this requires fenestrae or specific receptors. Change in the pH of the medium or a sudden oxidative burst can facilitate the delivery of the drug to its required target. Locally they can be transported with the aid of magnetic guidance and radio frequency-mediated delivery.

14.7.1.5 Immunomodulatory Effects

The immune system helps the body to fight against foreign substances including pathogens. It is broadly classified into innate and adaptive systems. The nonspecific immune response is termed innate immune response, which involves the recognition of the pathogen-specific molecular patterns (PAMPs) of the invading pathogens (Plummer and Manchester 2011). Antigen presenting cells (APCs) engulf the pathogen after the PAMPs have been recognized by the pattern recognition receptors (PRPs) present on cells. The cascade of events following the APCs engulfing and presenting the antigens to the cells of the adaptive immune system culminates in the activation of CD4 and CD8 lymphocytes subsequent to the induction of T and B cells (Plummer and Manchester 2011). The entire machinery works on an integrated and coordinated network of events mediated by cytokines which decides on the type of response to each pathogen. For example, Interferon gamma activation

promotes T helper type 1 (Th1) response while Interleukin-4 (IL-4) and IL-5 activation results in a Th2 response (Sun et al. 2009). A synchronized interaction between APCs, T and B cells and inflammatory cytokines is essential for a functionally robust immune system.

Vaccines play an integral part of infectious disease control and require a balanced stimulation of both innate and acquired immune systems. Vaccines basically belong to either of the three categories viz., live attenuated, killed or fragmented (subunit) vaccines. With respect to the fairness of immunogenic response generated, live attenuated vaccines are the best, but they pose a threat of reactivation and attaining virulence inside the host. While killed and subunit vaccines are devoid of this threat, their immunogenicity is very poor, requiring repeated dosing and thereby increasing the cost. Since a trained personnel is essential to administer a vaccine in the form of injection, vaccine coverage is decreasing in many countries in spite of a global intervention. Mucosal application with the help of nanotechnology is one alternative to overcome this hurdle. There are several barriers to cross for the vaccine to reach the APC and induce a strong enough immune response. In intranasal or inhalational vaccines, the vaccine components should be smaller (< 5um) and not to be cleared by the exhalation (Chadwick et al. 2010). As the size specified is in accordance with that of a nanomaterial, nanoparticles are capable enough to modulate and influence the immune system at various levels of interaction. Nanoparticles can thus augment the efficacy of both oral and injected vaccines by enhancing the vaccine exposure time to the immune system as well as an increase in the uptake of antigens by APCs (Bal et al. 2010). Thus they improve the immune response to microbes like viruses and bacterial components and also lead to a more controlled and modified cytokine response (Huang et al. 2010).

14.7.2 Nanotechnology-Based Vaccines and Immunostimulatory Adjuvants

14.7.2.1 Synthetic Polymers

Polymeric nanoparticles are utilized as carriers for different vaccines like DNA vaccines and for proteins as well. Choice of nanomaterial is based on the requirements of the vaccine. Poly ε-caprolactone polymers are used to overcome the physicochemical differences in the digestive tract in the case of oral vaccines. Multicomponent particles are created encapsulating DNA in a PCL microparticle and this system is named nanoparticle-in-microsphere hybrid oral delivery system (NiMOS). The central core of NiMOS is susceptible to proteolytic degradation while the exterior is susceptible to lipase digestion. As the particles transit through the gut, the outer coat survives the proteolytic degradation and as they reach the intestines, got acted on by lipases and release the inner gelatinous core containing the vaccine which gets absorbed from the intestines and produce the antigenic effect. Many of the synthetic polymers used for vaccine delivery are found to be

non-immunostimulatory. Poly(lactide-co-glycolide) (PLGA) particles does not lead to the rise in pro-inflammatory cytokine levels even after being taken up by the macrophages. But they produced stronger and sustained IgG response when encapsulating plasmid DNA owing to the stability of PLGA nanoparticles during their delivery into appropriate cells. This highlight the fact that nano polymers alone cannot be used as immunostimulants, but they can enhance immunization when they cross the mucosal barriers. A polymeric nanoparticle, Polymethyl methyl methacrylate (PMMA) is highly immunostimulant when administered as a vaccine adjuvant. It increased the antibody titre to 100-fold in HIV2 virus vaccine in animal models and also exhibited enhanced IgG and IgM antibody production against ovalbumin. Several other nanomaterials have also shown immunomodulatory activity for example; Carboxyfullerene nanoparticles increased immunologic activity by neutrophil activation resulting in microbial death in a *S. pyogenes* infection model in mouse. Some nanoparticles enhanced immune responsiveness in conjunction with Toll-like receptor agonists. PLGA NP modified with tetanus toxoid and MUCI lipopeptide (a TLR ligand) showed significant T cell activation and responsiveness in comparison to PLGA NP and tetanus toxoid or MUCI lipopeptide alone (Diwan et al. 2003).

Polymeric oligonucleotides of DNA or RNA termed Aptamers, which folds in 3-dimensional configuration with high affinity to target proteins, peptides or small molecules of drug or vitamin showed pronounced antimicrobial activity, inhibition of HIV reverse transcriptase and vaccinia virus replication and to overcome β-lactamase resistance in Gram-positive and Gram-negative bacteria. Aptamers are selected from random nucleic acid libraries and technologies are now available to prepare them with highest degree of purity, stability and selectivity.

14.7.2.2 Nanoemulsions

Nanoemulsions constitute lipophilic or hydrophilic substances dispersed as either water-in-oil or oil-in-water forms. Such carrier systems are engaged in vaccine delivery through mucosal barriers as they are easily endocytosed by the surface cells of the mucosa and easily presented to the APCs. Nanoemulions have also showed good immunostimulatory effect. The hepatitis B vaccine currently in use is given as an IM injection of recombinant hepatitis B surface antigen (HBsAg), containing aluminium salt (alum) as an adjuvant. Alum stimulates a Th2 immune response in the host with an ineffective CD8 response to the virus infected hepatocytes. Alum is also responsible for other complications like the formation of erythema and nodules over the injection site. On the contrary, recombinant HBsAg nanoemulsion (HBsAg – NE)-based intranasal vaccine produces an effective Th1 response in the host without any chance for local inflammation (Muttil et al. 2010). They are also capable of producing comparable levels of IgG antibody body level and significant levels of mucosal IgA antibodies as well. Nanoemulsion vaccines are also being tried for inactivated influenza and vaccinia virus infections.

14.7.2.3 Immune Stimulating Complexes

Immune-stimulating complexes (ISCOMs) are carriers and immunostimulatory adjuvants, which are nanosized spherical micelles containing saponin-derived components like Quil A, derived from the tree bark Quillaja (Helgeby et al. 2006). They are efficient carriers easily taken up by APCs and can activate and upregulate the expression of MHC I and II on APCs, even in the absence of an antigen. The overall result of this is the induction of pro-inflammatory cytokines like IL1, IL6, IL8 and IFNχ. Carriers containing saponin-derived components produce Th1 type response, but this may change depending on the adjuvant carried (Sun et al. 2009). ISCOMs carrying Leishmania antigen induce a Th2 response. Studies on various antigens incorporated on ISCOMs are available including influenza, hepatitis B, herpes virus, *Helicobacter pylori* and *Corynebacterium* (Sun et al. 2009).

14.7.2.4 Cytidine-Phosphate-Guanosine (CpG) Motifs

Bacterial oligodeoxynucleotides containing unmethylated CpG motifs are used as vaccine adjuvants with good immunostimulatory activity. They lead to enhanced secretion of IL12, surface expression of MHC, Th1 recruitment and activation and secretion of IgG antibodies as they are recognized by the APCs. They are recognized by the APCs through the activation of Toll-like-receptor 9 (TLR-9). CpG motifs incorporated into a nanoemulsion of water-oil-water has inactivated influenza virus and induced strong and sustained immune response when compared to conventional vaccines.

14.7.2.5 Chitosan

Chitosan improved vaccine delivery in the case of oral vaccines, as it proved to be an efficient carrier system to transport vaccines across mucous membrane. It also find its use as an immune adjuvant as it promotes antigen uptake and cytokine production. When incorporated with the glycoproteins present over the surface of influenza virus like HA and NA, a pronounced immunological response in the form of high titres of serum IgG and mucosal IgA antibodies were observed after intranasal administration (Brunner et al. 2000). Escalated IgA levels are attributed to the relatively strong interaction of chitosan with the sialic acid residues over the mucin. This interaction results in the opening up of the mucosal tight junctions enhancing the mucosal membrane transport and vaccine retention time (Florindo et al. 2009). Chitosan has gained importance as vaccine adjuvants with immunomodulatory stimulation capability. N-trimethyl chitosan (TMC) nanoparticles coupled with ovalbumin and diphtheria toxoid where swiftly internalized by the APC of the skin, Langerhans cells, and induced a profound expression of CD83, CD86 and MHC-II in murine models on intradermal administration. Once they are internalized, the

antigens set free from the chitosan after lysosomal degradation, the immunological processes unfurl inside the body and the antigen will be presented to the T cells followed by a Th2-mediated antibody response. The antibody titre is higher than either of the antigen alone and this establishes its immunostimulatory effect as an adjuvant.

14.7.2.6 Metallic Nanoparticles

Every drug or gene transported in a nanoparticle should be well protected against the immune recognition by the host's body because of the activation of the innate immune response and subsequent inactivation of the drug. To a great extend this property is well exhibited by metal nanoparticles (Massich et al. 2009). Polyvalent oligonucleotide coupled with gold nanoparticle produced only 25% less macrophage activation evidenced by IFNβ when compared to lipid-complexed DNA.

14.8 Role of Nanomaterials in Other Diseases

14.8.1 Neurodegeneration

Neurodegeneration is defined as the destruction in the structure and function of neurons leading to their loss. This basic event cascades to a plethora of incurable pathological anomalies to central nervous system collectively called as neurodegenerative disorders which include Alzheimer's disease, Parkinson's disease, Prion disease, amyotrophic lateral sclerosis and Huntington's disease (Rubinsztein 2006). Neurodegenerative changes occur at different levels in the nervous system ranging from molecular level to systemic level. Distorted synaptic functions, a higher prevalence of intra-neuronal deposits resulting from misfolded proteins are some of the common events related with many neurodegenerative disorders, which helps in devising therapeutic modalities. Many more pathological events like genetic mutations, protein misfolding, protein aggregation, mitochondrial dysfunction, damage to the nucleic acid (DNA), structural and functional disruption of organelle membranes, neuronal and microglial apoptosis, autophagy and transglutaminase binding strongly influence the manifestation of neurodegenerative diseases. As neurodegenerative diseases occur during the later decades of life, the events leading to its manifestations ae attributed to mitochondrial DNA mutations and oxidative stress. Progression of neurodegenerative disease with advancing age is proportionated with the amount of neuronal loss and contributes a great deal of stress on the families emotionally, socially and financially. Considering the therapeutic challenges in neurodegenerative diseases, blood-brain-barrier (BBB) poses the greatest challenge. BBB represents a selectively semipermeable barrier between the nervous tissue and the blood compartments. It helps in the maintenance of neuronal cell functions, regulation of transport of nutrients and metabolites and the overall protection of the

brain tissue. It avoids the entry of large therapeutic molecules as well a small molecule drugs from entering brain. Carrier-mediated transporters like large neutral amino-acid transporter, glucose transporter (GLUT1), cationic amino-acid transporter (CAT1), adenosine transporter (CNT2) and monocarboxylic acid transport small molecules to brain (Pardridge 2003). Certain circulating blood elements like leukocytes, erythrocytes, neutrophils, and other cells like exosomes can cross BBB at a faster rate. Drug delivery utilizing these living cells and exosomes paved way to the discovery of novel chemotherapeutic drug delivery to treat disorders of brain. Curcumin loaded exosomes experimentally showed improved cognitive function in mouse. Receptor-mediated transcytosis (RMT) is the common modality now used to deliver chemotherapeutic drugs to brain tissue across BBB. Endogenous macromolecular neuropeptides including transferrin, hormones, lipoproteins and insulin reaches brain tissue through RMT from blood through specific receptors. RMT are expressed on the luminal side of the endothelial cells and they favour endocytosis and transcytosis of molecules across the BBB (Abdul Razzak 2019). In RMT, nanoparticles are utilized after surface modification to bind to the transmembrane receptor associated with its transport. Macromolecular drug delivery to brainrelated diseases can also be increased tremendously by delivering drugs directly into the brain tissue with the help of electrostatic interactions between nanoparticle, which bears a positive charge, and the negatively charged BBB membrane through a process termed adsorptive-mediated transcytosis (AMT). AMT does not interfere with the normal cellular physiology as other drug delivery methods do. Nanocarriers used to cross BBB are;

14.8.1.1 Metal Nanoparticles

Transition metals like Zn, Cu and Fe are present in a sufficiently large amount in the brain and they play a crucial role in their cellular physiology including the metalloenzyme function. They act as a therapeutic agent as well as an agent that carries diagnostic agent due to its specific physicochemical properties. These metal NPs are also used for the detection of biomarkers. They are used in various shapes and sizes, surface charge and by coupling with various surface ligands for targeting for effective drug delivery for NDs. Functionalized super-paramagnetic iron oxide (SPION) is presently used for theranostic applications in imaging techniques like MRI and targeted therapy in NDs (Luo et al. 2020).

14.8.1.2 Lipid-Based Nanoparticles

Lipid-based NPs are developed as theranostic agents in the treatment of various NDs, and they are unique in the aspect of negligible side effects when compared to other technologies. This is achieved through modifying their properties by enabling drugs and ligands to bind on to their surface (Niu et al. 2019). The well-known phytoconstituents in NDs is curcumin, which has many limitations due to its poor

solubility, low bioavailability and instability. Soft lipid-based nanocurcumin has provided a new hope in inhibiting neuronal loss in Parkinson's, Alzheimer's, ALS and Huntington's diseases (Rakotoarisoa and Angelova 2018).

14.8.1.3 Hydrogels

Hydrogels are 3D polymeric mesh-works capable of holding water. They find extensive use as a neuroprotective agent. Hydrogels are capable of systemic delivery of drugs directly into the brain tissue for targeted action in NDs. Activin B-loaded hydrogels have been developed, capable of slowly releasing activin-B over a period of several weeks for the treatment of Parkinson's disease (Albani et al. 2013).

14.8.1.4 Dendrimers

Dendrimers are credited with the position of one of the smallest nano-formulations used in the treatment of NDs. Dendrimers are manipulated by changing their size, core-shell or the surface functional groups to be used as nanocarriers for drug or gene delivery to the brain tissue. Moreover, they have strong anti-amyloidogenic activity that makes them ideal for the treatment of PD, Prion diseases and Alzheimer's. They also find their application in other areas like sterilization of medical instruments by phosphorus-containing dendrimers specially to prevent transmission of Prion disease (Šebestík et al. 2012).

14.8.1.5 Polymeric Nanoparticles

Polymer nanoparticles have the advantage of very low toxicity due to their fast excretion rate. They are block co-polymeric molecules that are biocompatible and biodegradable, and made up of lactic-co-glycolic acid (PLGA), polylactic acid (PLA), PLGA-PEG etc. (Calzoni et al. 2019; Prasad et al. 2017). Promising results have been shown by curcumin-loaded PLGA nanoparticles in the treatment of Alzheimer's disease, showing an enhanced drug delivery and reduced oxidative stress and inflammation (Barbara et al. 2017; Mukherjee et al. 2020).

14.8.2 Cancer Therapy

Cancer therapy protocols of current era are restricted to surgery, radiation and chemotherapy. These treatment regimens, though successful to some extent, will not provide complete eradication of disease and on the contrary damage healthy tissues also. The limited success rate of the conventionally used chemotherapy is due to the lack of water-soluble chemotherapeutic agents, lack of drug sensitivity of the cancer

cells and resistance to multiple chemotherapeutic drugs developed due to their repetitive administration. The modern-day cancer therapeutics aims at boosting the natural capacity of the body to identify and destroy abnormal cells. Cancer cells have also adapted to evade the body's immune response by downregulating tumour surface antigen expression, extrusion of certain proteins to deactivate the immune cells or altering the cells in the surrounding microenvironment in order to suppress immune response. Immunotherapy acts by either stimulating the activities of components of immune system or by inhibiting the signals produced by the cancer cells that suppresses the immune responses.

14.8.2.1 Treatment Modalities in cancer

Immune Checkpoint Modulators

Natural proteins secreted by the cancer cells to prevent the damage of the normal and tumour cells by triggering the immunological responses are called immune checkpoint modulators. Suppressing the stimulation of immune response proteins will result in the activation of immune responses and their capability to destroy cancer cells. Activated cytotoxic T lymphocytes expressing CTLA4 on their surface is an FDA approved immune checkpoint inhibitor.

Adoptive Cell Transfer

Adoptive cell transfer is a promising treatment modality in cancer therapy where infiltrated T cells are isolated from the tumour samples of the patient and they are segregated based on their highest response shown to recognize patient's tumour cells. These cells are isolated in a laboratory, cloned and cultured to generate a large population, which are later activated by immune signalling proteins, cytokines, and are reinfused into the patient's body (Perica et al. 2015).

Therapeutic Antibodies

Therapeutic antibodies are lab-designed therapeutic molecules like antibody-drug conjugates (ADCs) that selectively destroy the cancer cells. In ADCs, a cytotoxic substance like bacterial toxin or cytotoxic small molecule drug or a radioactive compound is coated with antibodies or fragment antibodies by chemically linking them on to their surface. The target molecule expressed over the surface of the tumour cells will bind with the antibodies over the ADCs. The ADCs will be subsequently internalized by the tumour cells and the cytotoxic substance will destroy the cell (Scott et al. 2012).

Cancer Treatment Vaccines

Cancer vaccines are prepared from patients' own tumour cells or substances produced by the tumour cells. They are designed to treat already developed cancers by strengthening the body's natural defences against the cancer (Guo et al. 2013). Several new approaches have been developed in this novel treatment strategy. Contrary to the vaccines developed for other diseases, which prevent the occurrence of the disease, cancer vaccines are effectively utilized for their curative aspects. Vaccines targeting the tumour antigens form a major group of vaccines. As the tumour antigens vary drastically with the types of tumour as well as with individuals, two categories of cancer vaccines are identified; vaccines against tumour antigens that are specific to a particular tumour (Molecular vaccines) and those that are non-specific (Cellular vaccines) (Cheever et al. 2009). The efficacy of a vaccine relies on effectiveness of the adjuvant. Different adjuvants like incomplete Freund's adjuvant in emulsified form, particulates and saponins are extensively researched. Many cancer vaccines act by modulating T cell immunity. Generation of CD8+ T effector and memory cells from CD4+ T cell help response is crucial in the effectiveness of cancer vaccines. Several other strategies including patient-derived immune cell vaccines, expression of tumour antigens with the help of recombinant viral vaccines, peptide vaccines, DNA vaccines and whole cell vaccines have been developed against cancers (Hearnden et al. 2013).

Chimeric Antigen Receptor T-Cell Therapy (CAR-T Cell Therapy)

CAR-T cell therapy which is an advanced Adoptive cell transfer technology involving harvesting of T cells which are then genetically engineered to express specific chimeric antigen receptors (CARs) on their surface with which the tumour cells are identified. The CAR-T cells are then proliferated to a population of billions or more in laboratory and are then introduced to the bloodstream of the patient where they proliferate and identify the tumour cells with the help of the genetically engineered receptor and destroys them. Though they are being used clinically, they have some untoward effects like toxicity related to uncontrolled T cell activity, cytokine release syndrome, shared expression of tumour-specific antigens by healthy cells and "on-target, off-tumour" toxicity (Zhang and Xu 2017).

Stem Cell Transplant

Stem cell transplant is another area of interest that provided positive results. Autologous, allogenic and syngeneic transplantation of marrow cells collected from healthy subjects are transfused through a vein of the patient which gets engrafted in the bone marrow produces a new lineage of blood cells. Autologous transfusion represents self stem cell transplantation before chemotherapy, while allogenic transplantation is the stem cell transplantation from a suitable donor; whereas syngeneic

transplantation is done using stem cells from an identical sibling. In all the three types of transplantations, the marrow stem cells are harvested in aseptic conditions and are stored in a specific nutrient medium at particular freezing temperature after filtration.

14.8.2.2 Nanotechnology Used in cancer Treatment

Nanocarriers

Chemotherapy utilizes the drugs that kill cancer cells, but many of these agents also destroys healthy cells also leading to adverse events. Nanoparticles are utilized as the vehicles to deliver chemotherapeutic medications directly to the tumour site sparing the healthy tissue. Nanomaterials provide an effective size of the particles between 10 and 100 nm which enables them to reach the cells more efficiently. Secondly, nanoparticles can easily adsorb onto the cell matrix and thus becomes easily integrated into the cell and thus increases the effectiveness of the drug. This is partly contributed by the high dissolution rate of the nanoparticles owing to its larger surface-to-volume ratio. Thirdly, they exhibit drug delivery to specific target site and thus overcomes the hurdle of poor solubility and drug uptake. Fourthly, they can prevent dose related adverse events effectively by controlled drug release. Various pharmaceutical techniques like nanosphere encapsulation has provided efficient methods to prolong exposure to drug by slow and controlled drug release which is the most desirable property for a chemotherapeutic agent. Thus, utilization of nanotechnology in pharmaceutical industry improves therapeutic index, solves problems in drug delivery, protects drug from degradation prior to their binding to the target site, enhances bioavailability, facilitates drug absorption by the tumours cells and prevents interaction with normal cells.

Passive Targeting

Nanoparticles can easily pervade to tissues from the blood stream due to their nanoscale size and surface properties. This property is utilized in cancer therapy as many tumours contain blood vessels with leaky walls which help the drug to concentrate in the tumour tissue and exert its cytotoxicity only to the tumour cells, sparing the healthy normal cells. This property is termed as enhanced permeability and retention (Jasim 2017; Greish 2010).

Active Targeting

Active targeting refers to the properties of a nanoparticle to target cancer cells selectively based on the chemical affinity to the molecules expressed on their surface. Molecules attached to a nanoparticle can target and interact with the receptor expressed over the cancer cells. Thus, the drug can be delivered into the cancerous cells letting free the normal cells (Kumar 2012).

Destruction from inside the Cell (Photothermal Targeting)

Photothermal targeting is utilizing the capability of nanomaterials to convert specific wavelengths of light to thermal energy which can be used for the purpose of treatment in conditions like cancers. Photothermal therapy (PTT) are highly efficacious yet with minimal side effects when compared to traditional therapies (O'Neal et al. 2004. They precisely exterminated the tumour tissue without damaging any of the normal tissues. PTT is attributed with the advantage of producing minimal trauma, less toxicity, precise targeting, wide applicability, repeatability in targeting, usefulness in palliative treatment, improvising disease curability in association with surgical procedures, elimination of occult cancers, preservation of aesthetic appeal of the patients and protection of organ functions. They utilize the near-infrared region of the electromagnetic spectrum (700–1000 nm), which has the highest penetrating power in biological tissue. Nanomaterials with photothermal properties are injected into the patient which then accumulates in the cancer cells due to its enhanced permeability and retention (EPR) effect (Yavuz et al. 2009). On reaching the target site, they absorb wavelengths in the near-infrared region and generate heat energy from them sufficient to kill the tumour cells. It is explained that the light energy is absorbed by the nanomaterial in the form of photons, a part of which is then transmitted as photons and part of it is converted into heat energy which raises the temperature of the nanomaterial. The local rise in temperature around the tumour cells causes dilatation of vessels around the tumour mass leading to accelerated blood flow into the tumour tissue dissipating the enhanced temperature into the cancerous cells. As tumour mass is attributed with poor blood flow rate (less than 5% of normal tissues), the hyperpyrexia induced by the photothermal agent will not be dissipated out of the tumour mass leading to a swift rise in temperature of the tumour of the order of 42 degrees, which is sufficient to damage and kill the tumour (Shah et al. 2008). The nanosized photothermal agent injected into the body are excreted through two major routes – through kidneys (when their diameter is around 5 nm) or through liver (when their diameter is around 20–25 nm). Based on the nature of the nanomaterial used, there are four broad categories of photothermal agents: (1) Noble metal photothermal agents: gold, silver, platinum etc. (2) Photothermal agents made of carbon materials: graphene oxide, carbon nanotubes etc. (3) Photothermal agents from transition metal dichalcogenides: copper sulphide, zinc sulphide, bismuth sulphide, tungsten sulphide, bismuth selenide etc. (4) Organic- and dye-based photothermal agents: prussian blue, indocyanine green, polypyrrole, polyaniline, dopamine, melanin, thiophene etc. Noble metals like gold, silver and platinum exhibit a phenomenon called surface plasmon resonance (SPR) effect due to their highly ordered electromagnetic field and a greater electromagnetic absorption owing to their electronic structure in the conductive band. (Zhang et al. 2018). Gold is considered as an ideal material for photothermal effect due to its strong surface plasmon resonance effect. Gold nanoparticles of varied shapes like nanorods, nanoshells, nanostars, nanocages and nanobranches are used as photothermal agents owing to its extended stability, biocompatibility and non-toxic nature (Cobley et al. 2010). Silver nanoparticles, being one of the most widely used and cheapest of all noble metal in nanoscale, is possessing a unique property of surface enhanced Raman scattering (SERS) effect

which is considered as an abnormal surface optical phenomenon due to which it has an immense absorptive capability at near-infrared wavelengths. Silver also exhibits strong localized surface plasmon resonance quality and as the near-infrared wavelengths fall on them, causes surface free electron resonance leading to the formation of an exothermic electron gas which transfers its energy to the surrounding environment through the medium of the nanoparticle resulting in rise of temperature. Platinum is also sharing properties similar to gold and silver yet will lower toxicity and high biocompatibility. They are being used in cancer therapy to scavenge oxygen free radicals generated in cancer cells by enzyme mimetics. Carbon materials like Graphene has greater absorption coefficient in near-infrared wavelengths with additional electrical, mechanical, optical and thermal properties making it more advantageous in PTT. They have added advantages of having large functional groups containing oxygen, low toxicity and production cost and highly biocompatible. It is being considered as the most promising and reputed carbon nanomaterial of the twenty-first century. Nanotubes made of carbon also show tremendous photothermal properties and can be utilized for thermal destruction of tumour cells. They can also be used as a drug carrier and can load chemotherapeutic agents on their surface and helps in combining phototherapy with chemotherapy synergistically. Transition metal chalcogenides attracted tremendous research interest recently due to its excellent thermal effect. They are being used as layered structures like tungsten disulphide and molybdenum disulphide or bismuth selenide, bismuth sulphide, silver sulphide and copper sulphide exhibiting high extinction coefficient and enhanced absorption in the near-infrared region and visible light.

Simultaneous Delivery of Two Drugs

Multidrug delivery using nanoparticles is utilized in resistant cancers with the tendency to relapse frequently. In the most resistant form of cancers like the triple-negative breast cancer treatment, they have been successfully implemented. Simultaneous delivery of multiple interventions like small interfering RNA (siRNA) along with chemotherapeutic agent doxorubicin in the treatment of breast cancer has been carried out successfully (Jiang et al. 2014; Sebastian 2017). These researches promise a new ray of hope even to the most resistant type of cancers.

14.8.3 Nanotechnology in Diabetes Mellitus

With the rising prevalence of obesity and aberrant lifestyle habits, the diabetes disease burden is rising globally. The global prevalence of diabetes is expected to touch 600 million mark by the turn of 2035 (Forouhi and Wareham 2010). Diabetes mellitus (DM) is a metabolic disorder caused by insufficient or absent secretion of insulin, which is secreted by a group cells in the pancreas termed islets of Langerhans. DM is classified mainly into two – Type 1 and Type 2 DM. Type 1 DM also called

insulin-dependent DM is caused by the extensive destruction of the beta cells of islets of Langerhans by an autoimmune response involving the T-cells. Type 2 DM on the other hand is caused due to insulin resistance or sensitivity associated with decreased production (Subramani et al. 2012).

14.8.3.1 Nanoparticles for Insulin Delivery

Some of the common drug delivery systems utilizing nanotechnology are listed below; (Yih and Al-Fandi 2006; Attivi et al. 2005)

- Polymeric biodegradable nanoparticles
- Ceramic nanoparticles
- Polymeric nanoparticles
- Dendrimer
- Liposomes

Polymeric nanoparticles are manufactured as colloidal solid particles (with dimensions ranging from 10 to 1000 nm) and based on the difference in their preparation they are of two types – Nanospheres and Nano-capsules. Nanospheres are polymeric nanoparticles having the drugs uniformly dispersed. Nano-capsules on the other hand have drugs dispersed in polymer membrane bound cavities that form vesicular systems (Tsapis et al. 2002; Si et al. 2003). These nanomaterials degrade on hydrolysis and delivers the medication to the targeted tissue.Polymeric nanoparticles are utilized for insulin transport utilizing a nonporous membrane bound polymer-insulin matrix containing glucose oxidase grafted on to their surface. An escalation in blood glucose level results in release of insulin after the biodegradation of the membrane of these nanoparticles (Morishita et al. 1992). Successful trials for oral insulin regimens with casein combined polymeric calcium phosphate-polyethylene glycol containing insulin have been undertaken (Sarmento et al. 2007). Casein prevents inactivation of insulin by gastric enzymes and the nanoparticles remain in small intestine for a longer duration favouring prolonged slower absorption and bioavailability due to its muco-adhesive property. Ceramic nanoparticles have high biocompatibility, low size (50 nm) and dimensional stability and are made up of materials such as calcium phosphate, alumina, titanium or silica (Rai et al. 2016). Porous hydroxyapatite nanoparticles have been used for delivering insulin into the intestines. Similarly, insulin-loaded poly nanoparticles are developed as nasally administered insulin. Bio Micro Electro Mechanical Systems (BioMEMS) are developed to implant them for controlled and prolonged release of insulin for long-term blood glucose control. Apart from these systems, gold nanoparticles along with chitosan as a reducing agent are being developed to carry insulin (Rai et al. 2016). Gold nanoparticles served a dual purpose in this case as a reducing agent as well as enhancing the penetration and uptake of insulin.

DM is also associated with lot of systemic complications like retinopathy, coronary artery disease (CAD), nephropathy, inflammatory gum diseases, delayed wound healing, inflammatory skin diseases and neuropathy. Polyacrylic acid,

polylactide and chitosan have been used as carriers for ophthalmic drug delivery in DM.

Though nanomaterials find their application in almost all types of diseases, this section has been devoted to the most 'notorious' and most prevalent diseases of public health importance. Hence, we discussed the use of nanomaterials in cancers and neurodegenerative diseases. This does not in any way cut down the importance of research and use of nanomaterials in other diseases like cardiovascular, respiratory, reproductive and endocrine disorders. It is also worthwhile to discuss here the rising concern regarding the use of nanomaterials in medicine as diagnostics and therapeutics, that is, their role as an endocrine disruptor is gaining momentum in many spheres of health. Though they appear as a 'sole curse to a billion boons', yet researches in this area must go on and, in its run, should also solve this 'blotch on its face' permanently.

14.9 Future Perspective of Nanomedicine and Biology

The possibilities of nanotechnologies are immense and beyond every known boundary. As we have been discussing the positive aspects of nanotechnology so far, it is time to see some of vices that this technology brings to humans. When it comes to its application in the field of medicine and biology, the dose and toxicity are of major concern. Even with the first medically used nanoparticle, nanosilver, itself toxicities have been noticed in the form of permanent pigmentation over the skin at higher doses which has been termed 'Argyrosis' (McShan et al. 2014; Korani et al. 2011). Similarly, titanium dioxide nanoparticles in inhalation and ingestion have produced pathological lesions on lung, liver, kidneys, spleen and brain in animal models. The first and foremost concern in the future perspective is to bring down the toxicity. As we are facing the global transmission from SARS -CoV-2, the world is still lurking in the dark for a permanent cure in the form of a vaccine (Liu et al. 2020; Singh 2020). The percentage of susceptible population is very high and the infection can take a serious turn at any point in the form of cytokine storm, septic shock, metabolic acidosis, coagulation dysfunction, acute respiratory distress syndrome (ARDS) finally leading to death. An effective treatment is still lacking due to drug resistance and non-specific targeting. This highlights the need for a vaccine immediately to put a stop to this scourge. Nanotechnology is the only solution to design new strategies to design vaccines against this virus and the preparedness to oversee the emerging outbreaks yet to come in the future. Cancer treatment is yet another field requiring improvisation. We are still not in a position to get rid of the cytotoxic drugs out of our cancer armamentarium. Targeted therapies are to be refined to spare the healthy tissue from the toxicity of the chemotherapeutic agents. As we are moving back to the era of high mortality from infectious diseases, it is high time to move to the phytoremedies coupled with nanotechnologies in the cure of infectious diseases. In-depth researches are needed to ascertain effective drug delivery systems in this regard. Nanotechnology still stands the forerunner to advance all technologies to the next millennium.

14.10 Conclusion

Nanotechnology has been in existence from the time humans started to live in communities in this planet. Every aspect of life has been touched by nanoscience. Application of nanotechnology in biology and medicine revolutionized health care. Nanoscience gained entry in prevention, diagnosis and treatment of diseases. The spectrum of diseases ranging from the non-communicable diseases to communicable diseases equally shared the benefits of nanoscience. Though the world has been benefited from nanotechnology and its applications, the inherent toxicity is masquerading its benefits. The future is for the technologies that address the toxicities arising from the nanomaterials used for medical purposes.

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Chapter 15
Perspectives of Nanotechnology in Aquaculture: Fish Nutrition, Disease, and Water Treatment

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15.1 Introduction

Globally, food fish demand has been on the rise for the past seven decades (annual consumption rate at 3.1%), at a rate nearly double that of the annual global human population growth (1.6%) (FAO 2020). The sad reality is that the fishing sector (capture fisheries) which has been the main supplier of food fish over the years is alone unable to meet the current and future global food fish demand. To meet the global food fish demand, aquaculture, which is one of the fastest growing food-producing sectors, is believed to be a good opportunity to complement capture fisheries. The stress on aquaculture to close the supply and demand gap of food fish has led to a shift from extensive to intensive methods such as the recirculatory aquaculture systems (RAS). In the intensive systems, fish are stocked at high density, and this has been shown to cause stress in farmed fish, thereby affecting fish performance and welfare (Sneddon et al. 2016; Hoseini et al. 2019). In addition, these systems could also be accumulation grounds for pollutants either from water sources or fish feeds (Wang and Wang 2012; Boonanuntanasarn et al. 2014) and diseases (Romero et al. 2012; Culot et al. 2019). Thus, since the emerging of intensive farming systems, the sustainability of aquaculture has been predominantly criticized.

The benefits associated with aquaculture such as the provision of accessible food, income generation, and community empowerment could have led to the radical search for effective strategies to mitigate negative impacts, instead of discouraging the practice. One of the emerging technologies is nanotechnology, which is defined as the "science and engineering concerned with the design, synthesis, characterization, and application of materials that possess a functional organization on the nano-metric scale (10^{-9} m) (Silva 2010)". Nanoparticles are characterized by higher reactivity and can change the pharmacological properties of active principles (Jiang et al. 2019). This technology is widely researched in aquaculture for various purposes such as vaccine delivery (Rajeshkumar et al. 2009), gene transfer (Murata et al. 1998), drug delivery (Lavertu et al. 2006; Wei et al. 2007), delivery of nutrients (Ashouri et al. 2015), nutraceuticals (Aklakur et al. 2016), and water filtration and remediation (Khosravi-Katuli et al. 2017). Therefore, this chapter reviewed the application of nanotechnology in aquaculture with specific focus on fish nutrition, diseases, and water quality management (Fig. 15.1), presenting trends and perspectives.

15.2 Nanotechnology Application in Fish Nutrition

Traditionally, feeding fish has relied on providing fish with food in the form of a pellet/ bycatch/ fish-offal. The pellet is chiefly formulated based on the daily nutritional fish requirements for major components such as proteins, carbohydrates, fats, minerals, and vitamins. Recently, nutritionists utilized nanotechnology to create various delivery systems such as encapsulation, protection, and controlled release of

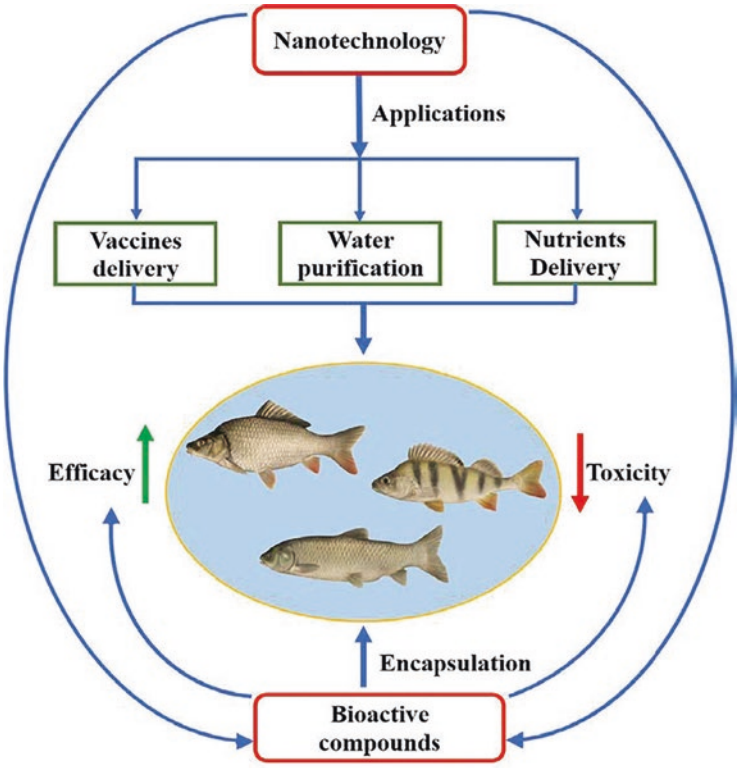

Fig. 15.1 Schematic representation of nanotechnology applications in aquaculture. (Adapted from Shah and Mraz (2020))

micronutrients. Hence, nanotechnology has an important potential to boost nutritional assessment and measures of bioavailability. For instance, ultrasensitive detection of nutrients and metabolites increases the understanding of nutrient and biomolecular interactions in specific tissues.

In nutritional research, gastrointestinal tract has always been the preferred and most important route of feed/food delivery principles including for nanoparticles. Nanoparticles can route to the gastrointestinal tract in many ways such as (1) ingestion or swallow pathway: ingestion directly from food and water and from therapeutic nano-drugs administration; (2) inhalation pathway: inhaled nanoparticles can be swallowed and enter to the gastrointestinal tract following clearance from the respiratory tract; and (3) oral pathway: oral or smart delivery into gastrointestinal tract, in which particle uptake in the gastrointestinal tract depends on diffusion and accessibility through mucus and contact with the cells of the gastrointestinal tract (Hoet et al. 2004). The smaller the particle diameter the faster is the diffusion through gastrointestinal tract mucus to reach the cells of intestinal lining, followed by uptake through gastrointestinal tract barrier to reach the blood (Hoet et al. 2004).

In fish, one important idea is that nanoparticles will enhance aquafeeds by increasing the proportion of fish feed nutrients that pass across the gut tissue and into the fish, rather than passing directly through the fish digestive system unused (Handy 2012). Specifically, the delivery systems of nanoparticles are aimed to improve the bioavailability, bioaccessibility and hence efficacy of the nutrients by improving their solubility and protection of fish gut. The delivery systems specifically consist of micronutrients trapped within nanoparticles that may be fabricated from surfactants, lipids, proteins, and/or carbohydrates (Joye et al. 2014). The small particle size in these systems has several advantages over the conventional delivery systems including improved bioavailability, higher stability to aggregation and gravitational separation, and higher optical clarity (Joye et al. 2014). For instance, immuno-modulatory ingredients such as phenolic compounds, vitamins, and minerals are being increasingly introduced into aquafeeds to improve fish health and growth performance. Nevertheless, incorporating these nutraceuticals into feeds is often challenging due to their low bioavailability, which can be solved by encapsulating the bioactive components. As the size of a particle containing encapsulated bioactive agents decreases their bioavailability increases, enabling their faster digestion and absorption. Besides, nanoparticles can be formulated to survive passage through specific regions of the gastrointestinal tract and then release their payload at a specified point, thus maximizing their potential immune-nutritional benefits (Jafari and McClements 2017).

15.2.1 Nanoparticles' Role in Fish Nutrition

In fish nutrition, nanoparticles are playing an important role in improving growth performance and immuno-biochemical (health) status of fish. They are usually incorporated in little amount, however, at a higher cost. Therefore, intensive care should be taken in their usage to maximize their utilization and avoid wastage (Friends of the Earth 2008). Consequently, many studies have been reported to address the functions and levels of nanoparticles and various methods have been adopted in aquatic animals (Table 15.1):

Sahu et al. (2008) conducted a 60 days experiment to investigate the effect of dietary *Curcuma longa* nanoparticles (0.1, 0.5, 1.0 and 5.0 g kg^{-1} of orally supplemented feed) on enzymatic and immunological profiles of rohu, *Labeo rohita* (Ham.), infected with *Aeromonas hydrophila*. Dietary *C. longa* nanoparticle significantly enhanced lysozyme activity, superoxide anion production, and serum bactericidal activity; and promoted protection against *Aeromonas hydrophila* (Sahu et al. 2008). In vitro and in vivo studies on the effects of dietary curcumin nanoparticles (0.5 & 1%, orally supplemented feed) reported that dietary curcumin nanoparticles (1) significantly enhanced growth, survival rates, and disease resistance; (2) decreased lipid peroxidation product; (3) promoted antioxidant status and protein content; (4) improved liver proactive effects; (5) increased haemoglobin content, RBC count and haematocrit; and (6) enhanced overall growth performance and

Table 15.1 Application of nanotechnology/ nanoparticles role in fish nutrition

Nanoparticles	Function	Fish Species	References
Aloe vera	A diet supplemented with 1% *Aloe vera* nanoparticles significantly promoted the growth parameters of fish in contrast to a control group.	Siberian sturgeon (*Acipenser baerii*)	Sharif Rohani et al. (2017)
Ginger	Fish fed with 1 and 0.5 g ginger nanoparticles per kg feed showed 100% relative percentage survival, whereas fish fed with 0.5 g ginger per kg feed showed 20% mortality rate and 71% relative percentage survival. These findings confirmed that ginger nanoparticles as a successful formulation in the prevention of motile *Aeromonas septicaemia* in common carp fingerlings compared to ginger.	Common carp (*Cyprinus carpio*)	Korni and Khalil (2017)
Azolla microphylla	Significantly ameliorated the levels of metabolic enzymes, hepatotoxic markers, oxidative stress markers, altered tissue enzymes, reduced hepatic ions, abnormal liver histology, etc. Based on those results, it was suggested that *Azolla microphylla* phytochemically synthesized gold nanoparticles as an effective protector against acetaminophen-induced hepatic damage in fresh water common carp.	Common carp fish (*Cyprinus carpio* L.)	Kunjiappan et al. (2015)
Azadirachta indica (neem)	Significantly elevated functional activity of immunological parameters in fish treated with these nanoparticles. It was concluded that they have a potential immunomodulatory and antibacterial activity.	Mrigala carp (*Cirrhinus mrigala*)	Rather et al. (2017)
Curcuma longa	Significantly enhanced lysozyme activity, superoxide anion production, and serum bactericidal activity; and improved protection against *Aeromonas hydrophila.*	Rohu (*Labeo Rohita*)	Sahu et al. (2008)

(continued)

Table 15.1 (continued)

Nanoparticles	Function	Fish Species	References
Curcumin	Enhanced growth, survival rates, and disease resistance of *A. testudineus* (Bloch). Promoted antioxidant status and protein content of the fish. Decreased lipid peroxidation product. Increased haemoglobin content, RBC count, and haematocrit in the fish. Improved over all health status of the fish.	*Anabas testudineus* (Bloch)	Manju et al. (2009, 2012, 2013)
Curcumin	Remarkably minimized CCl4-induced liver damage by upregulating hepatocyte antioxidative capacity and inhibiting NF-kB, IL-1b, TNF-α, and IL-12 expression in Jian carp.	Jian carp (*Cyprinus carpio* var. Jian)	Cao et al. (2015)
Curcumin	Notably improved growth performance, feed utilization, oxidative status, immune responses, and disease resistance of fish. Promoted non-specific immune defense mechanisms against *Vibrio alginolyticus*. Enhanced hepatic lesions in aflatoxin B infected fish.	Nile tilapia (*Oreochromis niloticus*)	Elgendy et al. (2016); Mahmoud et al. (2017); Manal (2018)
Curcumin	Enhanced growth performance and increased disease resistance against *Edwardsiella tarda* infection.	Mrigala carp (*Cirrhinus mrigala*)	Leya et al. (2017)
Curcumin	Promoted performance of catfish and increased their disease resistance, reducing use of antimicrobials in fish farming.	Channel catfish (*Ictalurus punctatus*)	Hafiz et al. (2017)
Curcumin	Enhanced the activities of digestive enzymes. Modulated the expression of GH in brain and growth factors such as IGF-1 and IGF-2 in muscle of *O. mossambicus.*	Mozambique tilapia (*Oreochromis mossambicus*)	Midhun et al. (2016)
Selenium (Se)	Nano-Selenium (Se, 1 mg kg^{-1} diet) showed significant improvement in the growth and antioxidant defense system of common carp in contrast to a control group.	Common carp (*Cyprinus carpio*)	Ashouri et al. (2015)
Selenium (Se), zinc (Zn) and manganese (Mn)	Dietary nanoparticles such as nano-selenium (Se), zinc (Zn), and manganese (Mn) in early weaning diets enhanced stress resistance and bone mineralization of gilthead seabream.	Gilthead seabream (*Sparus aurata*)	Izquierdo et al. (2017)

(continued)

Table 15.1 (continued)

Nanoparticles	Function	Fish Species	References
Iron (Fe)	A diet supplemented with iron (Fe) nanoparticles and *Lactobacillus casei* as a probiotic significantly promoted growth performance of rainbow trout.	Rainbow trout (*Oncorhynchus mykiss*)	Mohammadi and Tukmechi (2015)
Manganese (Mn)	Dietary MnO nanoparticles (16 mg kg^{-1} diet) significantly elevated the growth performance and antioxidant defense system of freshwater prawn.	Freshwater prawn (*Macrobrachium rosenbergii*)	Asaikkutti et al. (2016)
Copper (Cu)	Supplementation of dietary copper (Cu) nanoparticle (20 mg kg^{-1} diet) significantly improved the growth, biochemical status, digestive and metabolic enzyme activities, antioxidant, and non-specific immune response of aquatic animals.	Freshwater prawn (*M. rosenbergii*) and Red sea bream (*Pagrus major*)	Muralisankar et al. (2016); El Basuini et al. (2017)

health status of *A. testudineus* (Bloch) (Manju et al. 2009, 2012, 2013). Cao et al. (2015) studied the effects of curcumin nanoparticles (0.1%, 0.5%, or 1.0% of orally supplemented feed) on antioxidative activities and cytokine production in Jian carp (*Cyprinus carpio* var. Jian) with CCl_4-induced liver damage. Dietary curcumin nanoparticles significantly reduced CCl_4-induced liver damage in Jian carp by upregulating hepatocyte antioxidative capacity and inhibiting NF-kB, IL-1b, TNF-a, and IL-12 expression (Cao et al. 2015). Supplementation of curcumin nanoparticles (0.5, 1, or 2% of diet) significantly improved non-specific immune defense mechanisms of fish against *Vibrio alginolyticus*; promoted hepatic lesions in aflatoxin B infected fish; improved hepatosomatic index (HIS) values; and enhanced growth performance, feed utilization, oxidative status, immune responses, and disease resistance of tilapia, *Oreochromis niloticus* (Elgendy et al. 2016; Mahmoud et al. 2017; Manal 2018). Leya et al. (2017) evaluated the effects of curcumin nanoparticles supplemented diet (0.25, 0.5, 1, 1.5 and 2% of orally supplemented diet) on growth and non-specific immune parameters of mrigala carp (*Cirrhinus mrigala*) against *Edwardsiella tarda* infection. Dietary curcumin nanoparticles improved growth performance and increased disease resistance against *Edwardsiella tarda* infection in *C. mrigala* (Leya et al. 2017). Curcumin nanoparticle supplementation (0.5 & 1% of orally supplemented diet) significantly enhanced performance and increased disease resistance of catfish, *Ictalurus punctatus* (Hafiz et al. 2017). Midhun et al. (2016) evaluated modulation of digestive enzymes, GH, IGF-1, and IGF-2 genes in the teleost, Tilapia (*Oreochromis mossambicus*) by dietary curcumin nanoparticles (0.5 & 1%). Dietary curcumin nanoparticles significantly improved the activities of digestive enzymes and modulated the expression of GH in brain and growth factors such as IGF-1 and IGF-2 in the muscles of tilapia, *O. mossambicus* (Midhun et al. 2016).

Studies in other nanoparticles, Sharif Rohani et al. (2017), evaluated the effects of three different levels (0.5, 1.0, and 1.5% of the diet) of *Aloe vera* nanoparticles on the growth performance, survival rate, and body composition of Siberian sturgeon (*Acipenser baerii*). This study reported that a diet supplemented with 1% *Aloe vera* nanoparticles significantly promoted the growth factors of fish in contrast to a control group but did not find significant difference in body composition of fish (Sharif Rohani et al. 2017). Korni and Khalil (2017) studied the effect of ginger and its nanoparticles on growth performance, cognition capability, immunity, and prevention of motile *Aeromonas septicaemia* in common carp (*Cyprinus carpio*) fingerlings. Fish fed with ginger nanoparticles (1 and 0.5 g kg^{-1} of diet) showed better growth performance, and significantly increased total protein, globulin, and lysozyme of fish; and showed 100% relative percentage survival (RPS) compared to control group (Korni and Khalil 2017). Kunjiappan et al. (2015) investigated the hepatoprotective and antioxidant effects of *Azolla microphylla*-based gold nanoparticles against acetaminophen-induced toxicity in a fresh water common carp fish (*Cyprinus carpio* L.). Their results showed that gold nanoparticles significantly ameliorated the levels of metabolic enzymes, hepatotoxic markers, oxidative stress markers, altered tissue enzymes, reduced hepatic ions, abnormal liver histology etc. Based on those results, it was suggested that *A. microphylla* phytochemically synthesized gold nanoparticles as an effective protector against acetaminophen-induced hepatic damage in fresh water common carp (Kunjiappan et al. 2015). Rather et al. (2017) evaluated the immunomodulatory potential of green synthesis of silver nanoparticles (G-AgNPs) using *Azadirachta indica* (neem) in *Cirrhinus mrigala* fingerlings challenged with *Aeromonas hydrophila*. This study reported that dietary G-AgNPs significantly increased the functional activity of immunological parameters (nitro-blue tetrazolium assay, myeloperoxidase activity, phagocytic activity, anti-protease, and lysozyme activity), enhanced disease resistance and improved survival rate; and it was concluded that biosynthesized silver nanoparticles have immunomodulatory and antibacterial activity (Rather et al. 2017). Formulation of solid lipid nanoparticles-encapsulated 6-coumarin-loaded pectin microparticles showed improved uptake of the compound by two gilthead seabream (*Sparus aurata* L.) cell types compared to a competitor 6-coumarin-loaded pectin microparticles, which makes solid lipid nanoparticles as suitable nanocarriers for the delivery of biologically active substances in fish (Trapani et al. 2015).

Furthermore, dietary nano-minerals or dietary minerals at the nanoscale size may pass into cells more readily than their larger counterparts, and this accelerates their assimilation process into the fish. For example, dietary selenium (Se, 1 mg kg^{-1} of diet) nanoparticles significantly promoted growth and antioxidant defense system of common carp (*Cyprinus carpio*) in contrast to a control group (Ashouri et al. 2015). In rainbow trout, a dietary iron (Fe) nanoparticles and *Lactobacillus casei* as a probiotic significantly improved growth performance and feed utilization, such as weight gain, specific growth rate, daily growth rate, condition factor, and food conversion rate (Mohammadi and Tukmechi 2015). Nanoparticles such as nano-selenium (Se), zinc (Zn) and manganese (Mn) in early weaning diets for gilthead seabream (*Sparus aurata;* Linnaeus, 1758) enhanced stress resistance and bone

mineralization (Izquierdo et al., 2017). Dietary copper (Cu) nanoparticle (20 mg kg^{-1} of diet) significantly improved the growth, biochemical status, digestive and metabolic enzyme activities, antioxidant, and non-specific immune response of red sea bream, *Pagrus major* (El Basuini et al. 2017) and freshwater prawn, *M. rosenbergii* (Muralisankar et al. 2016). Supplementation of manganese oxide (MnO) nanoparticles (16 mg kg^{-1} diet) significantly elevated the growth performance and antioxidant defense system of freshwater prawn (*Macrobrachium rosenbergii*) (Asaikkutti et al. 2016).

15.2.2 Nanotechnology Application in the Aquafeed Industry

There are numerous potential applications of nanotechnology in feed industry, including: (i) minor modifications of natural ingredients to enhance taste, palatability and sensory improvement such as flavor, color, and texture; (ii) enhancing nutrition quality of foods by stabilizing active ingredients such as nutraceuticals in feed matrices, packaging, and product innovation to extend shelf-life, (iii) increasing bioavailability of essential nutrients (Food Safety Authority of Ireland 2008). Nano-delivery of bioactive/nutrient in feedstuffs or in vivo in fish is enabled through improved knowledge of feed materials at the nanoscale. The different nanomaterials that have the potential to be used for this purpose are nanocomposites, nanoclays, and nanotubes. The nanoproducts that would find applications are nanosensors, nanoimaging, and nanochips and nanofilters. Similarly, the potential nano-delivery systems are nanocapsules, nanocochleates, nanoballs, nanodevices, nanomachines, and nanorobots (Thulasi et al. 2013).

In aquafeed, nanotechnology may also play significant roles in the delivery of micronutrients to aquatic animals. For instance, nanomaterials can be used to coat nutrients that could normally degrade, such as fatty acids, or have limited assimilation efficiency across the gut of fishes, because they are poorly soluble (i.e. fat-soluble vitamins) (Handy 2012). Nanoencapsulation technology has been suggested for vitamins, minerals, carotenoids, and fatty acids, with increasing bioavailability being the main goal (Acosta 2009; Bouwmeester et al. 2009).

Several vitamins and their precursors, such as carotenoids, are insoluble in water. Nevertheless, nanotechnology helps to address these problems. Specifically, when prepared as nanoparticles, these vitamins and their precursors can easily be homogenized with cold water, which enables to increase their bioavailability. For example, Vitamin B_{12} absorption from the gut under physiological conditions occurs via receptor-mediated endocytosis; and the ability to increase oral bioavailability of various peptides (granulocyte colony stimulating factor, erythropoietin) and particles by covalent coupling to vitamin B_{12} has been reported by Russell Jones (2001) and Russell Jones et al. (1999). Vitamin E is a term describing all tocopherol and tocotrienol derivatives, which exhibit the biological activity of alpha tocopherol. Its structure is sensitive to light, heat, and oxygen; consequently, synthetic versions of vitamin E are less expensive, but have lower biological activity (Thulasi et al. 2013).

Nano-micelles made from casein can be used as a vehicle for hydrophobic ingredients such as vitamin D_2 (Semo et al. 2007).

Nanoscale mineral supplements might provide a source of trace metals, without the extensive faecal losses normally associated with mineral salts (e.g. Fe salts; Carriquiriborde et al. 2004). Nanomaterials may also offer an alternative to organic forms of food supplements, where antinutritional factors (incidental pesticides, toxic metals, etc.) in the ingredient can sometimes be a problem (Berntssen et al. 2010).

Nanomaterials can be used to change the physical properties of aquafeed in addition to enhancing the bioavailability and stability of aquafeed. For example, feed wastage and pollution in aquaculture due to poor feed quality (stability, texture or inappropriate buoyancy of the pellet) is a continuing problem (Handy and Poxton 1993); and small supplementations of nanomaterials can significantly alter the physical properties of these pellets. Specifically, the additions of single-walled carbon nanotubes to trout feed can result in a hard pellet that does not fragment easily in water (Handy 2012). Rainbow trout readily eat feed containing nanomaterials up to 100 mg kg^{-1} TiO_2 nanoparticles (Ramsden et al. 2009) and/or 500 mg kg^{-1} C60 and 500 mg kg^{-1} single-walled carbon nanotubes (Fraser et al., 2010) without loss of appetite or growth rate. Therefore, adding a few milligrams of nanomaterial/nanoparticles to aquafeed modify the physical properties of pellets, which could play important roles in the development of aquafeed industry, ultimately sustainable growth of aquaculture industry.

15.3 Nanotechnology Application in Aquaculture Disease Control

Aquaculture sector (especially intensive and super-intensive commercial farms) has grieved major economic losses because of disease outbreaks caused by several pathogenic agents (i.e. bacteria, viruses, and parasites) (Huang et al. 2015; Shinn et al. 2015; Tandel et al. 2017). Traditionally, these pathogens could be treated with chemical disinfectants and antibiotics either through feed, immersion, or injection. However, the use of these chemicals in aquaculture has been criticised, because, they are no longer effective i.e. several pathogenic bacteria i.e. *Aeromonas hydrophila, A. salmonicida, Yersinia ruckeri, Vibrio, Listeria, Pseudomonas*, and *Edwardsiella* species have been reported to be insensitive against most common antibiotics used in aquaculture (Sørum 2008; Swain et al. 2014). In addition, the excessive use of these chemicals in aquaculture could be toxic to other organisms including humans and the environment (Shah and Mraz 2019; Malheiros et al. 2020). This could have paved ways to the search for better alternative technology to control bacteria, viruses, and parasites in aquaculture. Today, nanotechnology has become the new alternative with potential to be used as antimicrobial agents, vaccines, and diagnosis tools for disease causing agents in fish farming (Shaalan et al. 2016).

15.3.1 Nanoparticles as Antibacterial Agents in Aquaculture

Different metal nanoparticles (biologically or chemically synthesized) have been recommended as alternative antibacterial agents, with potential to eradicate or reduce the use of traditional antibiotics in aquaculture (Gunalan et al. 2012; Shaalan et al. 2016) (Table 15.2). Biologically synthesized metal nanoparticles (derivatives of plants, bacteria and fungi) are more advocated over chemically synthesized ones because of their high antimicrobial activity, environmental friendliness, simplicity and affordability (Kalishwaralal et al. 2008; Gunalan et al. 2012; Prasad 2014; Prasad et al. 2016, 2018; Srivastava et al. 2021; Sarma et al. 2021). Some of the antibacterial metal nanoparticles studied in aquaculture include zinc nanoparticles (ZnNPs), silver nanoparticles (AgNPs), copper oxide (CuONPs), gold nanoparticles (AuNPs), and titanium dioxide (TiO_2NPs) (Swain et al. 2014), with AgNPs, ZnNPs, and AuNPs being the widely studied nanoparticles. These nanoparticles could be used either alone or in combination with each other (Venegas et al. 2018). This section reviews the commonly reported metal nanoparticles as antibacterial agents in aquaculture (Table 15.2).

Zinc Nanoparticles (ZnNPs) These nanoparticles are gaining popularity due to their multifunctional properties; antibacterial and antifungal properties (Wang et al. 2008; Di Cesare et al. 2012). Zinc-oxide (chemically synthesized) reportedly showed broad spectrum antibacterial activity against *Aeromonas hydrophila*, *Edwardsiella tarda*, *Flavobacterium branchiophilum*, *Vibrio* sp., *Staphylococcus aureus*, *Bacillus cereus*, and *Citrobacter* sp. (Swain et al. 2014), which are some of the important pathogenic bacteria in aquaculture. Remarkably, ZnO-NPs synthesized with aloe extracts showed high broad antibacterial activity when compared to the chemically synthesized ZnO nanoparticles (Gunalan et al. 2012). Similarly, ZnO-NPs synthesized with *A. hydrophila* showed antibacterial activity against *Enterococcus faecalis*, *Pseudomonas aeruginosa*, *Candida albicans*, *Escherichia coli*, and *Aspergillus flavus* (Jayaseelan et al. 2012). In addition, dietary supplementation of ZnO-NPs reportedly enhanced resistance of *Labeo rohita* (Swain et al. 2019), and *Oreochromis mossambicus* (Anjugam et al. 2018) against *A. hydrophila*. Generally, the antibacterial mechanisms of nanoparticles are fairly understood. The active oxygen species generated by the metal oxide particles is considered the main mode of action, thereby these particles inhibit bacterial proliferation by disrupting the bacterial cell membrane, hence destroying the cell content (Liu et al. 2009; Gunalan et al. 2012; Bhuyan et al. 2015).

Silver Nanoparticles (AgNPs) They have been widely reported to elicit antibacterial activity against a broad spectrum of pathogenic bacteria of economic importance in aquaculture. Silver nanoparticles are reported to inhibit bacterial growth through different mechanisms: Ag+ binds to the bacterial cell membrane proteins resulting in the distraction of the membrane (Lara et al. 2010; Aziz et al. 2014, 2015, 2016, 2019), and by disrupting the cell division or bacteria reproduction process (Huang et al. 2011). A study by Elayaraja et al. (2017) demonstrated that silver nanoparticles synthesised using bacterial cellulose (Ag-NPs-BC) had high

Table 15.2 Some nanoparticles studied as antibacterial agents in aquaculture

Nanoparticles (NPs)	Screened bacteria	Antibacterial activity (Yes/No)	References
Zinc nanoparticles (ZnNPs) Zinc oxide (ZnO) (chemical)	*Aeromonas hydrophila; Edwardsiella tarda; Flavobacterium branchiophilum; Vibrio* sp.; *Staphylococcus aureus; Bacillus cereus; Citrobacter* sp.;	Yes	Swain et al. (2014)
ZnO (chemical) Bulk-ZnO (chemical)	*Vibrio harveyi*	Yes No	Ramomoorthy et al. (2013)
ZnO (Chemical) ZnO-*Aloe vera* (biological)	*Serratia marcescens; S. aureus; Proteus mirabilis; C. freundii*	Yes	Gunalan et al. (2012)
ZnO-*A. hydrophila* (biological)	*Enterococcus faecalis; Pseudomonas aeruginosa; Candida albicans; Escherichia coli; Aspergillus flavus*	Yes	Jayaseelan et al. (2012)
Dietary ZnONPs	*A. hydrophila*	Yes	Anjungam et al. (2018)
ZnO (chemical)	*A. salmonicida; Yersinia ruckeri; Aphanomyces invada*	Yes	Shaalan et al. (2017)
ZnO-Ag (mixture) (chemical)	*Pseudomonas* spp.	Yes	Venegas et al. (2018)
Silver nanoparticles (AgNPs) AgNPs (chemical)	*A. salmonicida* subsp. *Salmonicida* *S. aureus;* *E. coli* O157:H_7; *Streptococcus pyogenes;* *V. fluvialis*	Yes Yes Yes Yes	Shaalan et al. (2018) Ayala-Nunes et al. (2009) Lara et al. (2010) Meneses-Marquez et al. (2019)
Ag-TiO_2(chemical)	*A. hydrophila; E. tarda; F. branchiophilum; Vibrio sp; S. aureus; Citrobacter* sp.	Yes	Swain et al. (2014)
AgNPs-*Citrus limon* (biological)	*E. tarda; S. aureus*	Yes	Swain et al. (2014)
AgNPs-Tea leaf	*V. harveyi*	Yes	Vaseeharan et al. (2010)
AgNPs-*Calotropis gigantea* extracts (biological)	*V. alginolyticus*	Yes	Baskaralingam et al. (2012)
AgNPs-BC (biological)	*V. harveyi; V. parahaemolyticus*	Yes	Elayaraja et al. (2017)
AgNPs-red algae (biological)	*V. harveyi; V. parahaemolyticus;* *V. alginolyticus;* *V. anguillarum*	Yes	Fatima et al. (2020)

(continued)

Table 15.2 (continued)

Nanoparticles (NPs)	Screened bacteria	Antibacterial activity (Yes/No)	References
Gold nanoparticles (AuNPs) Fucoidan-AuNPs (biological)	*A. hydrophila*	Yes	Vijayakumar et al. (2017)
Acanthophora spicifera-AuNPs (biological) Herbal extracts-AuNPs (biological)	*V. harveyi* *S. aureus*	Yes No	Babu et al. (2020)
	A. hydrophila *S. agalactiae*	Yes Yes	Fernando and Cruz (2020)
Anacardium occidentale-AuNPs (biological)	*A. hydrophila*	No	
	A. bestiarum	Yes	Velmurugan et al. (2014)
	P. fluorescens *E. tarda*	Yes No	
AuNPs-zeolites	*E. coli; Salmonella typhi*	Yes	Lima et al. (2013)
Nigella sativa essential oil-AuNPs (NsEO-AuNPs)	*S. aureus; V. harveyi*	Yes	Manju et al. (2016)
AuNPs (chemical)	*V. parahaemolyticus*	Yes	Tello-Olea et al. (2019)

Yes = inhibited bacterial growth; No = did not inhibit bacterial growth

bactericidal activity against *V. parahaemolyticus* and *V. harveyi*, which are some of the deadliest bacterial pathogens in shrimp aquaculture. Similarly, biologically synthesized Ag-NPs were recommended as alternative antibiotics in controlling *S. aureus* and *E. tarda* (Swain et al. 2014), and *V. harveyi* infection in *Feneropenaeus indicus* (Vaseeharan et al. 2010). Interestingly, AgNPs demonstrated effectiveness against multi-drug resistant bacteria such as methicillin-resistant *S. aureus* (MRSA) (Ayala-Nunez et al. 2009), ampicillin-resistant *E. coli* O157:H_7, and erythromycin-resistant *Streptococcus pyogenes* (Lara et al. 2010). This is indeed an indication that these nanoparticles have the ability to eradicate the use of ineffective antibiotics to fight bacterial diseases in aquaculture.

Gold Nanoparticles (AuNPs) They are one of the emerging nanoparticles, and they can be more preferred mainly because of their less toxicity to animals (Li et al. 2014). Different gold nanoparticles have been reported to possess antibacterial properties, with the potential to eliminate bacteria responsible for huge production and economic losses in aquaculture (Table 15.2). A study by Vijayakumar et al. (2017) demonstrated that fucoidan (marine polysaccharide)-coated gold nanoparticles (Fu-AuNPs) inhibited the biofilm of *A. hydrophila*, and reduced mortality in *A. hydrophila*-infected *Oreochromis mossambicus* juveniles. *Acanthophora spicifera* (marine red algae)-mediated gold particles (As-AuNPs) exhibited the highest

antibacterial activity against *V. harveyi* than *S. aureus* (Babu et al. 2020). Gold nanoparticles reportedly act against bacterial pathogens via a number of pathways such as their ability to collapse the bacterial membrane potential, inhibit ATPase activities, and subsequently the ATP level; and inhibit the subunit of ribosome from binding tRNA (Cui et al. 2012). In addition, AuNPs synthesized with crude herbal extracts reportedly inhibited *A. hydrophila* biofilm formation via the disruption of their quorum sensing ability (communication between cells) (Fernando and Cruz 2020). The communication between bacterial cells has been the target to control bacterial virulence for promising antibacterial agents (Rasmussen et al. 2005).

15.3.2 Nanoparticles as Vaccine/Drug Delivery Vector

In aquaculture, drugs are traditionally administered through feed, injection, or immersion. The traditional drug delivery methods are considered to be ineffective for several reasons such as poor bioavailability and absorption of the drugs to the targeted cells (Moges et al. 2020). Recently, the use of nanoparticles in drug formulation and delivery has gained attention in the fight against pathogens in aquaculture (Table 15.3). With this technology, the compound of interest (i.e. antibiotics, vitamins, vaccines, probiotics) is encapsulated into a compound of the nanoscale, thereby increasing absorption of the compound to targeted region, because nanoparticles are able to penetrate through cellular barriers (Sivakumar 2016; Moges et al. 2020); hence better protection against pathogens compared to traditional drug delivery methods.

Chitosan (Chit.) (polysaccharides) and poly-lactic glycolipids acid (PLGA) (copolymer) nanoparticles are the widely studied nanoparticles for drug delivery. These nanoparticles are commonly used due to their outstanding physiochemical properties such as biocompatibility, bioactivity, non-toxicity, and biodegradability (De Jong and Borm 2008; Lü et al. 2009). Chitosan nanoparticles combined with infectious salmon anaemia virus (ISAV) gene as an adjuvant were used to develop a DNA vaccine to control ISAV in Atlantic salmon culture (Rivas-Aravena et al. 2015). Chitosan nanoparticles-based vaccine was developed for *Lates calcarifer* against *V. anguillarum* (Rajesh Kumar et al. 2008). In addition, PLGA nanoparticles loaded with rifampicin were reported to show efficacy against *Mycobacterium marinum* in zebra fish larvae (Fenaroli et al. 2014). The use of chitosan and PLGA nanoparticles in combination were also reported in aquaculture. For instance, a plasmid DNA vaccine (pDNA) combined with PLGA and chitosan nanoparticles complex (pDNA-PLGA-Chit-NPs) significantly activated immune parameters in *Labeo rohita* and increased their survival after *Edwardsiella tarda* infection (Leya et al. 2020). This is said to be attributed to the ability of the complex vaccine to act synergistically to provide the host with amplified protective immunity against pathogens (Leya et al. 2020).

Table 15.3 Some chitosan and Poly lactic-co-glycotic acid nanoparticles studied as drug delivery agents in aquaculture

Nanoparticles (Chit-PLGA)	Pathogens	Fish species	References
pDNA-PLGA-Chit-NPs pDNA-PLGA-NPs PLGA-NPs Chit-NPs	*Edwardsiella tarda*	*Labeo rohita*	Leya et al. (2020)
Chit-ISAV	Alphavirus	Atlantic salmon	Rivas-Aravena et al. (2015)
Chit-DNA (pVAOMP38)	*Vibrio anguillarum*	*Lates calcarifer*	Rajesh Kumar et al. (2008)
Chit-DNA (pEGFP-N2OMPK, pDNA)	*V. parahaemolyticus*	*Acanthopagrus schlegelii* Bleeker	Li et al. (2013)
Chit-inactivated *E. ictaluri* and infectious spleen and kidney necrosis virus.	*E. ictalurid*	*Pelteobagrus fulvidraco; Siniperca chuasi*	Zhang et al. (2019) Zhu et al. (2019)
Chit-*Piscirickettsia salmonis* membrane	*Piscirickettsia salmonis*	*Dario rerio*	Tandberg et al. (2018)
PLGA-rifampicin	*Mycobacterium marinum*	*Dario rerio*	Fenaroli et al. (2014)

Chit Chitosan, *PLGA* Poly lactic-co-glycotic acid, *NPs* Nanoparticles, *p* plasmid; *ISAV* Infectious Atlantic salmon anaemia virus

15.4 Nanotechnology Application for Water Quality Management in Aquaculture

In aquaculture, animals are fed with high-protein feeds, and fertilizers, especially in semi-intensive systems, are used to stimulate natural feeds to sustain the growth of farmed animals and stimulate production. However, the challenge is in the handling/management of uneaten feed and waste products, which often contribute to the culture water quality (Ninh et al. 2016). Consequently, water in poorly managed aquaculture systems may be enriched with nutrients and organic and suspended matter (Boyd 2001; Sikder et al. 2016) which are associated with negative effects on fish growth, increased fish stress, and high risks of infectious diseases (Boyd and Tucker 1998; Boyd 2001). Water quality management is, therefore, vital for aquaculture operations.

Contrary to conventional wastewater treatment methods such as chemical treatment, filtration, and ion exchange (Muzammil et al. 2016), aquaculture effluents are treated via sedimentation, constructed wetlands, and water treatment reservoirs (Boyd 2001; Kerepeczki et al. 2011). However, these techniques are said to be ineffective in the complete removal of contaminants (Le et al. 2019). Therefore, the use of nanomaterials has been recommended as the best alternative technology in the purification of water either for human consumption (Gehrke et al. 2015) or fish culture (Sichula et al. 2011). This section outlines the use of nano-catalysts and nano-adsorbents for wastewater treatment in aquaculture.

15.4.1 Nanocatalysts and Nanoadsorbents in Aquaculture

Nano-catalysts are being employed in wastewater treatment for the chemical oxidation of organic and inorganic pollutants (Muzammil et al. 2016). Titanium oxide (TiO_2) and Zinc oxide (ZnO) are some of the widely used nanoparticles in photocatalysis. Their efficiency depends on the interaction with light energy and presence of metallic nanoparticles/semi-conductor metals (Acheampong and Antwi 2016). For instance, titanium oxide (TiO_2) was reported to remove bacterial cells (Litter 2015). This is because, TiO_2 possess high antimicrobial abilities that permits its use in inactivating pathogenic organisms such as bacteria found in wastewater (Wu et al. 2014; Amin et al. 2014). In another study, TiO_2 was reported to reduce the viability of several waterborne pathogens such as protozoa, fungi, *E. coli*, and *P. aeruginosa,* after 8 hours of simulated solar exposure (Amin et al. 2014). In addition, titanium was able to remove heavy metals such as chromium and arsenic from wastewater (Litter 2015).

A study by Le et al. (2019) tested the removal of heavy metal ions using rod-shaped ZnO particles under utraviolet light and visible light. This study observed that ZnO nanoparticles could remove heavy metal ions such as Cu(II), Ag(I) and Pb(II) at an efficiancy rate greater than 85%, but not very efficient at removing Cr(VI), Mn(II), Cd(II), and Ni(II) ions, regardless of the light source used. Similar to TiO_2, ZnO nanoparticle produced by solution combustion method (SCM) has also demonstrated effectiveness in removing *E. coli* from water (Masoumbaigi et al. 2015). Another important nano-catalyst in wastewater treatment is nanosilver. These nanoparticles synthesized with fungal species have been reported to remove *E. coli, Staphylococcus* sps, and *Pseudomonas* sps in wastewater (Moustafa 2017), which are some of the pathogenic bacteria in aqauculture as demostrated above in Sect. 15.3.

In addition to nanocatalysts, nanoadsorbents are likewise impressive water treatment methods, used to remove heavy metals, nutrients, and microbes from water (Thines et al. 2017). One such nanoadsorbent is activated charcoal (AC). A study by Aly et al. (2016) and Sichula et al. (2011) indicated that AC successfully removed ammonia from aquaculture production systems and reduced unionized ammonia concentrations in *O. niloticus* culture respectively. The application of nanocatalysts and nanoadsorbents is, therefore, a promising approach for the management of water quality in aquaculture production systems. By adopting nanotechnologies, microbial and heavy metal contamination can be adressed in aqauculture and in so doing, manage the challenges of nutrient accumulation, ultimately disease proliferation.

15.5 Conclusion and Future Perspectives

Challenges associated with increased intensification in aquaculture such as poor feed quality and utilization, increased disease outbreaks, and poor water quality cannot be overemphasised. This chapter has provided substantial evidence that

nanomaterials have the potential to enhance feed quality (nutritional and physical properties), feed utilization, drug formulation and delivery, disease treatment, and water quality management in aquaculture; hence improving fish growth and better economic return. Despite promising research findings, the speed of implementation of this technology in aquaculture is still limited. One of the limitations is the complex manufacturing process of nanomaterials, which requires expensive equipments and services, and this could directly influence the cost of nanoproducts. Therefore, small-scale fish farmers may be financially limited to participate in the manufacturing process of the nanomaterials. Another limitation is that some nanoparticles, particularly the chemically synthesized ones, are toxic to animals at higher dosages and may negatively affect the development of animals (Verma et al. 2017, 2018).

Moving forward, there is a need to adopt nanoparticles manufacturing approaches such as biological methods, which are described to be simple and produce non-toxic, environmentally friendly, and affordable products (Kalishwaralal et al. 2008; Prabhu and Poulose 2012; Thangadurai et al. 2020, 2021; Maddela et al. 2021). This way, aquaculture farmers at all levels (from small scale to commercial) would be able to harness the benefits associated with nanotechnology. All in all, nanotechnology is playing important roles in the sustainable development of aquaculture.

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Chapter 16
Nanomaterials in Electrochemical Biosensors and Their Applications

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Contents

16.1 Introduction

Recent advances in nanotechnology have highly influenced our lifestyle in the fields of medicine, environment, energy, engineering, construction, and telecommunication (Ozin et al. 2009). Moreover, its application in various disciplines also transforms the economy of countries and change the production process of industries. Nanoscale deals with the object having a size range from 1 to 100 nm. It is a

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complex challenge and achievement, with great effort from the scientific community, including both theoretical and experimental science. Initially, the physicist and Nobel laureate Richard Feynman was the first to introduce the concept of nanotechnology and later Prof. Norio Taniguchi of Tokyo University of Science (1974) created the term "nanotechnology" to describe the precision manufacture of materials at the nanoscale (Drexler 2004). In later years, nanotechnology research started to resolve many problems in science and technology, but the real wave of applications is only beginning to break in the last three decades.

Nanotechnology starts within the panel of the green innovation technologies, which impact the potential application and excellent vision towards social and economic development (Colvin 2003; Sarma et al. 2021). The scientists have dedicated years of research to understand the phenomena of atoms and molecules and discovered various nanostructured materials. For example, the discovery of quantum dots, nanowires, nanosheets, proteins, liposomes, viruses, antibodies, deoxyribonucleic acid, and antibodies. (Ramos et al. 2017). Moreover, based on the size and dimensions, nanomaterials are classified as zero dimension (0D), one dimension (1D), two dimensions (2D), and three dimensions (3D). Recently, the manipulation of nanomaterials and utilization with the technologies such as the controlled size, dimension, morphology and characterization, lead to a better understanding of the relationship between nanomaterials and their properties. The bulk materials engineered to the nanoscale can relatively contributes to a large surface area and makes the material more chemically reactive, mechanically stable, tune the optical, magnetic and electrical properties (Parikha 2016). Moreover, based on the size, dimension, and peculiar properties, nanomaterials are subjected to day-to-day applications in various commercial areas.

In environmental science and technology, nanomaterials have a considerable role in the development of nonpolluting materials to make the chemical reactions more perfect and effective during the manufacturing processes. Moreover, nanosensors are used to detect harmful or hazardous gases and chemicals. Also the nanomaterials can optimize the remediation of water, soil, and air contaminations (Karn et al. 2004). Conductive and semiconductor nanomaterials have used in energy conversion and energy storage systems. The nanomaterials such as quantum dots, graphene, carbon nanotubes, and nanowires are considerably increasing the processing speed in computers and other electronic devices (Zhang 2017). In the construction field, nanomaterials used in cement, mortar, concrete, paints, insulating materials and glass help to improve the durability, strength, fire resistance, and heat stability of the constructions. Besides, the fire-resistant, heat-controlling, and water-resistant textiles made utilizing nanomaterials have a significant interest in the commercial market (Oke et al. 2017). Similarly, in automobile industries, nanomaterials, carbon-based microfiber and nanofibers, are used to fabricate heat-resistant windows, reinforcement materials in tires, anti-rust coatings. and even help to make auto bodies lighter (Mathew et al. 2019).

In the medical field, nanomaterials and nano-based sensors are considerable for diagnosis and treatment of various diseases in their early stage without any side effects. For example, most of the glucose detectors in our daily life used to measure

blood sugar level are built based on nanomaterials. They are also been used to develop implants, prosthetics, and chip-based drug delivery systems (Srinivasan et al. 2015). Meanwhile, nanobiosensors are capable of detecting single cancer cells in blood or other regions of the patient's body enabling focused treatment (Tansil and Gao 2015; Kargozar and Mozafari 2018). Thus, the advancement of nanomaterials leads to the development of various emerging new smart biosensor devices. These smart biosensors can detect a low concentration of the desired analyte within a fraction of seconds. Moreover, the modified nanomaterials are predicted to increase the performance of the biosensor with high sensitivity, selectivity, and low limit of detection.

16.2 Nanomaterials in Biosensors

The pioneers Clark and Lyons first introduced biosensors in 1960, and in 1967 the scientists Updike and Hicks reported the first enzyme-based sensor. Followed by their inventions variety of research works have described the primary function and feature of biosensors, that sense biological and chemical materials. A biosensor is a smart analytical device that generates an electronic signal by receptor-target analyte interactions. It consists of a bioreceptor, a transducer, a signal processor for converting electronic to the desired signal and an interface. This sensing has been accomplished by another biologically active material called bioreceptor. The second component transducer system converts the analyte and its respective bioreceptor interactions into an electrical signal. The electric signals from the transducer are received by the third component called a signal processor, which amplifies to read and interpret the data. Besides these components, another essential requirement is the immobilization of bioreceptor which enhances the reaction with bioanalyte feasibly and efficiently. For the immobilization of biorecognition elements, various nanostructured materials like metal/metal oxides, carbonaceous materials, polymer, biomaterials and hybrid composites are used to enhance the electroanalytical performances of the biosensors (Fig. 16.1) (Pandit et al. 2016).

Recently, numerous biosensor devices utilize nanomaterials for improvising upon the sensing mechanism. However, the physicochemical properties of the nanomaterial control or determine its purpose in biosensor applications. For example, quantum dots are used as fluorescent sensing platforms for biomolecular

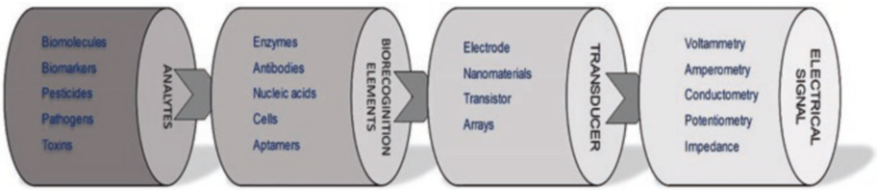

Fig. 16.1 Schematic illustration of electrochemical biosensor

detection, the colloidal nanoparticles conjugated with antibodies are used in immunolabeling and immunosensing applications. Moreover, metal compound nanomaterials are very effective in the detection of nucleic acid sequencing. Continuing along the same direction, metal oxides nanomaterials have been used for biochemical sensors, like glucose, cholesterol, urea, uric acid, ascorbic acid, and other metabolic intermediates. Similarly, carbon nanotubes have been widely used for glucose and insulin biosensor due to their rapid detection and biocompatibility (Gerwen et al. 1998).

In biosensor, the selection of nanomaterials for electrode fabrication depends upon a multitude of factors and their optimization processes. The most important factors are the physicochemical properties in addition to their selectivity and sensitivity. Foremost, the main focus is the nanofabrication process, which involves two critical procedures, namely the construction and design of the sensitive nanoscale surface. Four basic techniques are used for developing nanomaterial-based biosensor electrodes, namely lithography, surface etching strategies, thin-film strategies, and chemical bonding. Among these techniques, the lithography technique provides large surface areas for effective immobilization with high precision and sensing accuracy (Pak et al. 2001).

16.3 Types of Nanomaterials in Biosensor

16.3.1 Nanosized Metal Compounds

Metal and metal oxides nanoparticles (MNPs and MONPs) are widely used in highly sensitive novel electroanalytical devices. These nanostructures can enhance the selectivity of the device when conjugated with biorecognition molecules. Both MNPs and MONPs exhibit significant electrical and electrochemical properties because of their tunable bandgap, size, stability, and large surface area. In biosensor fabrications, the techniques like physical adsorption, electrodeposition, and chemical covalent bonding are employed to fix MNPs and MONPs on the surface of the working electrode. Generally, MNPs such as gold (Au), platinum (Pt), silver (Ag), and palladium (Pd) have been extensively used in biosensors. These MNPs are used alone or in combination with other nanostructures in biosensor electrodes. On the other hand, the transition MONPs are mainly used in biosensors, which include oxides of iron, silver, copper, zinc, cobalt, manganese, nickel, vanadium, zirconium, titanium, and tungsten. Biomolecular sensors fabricated using these metallic nanostructures can contribute to significant signal amplification, higher sensitivity, selectivity, and great advances in sensing as well as quantification of various biomolecules and ions (For example Table 16.1) (Lia et al. 2010).

Table 16.1 Metal and metal oxide nanomaterials-based biosensor and performances

S No.	Nanomaterial	bioreceptor	Sensing agent	Deduction limit	Reference
1	Au NPs-MoS_2	Laccuse	Catechol	2 μM	Zhang et al. (2020)
2	Ag-GQDs	ssDNA	*Legionella Pneumophila*	1 zM	Mobed et al. (2020)
3	Au-Pt NPs	—	Daptamycin	0.161 pM	Ozcelikay et al. (2020)
4	Pd NPs	A549 aptamer	Cancer cells	8 cells mL^{-1}	Cui et al. (2020)
5	Antimone (Sb) QDs	Catalase	H_2O_2 from ovarian cancer samples	4.4 μM	Fatima et al. (2020)
6	Fe_2O_3	—	Carcinoembryonic antigen	—	Kumar et al. (2019)
7	ZnO	Lectin	Arboviruses	—	Simão et al. (2020)

16.3.1.1 Gold Nanoparticles (AuNPs)

The unique properties of gold nanoparticles (AuNPs) like easy conjugation to biomolecules of interest and low toxicity increase their interest in the biological applications. The potential properties of AuNPs such as quantum scale dimension, extreme conductivity, high catalytic activity, high surface-to-volume ratio and excellent biocompatibility facilitate their wide application in biosensors. The AuNPs are transducers in a biosensor, which produce a detectable signal on biological recognition of the primary event originating on their surface or interfaces. Moreover, the adsorption of biomolecules on the AuNPs surfaces can retain their bioactivity and stability because of the biocompatibility and the high surface free energy of the AuNPs. Apart from the pristine AuNPs, the AuNPs coupled with or dispersed in polymeric compounds like polyaniline, polypyrrole, and chitosan are also potential for the fabrication of electrochemical biosensors. These AuNPs/polymer composite electrodes have considerable stability in different solvents, better biocompatibility, high processability, and are even retainable or reusable. For example, the carboxymethyl chitosan-AuNPs nanocomposite designed by Xu and coworkers is potential for H_2O_2 electrochemical sensing (Xu et al. 2006). This nanocomposite exhibited good hydrophilic nature with biocompatibility for enzyme immobilization and showed excellent biosensor performances with good stability and sensitivity.

The electrochemical glucose biosensor constructed by surface-immobilized periplasmic glucose receptors on AuNPs displayed a sensitive detection of glucose with a low detection limit (0.18 μM). In this, the genetically engineered cysteine is crucial for the immobilization of the receptor (protein) to the AuNPs by a direct sulfur-gold bond (Andreescu and Luck 2008). Similar to the polymer matrix, the AuNPs revealed excellent performance when worked in combination with other metal nanoparticles. For instance, the copper-nanoflower decorated

AuNPs-graphene oxide nanofiber-based electrochemical biosensor fabricated by Baek et al. showed high sensitivity and selectivity in glucose detection (Baek et al. 2020). The large surface-to-volume ratio, catalytic, and interface-dominant properties of AuNPs can decrease the overpotentials of many analytically important electrochemicals and even contribute to some reversible redox reactions. These advances appropriate the fabrication of enzyme-free AuNPs biosensors. Moreover, the AuNPs contributes to the oxidation and reduction of H_2O_2 and leads to the development of biosensors for the detection of various kinds of analytes. For example, Pekmez and coworkers reported an enzyme-free H_2O_2 electrochemical biosensor utilizing a disposable electrode fabricated by the poly(2-aminophenylbenzimidazole)/AuNPs-coated pencil graphite (Teker et al. 2019).

16.3.1.2 Silver Nanoparticles (AgNPs)

Silver nanoparticles (AgNPs) are another significant MNPs widely used in biomedical applications owing to their high conductivity, amplified electrochemical signal, high sensitivity, antibacterial activity, and excellent biocompatibility (Prasad 2014; Aziz et al. 2014, 2015, 2016, 2019). Recently, AgNPs and their nanocomposites have been extensively used for the design and construction of novel analytical techniques for various analytes like the early-stage diagnosis of diseases by disease markers, biosensors, and other disinfection agents. The silver nanoparticles composited with metal oxides, CNTs, silicates, graphene, polymers, dendrimers etc., considerably enhance the performance of biosensor. Since, the AgNP composites synergize the conductivity, electrocatalytic activity and biocompatibility of the materials. Researchers developed silver nanoparticles-based biosensor for the detection of H_2O_2, glucose, dopamine, uric acid, ascorbic acid, etc. For example, Xu et al. developed a high-performance enzymatic biosensor with polymeric nanoparticles and conductive silver nanoparticles for H_2O_2 detection. Here, horseradish peroxidase as a model enzyme was co-assembled with an amphiphilic and photo-cross-linked with polypeptides. This biosensor demonstrated high sensitivity and stability with low detection limit and wide detection range for H_2O_2 in milk and human urine samples. This promising feature of its application in the real samples can provide inspiring thoughts for the development of new biosensing systems (Xu et al. 2019).

16.3.1.3 Platinum Nanoparticles (PtNPs)

Recently, platinum nanomaterials (PtNPs) have engrossed in electrochemical biosensors for disease diagnosis and other biomedical applications, because these noble metal NPs have unique electronic properties and electrocatalytic activities for many chemical reactions. These properties completely depend upon size, shape, compositions, crystal orientation, surface reactive site etc., of the NPs. The PtNPs also ease the electron transfer and also easily modified with a wide range of

biomolecules and compounds. The PtNPs and nanocomposites exhibit fast, reliable, and precise bioanalytical methods. The electrochemical sensors based on platinum nanoparticles revealed enhanced sensitivity and selectivity towards the detection of various biomolecules. Various research reports are available for platinum nanoparticles and their nanocomposites-based biosensors. For instance, a novel glucose biosensor was constructed based on platinum nanoparticles into polyaniline-montmorillonite hybrid nanocomposites for glucose detection in human serum. This platinum nanocomposite biosensor exhibited excellent stability over two months and with high sensitivity and selectivity (Zheng et al. 2020).

16.3.1.4 Palladium Nanoparticles (PdNPs)

Similarly, the palladium nanoparticles are also an interesting candidate for the construction of biomedical devices due to their high catalytic activity and sensing properties. For the facile selective catalytic and sensing property of the PdNPs, the size and shape of the nanoparticles are very important, which can be attained during the synthesis process. Due to the unique catalytic performance, electronic properties and sensing behavior, different forms of palladium-based nanostructures like composites, bimetallic compositions, metal oxides, and carbon composites were used in biosensing devices. Most commonly, PdNPs and their composite-based biosensors have been utilized for the detection of glucose, H_2O_2, dopamine, cholesterol, etc. (Phan et al. 2020). Dopamine is a significant catecholamine neurotransmitter, which is used for the early diagnosis and treatment of diseases like Parkinson, Alzheimer's, and Schizophrenia. In a dopamine biosensor, the PdNPs are incorporated with the nanoporous gold for the construction of the sensor electrode. This combination of PdNPs enhances the electrocatalytic effects on the dopamine with the broad detection range, high sensitivity, and excellent selectivity (Yi et al. 2017).

16.3.1.5 Quantum Dots

Quantum dots (QDs) are another prominent 0D-nanomaterial used for the bioanalytics and biomedical applications. The QDs are luminescent semiconducting nanocrystals, mostly the metal chalcogenides (MX; M = Cd, Pb, Cu, etc., X = S, Se, Te). These QDs can provide a high absorption spectrum with a size-dependent narrow emission spectrum. Small-sized quantum dots have unique optical and electronic properties, which make them a promising candidate in biomedical, chemical, and physical applications. Especially in biosensors, the QDs are a construction element for efficient detection of various biomolecules. The surface of QDs can easily modify with biomolecules such as peptides, antibodies, enzymes, and DNAs for the construction of sensing devices. QDs with high photostability, high quantum yield, and long life makes them ideal for fluorescence-based biosensor. Interestingly, the

fluorescence resonance energy transfer (FRET) method has widely used for QDs-biosensors (Ma et al. 2018). Here, fluorescence signals can be detected by a single molecule detection method, as this technique has distinct advantages such as high signal-to-noise ratio, low sample consumption, rapid analysis time, and high sensitivity. This analytical method is used to detect various biomolecules including enzymes, microRNAs, DNA methylation, and DNAs.

For disease diagnosis, the target enzymes such as caspases, DNA glycosylase, DNA methyltransferase, terminal deoxynucleotide transferase (TdT), O-GlcNAc transferase, protease are detected by QD-based FERT biosensors. For instance, Petryayeva and Algar designed a QDs (CdSeS/ZnS) immobilized paper-based protease biosensor. They demonstrated that the QDs are viable probes that serve as alternatives to AuNPs for the next-generation paper-type diagnosing kits. This paper-based biosensor detected the analyte within 5–60 min at a low level of 1–2 nM protease (Petryayeva and Algar 2013). Similarly, glycoproteins, prostate-specific antigen, and carcinoembryonic antigen are also targeted for early diagnosis and treatment using QDs-based sensors.

Glycoproteins are essential large family proteins, and their abnormal expressions represent the presence of some dangerous diseases. So, glycoproteins are significant biomarkers for biomedical diagnosis and research. In recent work, a fluorescent FRET probe between the glucosamine-Mn-doped ZnS QDs and mercaptophenylboronic acid (MBA)-capped AuNPs is demonstrated for the detection of glycoproteins. The designed sensor probe was accurate to determine 10^{-9} M glycoproteins and showed wide linear detection range for glycoproteins like α1-acid glycoprotein (AGP; 0–0.5 μM) and immunoglobulin G (IgG; 0–2.4 μM). Further, the QDs-based FRET probe exhibited high selectivity and anti-interference ability in the detection of ACP from serum (Chang et al. 2017).

MicroRNAs are short noncoding RNAs, which are responsible for gene expression by binding to the 3′-untranslated regions of target mRNA. The microRNA dysregulation may lead to a variety of human diseases such as cardiovascular diseases and cancers. Ho and Willner fabricated a QD-based biosensor for the detection of miR-141 (microRNA), a promising biomarker for prostate cancer. This biosensor achieved the lowest of 1 pM detection limit and implemented for the analysis of miR-141 in serum samples. And the analysis showed impressive result between the serum samples of healthy individuals and prostate cancer patients (Jou et al. 2015).

16.3.1.6 Iron Oxide Nanoparticles

Magnetite (Fe_3O_4) and Hematite (Fe_2O_3) nanoparticles are widely used phases of iron oxides in electrochemical sensors. Because, the iron nanoparticles are excellent immobilization matrix due to its various interesting catalytic and physicochemical properties. Moreover, iron oxide nanostructures are used for the fabrications of biosensor electrodes, which are potential for sensing various analytes like glucose, H_2O_2, heavy metals, and organic entities (Kaushik et al. 2009; Lee et al. 2016;

Absalan et al. 2015; Fang et al. 2005; Zhang et al. 2011). Further, the combination of iron oxide nanostructures with various nanostructures like carbon, metal compounds, and polymer has considerably improved their electrocatalytic properties. Moreover, these compositions lead to the enhancement of electron-transfer kinetics, surface-to-volume ratio, biocompatibility, electrical conductivity, mechanical strength, etc. Besides, the iron oxide-polymer composites are used for the fabrications of lightweight, flexible disposable biosensors due to the synergetic effects rendered by the combination of metal oxide and polymer (Zhu et al. 2015; Wen et al. 2014). For example, Kumar et al. devised an iron oxide/poly(3,4-ethylenedioxythiophene): poly(styrenesulfonate) (PEDOT:PSS) modified conducting paper-based biosensor. The resultant biosensor was promising for the detection of cancer biomarker (carcinoembryonic antigen) and achieved a low detection rate of 4–25 ng mL^{-1} with high sensitivity (10.2 μA ng^{-1} mL cm^{-2}) (Kumar et al. 2019).

In addition, other magnetic nanoparticles, such as cobalt oxide, nickel oxide,-based biosensors have been broadly used to detect a wide range of analyte targets like proteins, enzymes, drugs, DNA/mRNA, pathogens, and tumor cells. Furthermore, these magnetic nanoparticles can be used as labels or integrated into transducer materials, which effectively enhance the sensitivity and stability of the biosensors. Moreover, high accessible active surface and superior electron-transfer behavior of magnetic nanoparticles are the bonus advantages of these magnetic materials for electrochemical biosensor (Rocha-Santos 2014). Furthermore, the noble metal nanoparticles supported with these magnetic metal oxide nanoparticles display much higher electrocatalytic activity. Recently, Lang et al., developed nanoporous supported cobalt oxide hybrid microelectrodes as a nonenzymatic electrochemical glucose biosensor. This amperometric glucose biosensor exhibited a multi-linear detection with high sensitivity (12.5 mA mM^{-1} cm^{-2}) and very low limit of detection 5 nM (Lang et al. 2013).

16.3.1.7 Zinc Oxide Nanoparticles

Zinc oxide is another important metal oxide widely used in biosensors. Its promising properties like wide bandgap, high exciton, better electrochemical activities, low cost, nontoxicity, chemical and photochemical stability, biocompatibility, and high-electron communication features attract the material for designing biosensors (Bhuyan et al. 2015). Different crystallite size and morphologies of ZnO can be synthesized by controlling various factors like pH, reaction temperature, capping agents and surfactants. Nanoflowers, nanorods, nanoplates, nanorods, nanocubes, and nanospheres are the versatile morphologies of ZnO nanomaterials. ZnO nanostructure exhibits good sensitivity and stability in electrochemical biosensors. The ZnO acts as an active platform with particular binding affinity for the immobilization of biological recognition component. The 1D ZnO nanostructures like nanorods, nanowires, and nanotubes are interesting due to their large surface area and can provide a direct and rapid electron transport pathway. In field-effect transistor biosensors, the vertical and lateral 1D ZnO have exhibited long-term monitoring

potential, large surface area, high enzyme immobilization efficiency, long-term stability, and simple fabrication techniques (Zhao et al. 2010). Further, the 3D ZnO nanoarchitecture is also demonstrated as a promising candidate, and this structure highly influences the biosensing process. Mostly, these nanostructures are synthesized by the bottom-up approach and are potential for developing amperometric, potentiometric, and impedimetric biosensors (Napi et al. 2019). Anusha et al., fabricated glucose biosensor with the aid of nanoporous ZnO with glucose oxidase enzyme. The cyclic voltammetry and impedance spectroscopic analysis showed enhanced glucose sensing property with good analytical performance and high sensitivity (Anusha et al. 2014).

16.3.1.8 Other Metal Oxide Nanoparticles

Manganese oxide nanoparticle is another beneficial and considerably studied material for electrochemical biosensor. Different crystalline phases like MnO, MnO_2, and Mn_3O_4 of the manganese oxide nanomaterials are significantly utilized in biosensors, since manganese oxide is a low-cost, nontoxic, environmentally friendly, and natural abundant material. In biosensor, various one-dimensional manganese oxide morphologies like nanowires, nanorods, nanobelts, and nanoneedles are widely used and showed promising sensing properties (Majd et al. 2016). In addition, the copper oxide (CuO or Cu_2O) is a p-type semiconductor which is an extensively studied metal oxide nanostructures for the electrochemical sensors. It can be easily synthesized with different morphologies, integrated with other nanostructures like CNTs, graphene, activated carbon, conducting polymers, and have potential applications in highly selective and sensitive electrochemical sensors (Li et al. 2015).

Similarly, the rare earth oxide, cerium dioxide has a considerable interest in the field of biosensors owing to its high catalytic activity and a better immobilization matrix. The electrochemical H_2O_2 sensor developed using single-walled carbon nanohorns/cerium oxide nanoparticles showed excellent H_2O_2 sensing with a low limit of detection 0.1 mM. Besides, it showed high stability, excellent reproducibility and increase sensitivity. The research team also examined the performance of biosensor in milk and cleaning liquid. The results showed a substantial selectivity towards H_2O_2 even such complex matrices and confirmed it as a highly promising material for the development of numerous biosensor (Bracamonte et al. 2017).

16.3.2 Carbon Nanomaterials

Carbon nanostructures are very popular due to their advanced physicochemical properties and specific structures. Carbon nanomaterials exist in a variety of dimensions: 0D, 1D, 2D, and 3D nanostructures. The graphene quantum dots (GQDs) are a zero dimensional carbon nanostructure consists of single or few layer of *sp2*

bonded carbon atoms (graphene). The GQDs exhibits excellent chemical, physical, and biological properties that allow them in numerous potential medical applications. The 1D carbon nanotubes have a peculiar tubular structure, high mechanical stability, good biocompatibility, and excellent electron transfer properties. Graphene is a 2D structure, which has many advantages such as large active surface area, excellent conductivity, high carrier capacity, and stability. Nanocrystalline diamond and fullerite are the best examples of three-dimensional structures. These carbon nanostructures have been potentially utilized for the development of biosensors, and they displayed sensing properties regarding their various structures. The biosensors fabricated using some technologically important carbon nanostructures are briefly discussed below.

16.3.2.1 Carbon Nanotubes (CNTs)

The carbon nanotubes (CNTs) have a unique one dimensional structure, a high electrical conductivity, large surface area, good chemical stability and excellent electron transfer properties arouse growing interest in modern electronic and biomedical devices. In electrochemical biosensors, CNTs are employed as transducers, which significantly enhance the sensitivity and detection properties. The high surface-to-volume ratio of CNT alters immobilization of greater concentrations of bioreceptor. The high electrical conductivity of CNTs and their feasible surface functionalization properties are highly appropriate for the recognition of a target and transduction of their signals (Clancy et al. 2018). Moreover, their ability to penetrate within the biological membranes makes them relevant for in vivo photoacoustic imaging. Based on the mechanism, target recognition, and transduction, the CNT-based biosensors are classified as electrochemical biosensors, immunosensors, and optical biosensors.

CNTs are highly appreciable for the development of sensitive biosensors, which enable the easy and early diagnosis of various diseases including cancer. Figure 16.2 schematically illustrates CNT biosensors for the detection of various cancer biomarkers coupled with DNA, enzymes, antibodies, proteins, aptamers, and peptides (Shobha and Muniraj 2015; Choi et al. 2010). CNT-based immunosensor is still in the incipient stage, and many challenges are there to overcome for successful commercialization. The multiwall carbon nanotubes (MWCNTs)-coated paper-based disposable bipolar electrode is used for the diagnosis of prostate-specific antigen, and this electrochemiluminescent detection showed high sensitivity and specificity in electrochemical biosensing (Feng et al. 2014). The multi-array sensor was fabricated using chitosan/MWNTs via electrodeposition technique. The resultant sensor array demonstrated the simultaneous detection of endogenous metabolites, drugs, pH, and temperature (Baj-Rossi et al. 2014). In another work, the early-stage diagnosis of prostate cancer has been achieved through a biosensor designed using DNA strands functionalized SWNTs and MWNTs electrodes for the effective detection of PSA in blood samples. Zheng and coworkers devised the electrochemical HeLa and HL60 cancer cell sensors using folic acid functionalized polydopamine-coated

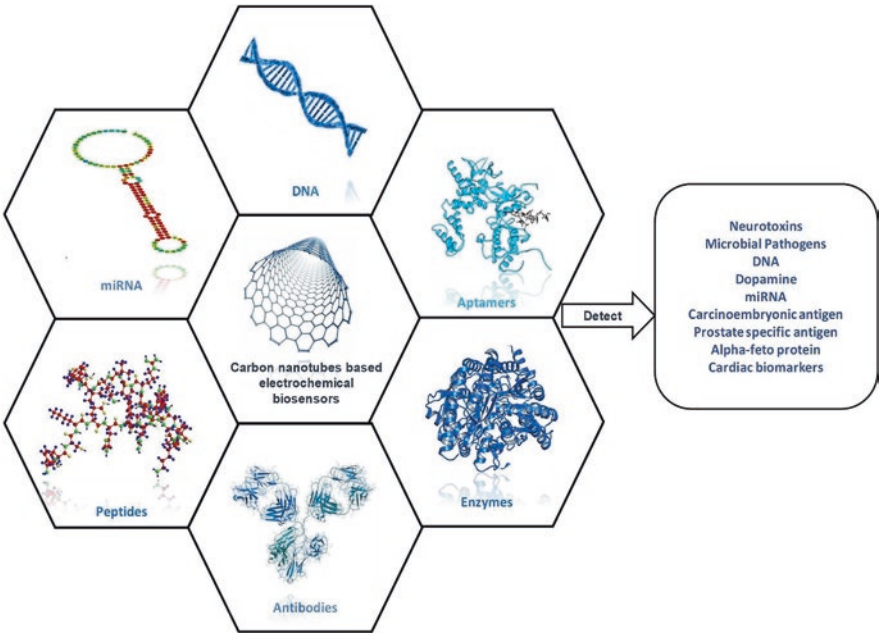

Fig. 16.2 Carbon nanotubes (CNTs)-based bio-recognition elements for the detection of analytes

CNTs. Here, the cancer cells were detected by evaluating the overexpressing folate receptors (Zheng et al. 2012).

CNTs-based biosensor electrodes are applicable for the detection of cancer biomarkers such as microRNA, DNA, alpha-fetoprotein, PSA, or CEA and quantified by the clinically significant metabolites like lactate, cholesterol, glucose, and glutamate (Dey et al. 2013). In recent years, a wide variety of CNTs-based amperometric sensors, field-effect transistors (FET) biosensors and impedimetric sensors have been designed and reported for the detection of various cancer biomarkers. For example, CNT-based impedimetric biosensor was fabricated using vertically aligned carbon nanotube on $Ni/SiO_2/Si$ layers by photolithography process for the efficient sensing of SW48 cells (Abdolahad et al. 2012). Similarly, Barekat et al. developed a screen-printed amperometric biosensor using CNT to detect the formaldehyde released from U251 human glioblastoma cells. The biosensor is comparatively cheap and displayed sensitive, selective, and rapid detection of the target (Bareket et al. 2010). Moreover, the CNT-based electrochemical biosensors are potential towards the detection of H_2O_2, ions, metabolites, and protein biomarkers (Tilmaciu and Morris 2015).

16.3.2.2 Graphene

Next to CNTs in the field of the biosensor, graphene is widely used 2D carbon nanomaterial with one atom to a few nanometers thickness. Graphene is the basic building block of all other dimensional graphite materials. Various forms of graphene such as graphene oxide, reduced graphene oxide, and graphene nanoribbons are prominently used in electroanalytical detection applications towards various disease diagnosis. The peculiar properties of graphene, like excellent electrical conductivity, high optical and mechanical properties, biocompatibility, rich active sites, and large specific surface area, make them a potential material for the construction of biosensors with the outstanding performance (Krishnan et al. 2019). Graphene with high water solubility and biocompatibility was rendered by an optimized chemical functionalization process. This graphene structure can be much easier to alter with some chemical and biological functionalities for better sensing properties. Similarly, the graphene oxide reduced to form functionalized graphene have a wrinkled structure due to the presence of lattice and edge defects, and this is different than the rippled structure observed in pristine graphene. These lattice or edge defects have a better affinity towards the biomolecules or other functionalities to determine the performance of biosensors. Among various graphene structures, the porous graphene (3D graphene) structure is recently confirmed as a promising candidate for immobilizing enzyme and enhancing performance in biomolecule sensing (Taniselass et al. 2019).

Recent reports establish that the graphene and its composite electrodes have extraordinary electron-transport property, high surface area, and anchoring site for the effective immobilization of enzymes. Liu et al. fabricated dopamine biosensor using PEDOT: PSS/graphene composites on fluorine doped tin oxide (FTO) electrode. The resultant biosensor detected dopamine from the aqueous medium in the presence of uric and ascorbic acid. The device showed an interference-free detection of dopamine with a detection limit of ~105 nM and sensitivity of ~27.7 μA μM^{-1} cm^{-2} (Liu et al. 2017). In another study, the $Ni(OH)_2$ nanoflakes/graphene oxide (GO) nanosheets were used for the fabrication of the dopamine electrochemical sensor, which exhibit an excellent selectivity under the interference of uric acid, also showed high repeatability and stability (Yue et al. 2019).

16.3.3 Polymeric Nanomaterials

Recently, polymeric nanomaterials were widely used in biosensor platforms due to their biocompatibility, long-term stability, tunable surface functionalities for the attachment of biomolecules, and flexibility (Prasad et al. 2017). For instance, polymeric structures with planned structure, homo-polymers, copolymers, and molecular shape recognition structures are utilized for the fabrication of biosensors. The most important factors that influence the performance of polymer-based sensor were biofunctionalization of the exposed active surface and biomolecules,

durability by the type of binding with biomolecules, high specificity towards bioanalytes, and increased electrochemical signal transduction. Generally, polymer-based biosensors are used for the detection of DNA, protein, antigens, carbohydrates, enzymes, and metabolites due to their high sensitivity, selectivity, and linearity.

16.3.3.1 Conducting Polymers

Conducting polymers have an immense interest in biosensor devices due to their special physical and chemical properties and scalable and easy processing. The considerable electrical conductivity, biocompatibility, possible surface modification, low cost, large surface area, etc., of the polymers added special advantage for developing sensing systems. Moreover, the lightweight, mechanical durability, and flexibility of the polymer nanostructures are viable for the construction of flexible biosensor devices. Conducting polymers nanomaterial-based biosensors, especially field-effect transistor biosensor, DNA chips, aptasensors, and immunosensors have exhibited high sensing performance towards biomolecules or biological species. Conducting polymeric nanostructures like polypyrrole, polyaniline, and poly(3,4-ethylene dioxythiophene) are commonly used to fabricate sensors.

Polypyrrole (PPy) is a well-known and widely used conductive copolymer formed by polymerization of pyrrole. Recently, PPy nanostructures such as nanoparticles, nanotubes, hollow nanospheres, and core-shell nanomaterials have been used in biosensor devices due to facile functionalization, high conductivity, and environmental stability and friendliness. The PPy can be electrochemically polymerized on any required electrode surface in a controlled and optimized manner, which is promising for designing biosensors. Moreover, the selected biological compounds or aptamers can easily dope or incorporate with PPy layer via electrodeposition to enrich the sensing properties. For a microfluidic aptasensor, the aptamer and PPy nanowire were integrated directly over gold electrode via one-step electrodeposition process by Huang and coworkers. The device detected IgE protein solutions in a linear range between 0.1 and 100 nM with excellent stability and specificity. Moreover, the microfluidic aptasensor exhibited a low detection limit for a cancer biomarker MUC1, which was found comparatively precise than the commercial MUCI diagnosis assay (Huang et al. 2011). Yuan et al. fabricated an ultrasensitive immunosensor on a disposable indium doped tin oxide (ITO) glass for the detection of gypican-3 (GPC3) in human serum (GPC3 is a tumor marker for hepatocellular carcinoma). In this sensor, the pyrrole-α-carboxylic layer was electrochemically polymerized on ITO and the GPC3 antibody was directly covalently bonded with the carboxyl group. The resultant immunosensor demonstrated high sensitivity towards the detection of GPC3 analyte with considerable stability and reproducibility (Yuan et al. 2015).

Polyaniline (PANI) nanomaterials are another widely used conducting polymers in sensors due to their high conductivity, good environmental stability, and diverse color change in response to different redox states. PANI has been used in biosensors, neural probes, tissue engineering, and controlled drug delivery applications. Zhai et al. fabricated an extremely sensitive enzymatic glucose biosensor with hydrogel heterostructure composed of platinum nanoparticles and PANI. The enzymes were immobilized onto the PANI porous hydrogel structure, and it effectively catalyzes the glucose oxidation reaction. Moreover, the platinum nanoparticles catalyzed the reduction of H_2O_2 produced during the enzymatic reaction. This glucose sensor exhibited enhanced performance with ultrahigh sensitivity, a low limit of detection, and a fast response (Zhai et al. 2013).

Poly(3,4-ethylenedioxythiophene) (PEDOT) is a polythiophene derivative synthesized by conventional oxidative or electropolymerization techniques. PEDOT is a transparent thin film, which exhibits high electrical conductivity, excellent stability in the oxidized state, high charge mobility, and serves as a suitable matrix for enzyme immobilization. The PEDOT 1D structures like nanorods, nanowires, and nanotubes have a unique mechanism of direct electron transfer during electrochemical detection. For example, Vasantha et al. modified glassy carbon electrode with PEDOT nanostructure and reported as a dual sensor for the detection of dopamine and ascorbic acid. From the analysis, they observed a hydrophobic interaction between the aromatic groups of dopamine and the PEDOT film. Meanwhile, ascorbic acid was detected using the electrostatic interaction between the heteroatom of PEDOT and ascorbate ions (Vasantha and Chen 2006).

16.3.3.2 Molecularly Imprinted Polymers

In recent times, a widely developing technique called molecular imprinting allows the formulation of specific recognition sites in polymer matrices. This molecular imprinted polymer is potential for the development of the efficient biosensor for sensing various chemicals and biological molecules (Behera et al. 2020). Molecularly imprinted polymers (MIP) has achieved by simple wet chemical techniques precipitation, dispersion and emulsion seed polymerization techniques. In biological sensors, MIPs have to couple with appropriate transducers for quantitative detection. The combination of metal nanoparticles and polymer provides excellent functional nanomaterials for biomedical applications. The molecularly imprinted electroactive nanoparticles of water dispersible quality and a macromolecular self-assembly technique were employed for the development of paracetamol sensor. The resultant sensor exhibited good sensitivity towards the detection of paracetamol with a low detection limit of 0.3 μM (Luo et al. 2016).

16.3.3.3 Dendrimers

Dendrimers are 3D, hyper-branched, monodispersed, nanoscale polymeric materials with a high density of surface functional groups with unique molecular weight, shape, and size. These dendrimers structures have a single chemically addressable group called core or focal point, the dendron, and the surface functional groups. Various techniques have been developed for the synthesis of dendrimers such as divergent approach and convergent approach. In biosensors, the high mechanical and chemical stability, presence of excess surface functional groups and hydrophilicity established dendrimers as a viable immobilization matrix for biomolecules. Moreover, these properties enhanced the overall performance of the sensor and increased the sensitivity, stability, reproducibility and reusability. Dendrimers are poor conductors, but metallic nanoparticles can easily be coupled with functional groups to improve conductivity. Besides, the dendrimers have a considerable amount of amine groups on the surface, which is a much favorable site for the conjugation of numerous bioreceptors (Satija et al. 2011). Shende and Sahu fabricated enzyme-conjugated PAMAM dendrimers for the estimation of glucose content in saliva. In this work, the Fe_3O_4 nanoparticles encapsulated in PAMAM dendrimers to immobilize glucose oxidase in the presence glutaraldehyde a cross-linking agent. The biosensor showed a rapid response and high reproducibility (Shende and Sahu 2021). A surface plasma resonance (SPR) sensor was reported based on self-assembled monolayer/reduced graphene oxide-polyamidoamine dendrimer thin film for the effective detection of DENV-2 E-proteins (a dengue virus envelop protein). The sensor revealed high specificity, sensitivity, binding affinity, and selectivity towards DENV-2E proteins for the diagnosis of dengue virus (Omar et al. 2020).

16.3.4 Nanosized Biomaterials

Over the last two decades, the nanoscale biomaterials like biopolymers, proteins, nucleic acids, enzymes, and their nanocomposites are widely used in the biosensor, drug delivery, bio-imaging, biocatalysts, and cell targeting applications. By the combination of biotechnology and nanotechnology, nanocomposite materials were synthesized with extreme catalytic and recognition ability for electrochemical biosensor platform. Recently, electrochemical biosensor designed utilizing bionanomaterials have great attention in research and clinical field owing to its excellent performance like high selectivity, reproducibility, sensitivity and biocompatibility. Few of these nano-sized biomaterials utilized for sensor applications are discussed in the following section.

16.3.4.1 Chitosan

Among numerous commonly available natural polymers, chitosan is a marine-based biopolymer widely applied in the biomedical field. Chitosan is a natural polysaccharide, the most important derivative of chitin and derived using the N-deacetylated method. Chitin is obtained from the hard outer skeleton of arthropods including crab, shrimp, lobster, and beaks of cephalopods. It is also present in the cell wall of insects and some microorganisms like fungi. Due to its biocompatibility, environmental stability, good mechanic strength, hydrophilicity, low cost, and easy-processability, it is used as a substrate material or immobilization matrix in electrochemical biosensors. The chitosan has some amino and hydroxyl groups in its structure which can easily crosslink with various nanomaterials and biomolecules. Recently, chitosan nanocomposites formed in combination with inorganic metal compounds, carbon nanostructures, and bio-complexes are used for biosensors and biomedical devices. The chitosan nanomaterials-based biosensors revealed good sensitivity, selectivity, and stability for the detection of an analyte such as H_2O_2, proteins, glucose, DNAs, uric acid, biomolecules, microbial pathogens (bacteria to viruses).

Chitosan also acts as a mediator material between the biological recognition element and electrode surfaces. Zhang et al. reported a single-wall CNT/chitosan composite electrode as an aflatoxin B1 biosensor, where the chitosan is entrapped and attached with the SWCNTs on the glassy electrode surface. The differential pulse voltammetry achieved 3.5 pg/mL limit of detection (Zhang et al. 2016). Similarly, an amperometric biosensor was developed based on glucose oxide immobilized chitosan nanoparticles/gold electrode. Interestingly, these chitosan nanoparticles were synthesized from gladius of squid, *U. duvauceli*, by ionic gelation process. The biosensor possessed good amperometric response with high sensitivity. In addition, the Michaelis Menten kinetics revealed that a low value represents excellent substrate affinity towards the enzyme due to the presence of chitosan nanoparticles (Fig. 16.3) (Anusha et al. 2015).

16.3.4.2 Aptamers

Aptamers are artificial oligonucleotide ligands that bind to a highly specific target with high affinity. Aptamers can be isolated from a large random sequence pool using an in vitro process called systematic evolution of ligands (SELEX) process. Currently, numerous highly specific and high-affinity aptamers have been produced for various target molecules like proteins, peptides, and whole-cell. These aptamers are employed in biosensors as a recognition element known as aptasensors. In aptasensors, the aptamers can be immobilized without influencing its affinity and stability during denaturation and renaturation process. In an electrochemical aptasensor, the aptamers are immobilized onto the electrode surface, and the analyte binding

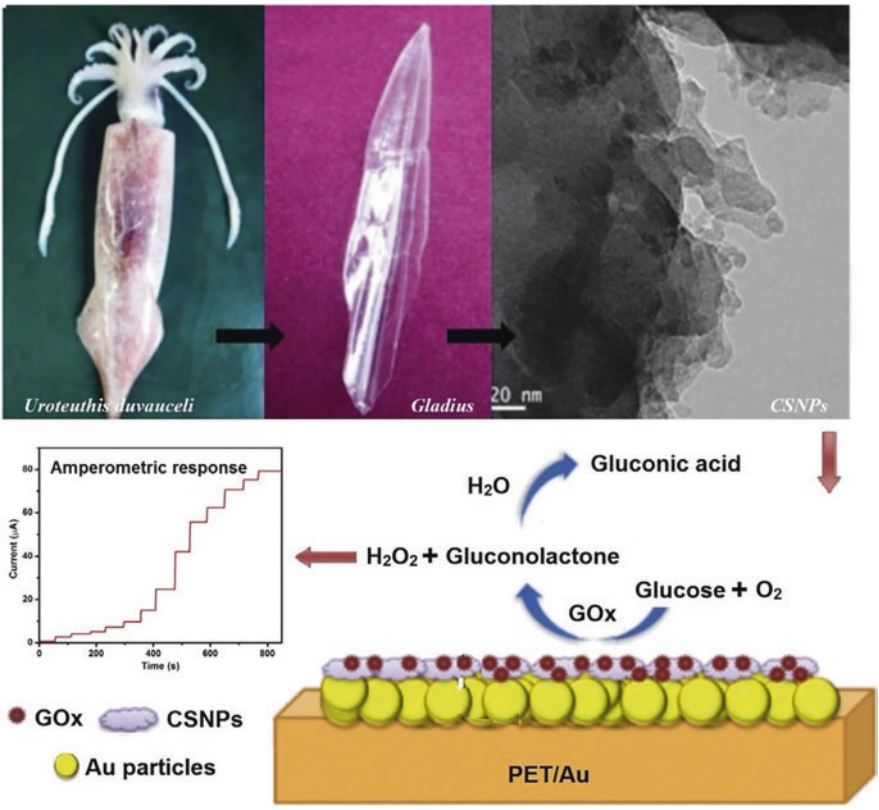

Fig. 16.3 Schematic illustration of electrochemical enzymatic glucose biosensor fabricated using chitosan nanoparticles from gladius of squid, *U. duvauceli* on PET/gold electrode. (Adopted from Anusha et al. 2015)

process is detected via the change in electrochemical signals. The main advantages of aptasensor are high sensitivity, miniaturized, and low fabrication cost (Hong et al. 2012).

Aptasensor is use for the diagnosis of cancer, and detection of various biomarkers and infectious disease-causing microorganisms. Generally, the aptasensors are used to detect biomarkers like thrombin, immunoglobulin E (Ig E), retinol binding protein (RBP4), C-reactive protein (CRP), N-terminal pro-brain natriuretic peptide (NT-proBNP), and interferon (IFN) in urine, blood, saliva, serum etc., for the early diagnosis of diseases. Zhang et al. developed an electrochemical aptasensor using functionalized mesoporous silica with MWCNT nanocomposites for thrombin detection. This device exhibited high sensitivity and wider linearity for the detection of thrombin in the range between 0.0001 and 80 nm with a low detection limit of 50 fM (Zhang et al. 2013). Using aptamer AS1411 and graphene modified electrode, a label-free cancer cell detection biosensor was developed by Feng et al. This cancer

aptasensor can distinguish cancer cells from the normal one and detect as low as 1000 cells (Feng et al. 2011).

Microbial infections caused by pathogenic bacteria and viruses can be detected and identified for public health protection. Mostly, the virus-infected cells can be detected by investigating the particular targets found on the host cell surface (Yao et al. 2020). For example, Tombelli et al. fabricated an aptasensor using RNA aptamers immobilized over piezoelectric crystal (quartz) for the detection of HIV-1 Tat protein based on QCM and SPR sensing. Both sensing platforms showed similar reproducibility, sensitivity, and specificity (Tombelli et al. 2005).

16.3.4.3 DNA Nanomaterials

DNA is a perfect material for biosensing applications due to its unique functionalities and structural versatility. The DNA biosensors are very sensitive, cost-effective and potential point-of-care diagnostic tools. Moreover, robust sensing and biocompatibility provide multiple readout strategies. Nanoscale DNA structures are used in devices such as fluorescence, FERT, electrochemical signaling, Raman spectroscopy and nanoparticle-based color change. DNA-based biosensor work based on the specific recognition events happens between a substrate and the target analyte. In particular, DNA tetrahedron-based biosensors combined with the surface-based assays are considerable for electrochemical detection (Arun 2017). For example, detection of Mucin 1 (MUC1) a tumor marker model, very significant for the early diagnosis of patients with tumor or carcinomas (Deng et al. 2017). A novel combination of aptamer and DNA nanostructure were utilized for the fabrication of biosensor. For the detection of acetamiprid, a partial paired complementary DNA of acetamiprid aptamer and four single-stranded DNA sequences were inserted at each side of tetrahedral DNA and modified with gold nanoparticles. The developed DNA -based aptasensor showed high performance with a low limit of detection and assists the selective detection of pesticide residues (Yao et al. 2020). Interestingly, electrochemical genosensors and immunosensors based on functional nanomaterials were used for new electroanalytical techniques, developing a perfect point-of-care diagnosis, DNA/enzyme amplification techniques, and miniaturization of devices.

16.4 Applications of Nanobiosensors

The highly versatile and multifunctional behavior of nanobiosensors leads to many and perhaps endless applications, from disease diagnosis to environmental monitoring, food industry, agriculture, marine sector, etc.

16.4.1 In the Medical Field

In medical science, nanobiosensors play a lead role in diagnosing various disease. Biosensors are applicable for the detection of metabolic disorders, serum antigens, and carcinogens (Table 16.2). Serum analysis is applied in some of the routine applications in diagnosis of diseases like cancer, diabetes, allergy, and many other disorders. The nanomaterials make the diagnosis of diseases further sensitive, rapid, and more precise. For the diagnosis of diabetes mellitus, glucose biosensors are being

Table 16.2 Summary of advantages and limitations of biorecognition elements used in biosensors for the detection of various analytes in the biomedical field

S No.	Biorecognition Elements	Analyte	Advantages	Limitations
1	Enzymes	Substrate	Strong binding capacity; excellent catalytic activity; ability to inhibit or catalyze reactions; significant stability over years	Less stability at harsh conditions; interfere with endogenous enzymes, and require multiple assays
2	Antibody	Antigen	Permit variable detection of bacterial cells and metabolite toxins; antibody-antigen binding specific interactions; noninvasive capability and direct recognition ability.	Unable to differentiate live from dead cells; highly challenging production; with high cost and long time.
3	Nucleic acid	Microbial pathogens, oligonucleotides, etc.	Promptly produced and regenerated in comparison with antibodies, and enzymes; and recognition is based on nucleic acid sequence identification base-pairing attribute.	Unstable at extreme conditions; poor solubility in aqueous media; high production cost
4	Whole cells	Antibiotics, proteins, vitamins, pollutants, etc.	Low production cost; highly stable; very few purification procedures.	Specific environmental conditions required; limited self-life; interfere with multiple biochemical pathways and create similar cellular response which produces false-positive results.
5	Aptamers	Pathogenic microorganisms, cancer cells, etc.	Easily prepared; highly stable; recognition and detection based on shape.	Produce false results when interacting with large molecules

used pervasively in the medical field, as they provide precise control over blood glucose level. Before the development of biosensors, the detection of blood glucose was complicated, time-consuming, and expensive. But the vast advances in blood glucose biosensors directed the usage at home in routine. The incorporation of nanomaterials in biosensors allows the enzyme immobilization easy, and this allowed the reuse and recycle of enzymes. In glucose biosensor, glucose oxidase enzyme is immobilized in polymer nanomaterials which improve the sensitivity and accuracy of the device. Moreover, the biosensors are widely used in hospitals to diagnose infectious diseases, particularly to diagnose urinary tract infections and to identify pathogens.

At present, more than one million people are suffering from heart diseases, so early phase identification is very important. A human interleukin (IL)-10 biosensor is used for the early diagnosis of heart failure (Lee et al. 2012). Various other methods have used for the diagnosis of cardiovascular diseases, including immunoaffinity column assay, enzyme linked immunosorbent assay and fluorometric assay require skilled personnel, laborious, expensive, and time-consuming. For cancer detection, immunosensor array for clinical immunophenotyping of acute leukemia, histone deacetylase inhibitor assay from resonance energy transfer, hormone-based biochip for a quick and accurate diagnosis. Dengue is a mosquito-borne virus, cause dengue fever. The early detection of this virus infection is very important for the control of the disease. The conventional methods used for the diagnosis such as immunological and molecular techniques are time consuming, expensive and require skilled professional. But the construction of electrochemical biosensors helps for the early diagnosis of dengue virus serotypes (Fig. 16.4) (Anusha et al. 2019).

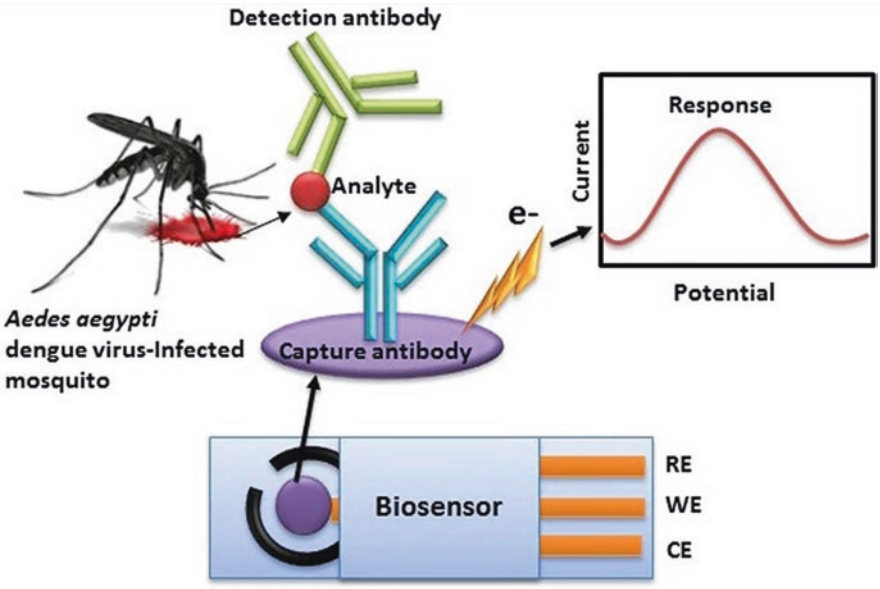

Fig. 16.4 The construction of electrochemical biosensor for the detection of dengue virus. (Adopted from Anusha et al. 2019)

16.4.2 In Environmental Monitoring

Our environment undergoes rapid change almost every second due to many factors, especially human activities. The detection of environmental pollutants, toxins, heavy metals, climate change, and many features are crucial to keeping the environment safe and healthy to live. The sensors play a vital role in the monitoring of the environment to rectify the problems. The nanomaterials-based devices with electronic probes require a small amount of analyte sample for analysis. Pesticide residue found in the soil, water, air and food cause major public health issues. Conventional methods used for the detection of pollutants involve liquid or gas chromatography (Zhao et al. 2007). This method is highly sensitive and reliable but requires skilled technicians, long process and procedure for meticulous sample preparation and very expensive. In contrast, electrochemical and immunoassay techniques are inexpensive, with simple fabrication and ease of miniaturization. Despite these advantages, the biosensors failed to conquer the market place. Hence nanotechnology is incorporated in biosensors to enhance sensitivity and reliability. Nanomaterials such as carbon nanotubes, graphene, quantum dots, and metal nanoparticles have been effectively used for novel biosensors (Fig. 16.5). For instance, acetylcholinesterase (AChE) enzyme is responsible for the destruction of neurotransmitter acetylcholine with nerve tissue, causing neurotoxicity and leads to death. The organophosphorus pesticides have an affinity for binding and inhibiting AChE. The AChE enzyme-biosensors have been used for the detection of pesticides and nerve agents, where AChE has been immobilized over nanomaterials to improve

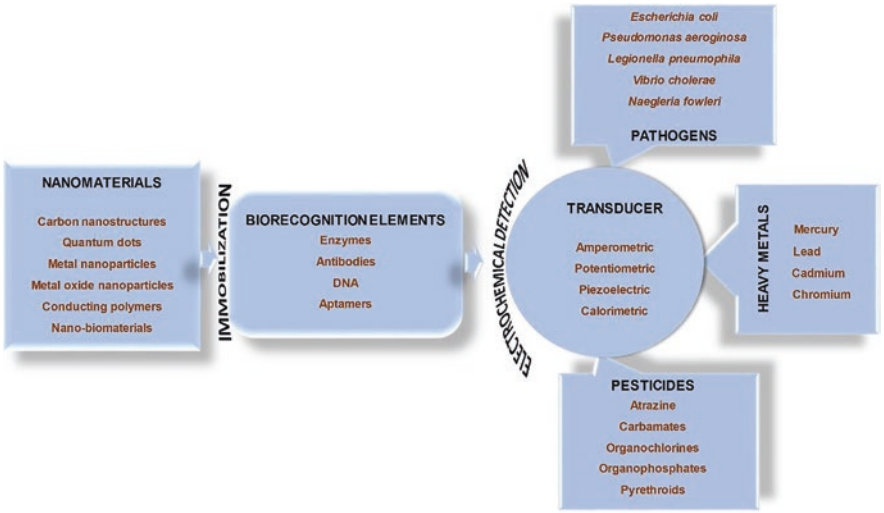

Fig. 16.5 Various nanomaterials and biorecognition elements utilized for the construction of electrochemical biosensor and analytical techniques used for the detection of environmental polluting agents such as heavy metals, pesticides, and pathogens

electrochemical response and stability. A self-assembled AChE on CNT- modified electrode was used for the detection of paraoxon (Liu and Lin 2006). Similarly, the substrate-specific detection mechanism has been developed for the detection of nitrates, inorganic phosphates, different contaminants, and parameters of biological oxygen demand. The application of nanobiosensors in environmental monitoring is highly time saving, energy saving, and economical.

16.4.3 In Food Industry

In the food industry, quality and safety are analyzed using traditional chemical experiments and spectroscopic analysis. These conventional methods are time-consuming, expensive, and require skilled laboratory technicians. The implementation of novel biosensors is a breakthrough in the food industry. The nanomaterials like CNTs, nanowires, MNPs, and other nanostructured materials are used as catalytic tools, immobilization platform to enhance biosensing. In most cases, the integration of enzymes, antibodies, and DNA sequences with nanomaterials provides a novel hybrid system for food industry applications (Chausali et al. 2021). Few examples that are applied in food analysis are pathogens, insecticides, and sugars. The main food poison or illnesses are caused due to having food contaminated by microbial pathogens like bacteria, fungi, or viruses. Microorganisms like *Salmonella, E. coli,* and *L. monocytogenes* are most examined pathogens regarding their detection and quantification in food. Biosensing platforms with nanomaterials are used to detect or identify these pathogens. For example, Dungchaia et al. developed a highly sensitive biosensor based on gold nanoparticles immobilized with monoclonal antibodies on polystyrene microwells for the detection of *S. typhi* (Dungchaia et al. 2008). The monitoring of carbohydrate level during the fermentation process is crucial in the food industry. Zhao and coworkers reported glucose detection in the food products using the Pt and Pd nanoparticles decorated graphite-based amperometric biosensor. This hybrid electrode increases the performance of glucose detection with high sensitivity and selectivity (Zhao et al. 2007).

16.4.4 In Agriculture

Nanobiosensors have a vital role in the detection of plant infections, and thus subsequent prevention of diseases is a considerable measure to sustain the availability of food and food products. The advances in the field of biosensor increase the growing global demands for higher food production, control diseases, food quality control and alarm climate conditions, which are very important in agriculture (Prasad et al. 2014, 2017a, b, c). Nanomaterial-based biosensors have a significant role in the detection of plant infections, phytohormones, metabolic content, abiotic stress, mi RNAs, etc., in a very short time of time. Traditionally, plant diseases have been

detected through direct observation of change in the plant morphology. Later, some laboratory techniques such as serological, electron microscope, and polymerase chain reaction have been used for the early detection. In general, the plant viruses are detected using immunoassays and optical DNA hybridization biosensor (Khot et al. 2012; Mufamadi and Sekhejane 2017). Gold nanoparticles are highly used in sensor functionalization systems for the detection of pathogens. Gold nanorods were utilized for the fabrication of SPR immunosensor to monitor dual viruses of an orchid plant, *Cymbidium mosaic virus* or *Odontoglossum ringspot virus,* which achieved LODs of 48 and 42 pg/mL respectively (Lin et al. 2014). Apart from gold nanoparticles, nanomaterials such as graphene, CNTs, metal oxide nanowires were also used for the construction of a biosensor for pathogen and mycotoxin detection. A DNA biosensor was successfully developed with ZnO nanoparticles and chitosan nanocomposite modified in the gold electrode for the identification of the soil-borne fungi, *Trichoderma harzianum.* The electrochemical analysis revealed good sensitivity and selectivity towards the target analyte (Siddiquee et al. 2014). In agriculture, soil humidity is an important factor for the effective yield of the crop. Various materials such as polymers, ceramics, and composites are utilized for the development of humidity biosensor. For example, $Na_2Ti_3O_7$ nanotubes coated on Al_2O_3 ceramic substrate in Ag-Pd as interdigitated electrodes are used for the fabrication of impedance-based humidity sensor (Zhang et al. 2008).

16.5 Challenges and Future Perspectives

Nanomaterials-based biosensors have been developed to answer many toughest analytical challenges. An ideal biosensor can detect a feeble quantity of analyte with more accuracy, precision, and rapidity. They must possess high mechanical, thermal, and chemical stability, and could be produced at low cost with easy procedures. In recent sensors, nanomaterials improve the features like biocompatibility, nontoxicity, and powerless operation, however, the desired properties and efficiency of the biosensors remain a challenge. But in electrochemical biosensors, the incorporation of nanomaterials leads to numerous challenges respective to the material of choice. Especially, the nanomaterials used in the fabrications of biosensors need high stability and operate under various conditions like strong ionic buffers, high temperature, and humidity and must be durable for even weeks and months. Nevertheless, these discrepancies can be overcome with surface modification or engineering the properties of nanomaterials in respective to their applications.

Another major advantage of nanomaterials is their surface-to-volume ratio. The main advantage of nanomaterials over bulk is their large specific surface area capable for the immobilization and better transduction. However, it is important to control and optimize the nonspecific binding over a large active surface, since it leads to the surface fouling. This surface fouling affects the signal intensity with a drop in relevant signal-to-noise ratio. This challenge can be overcome by real-world matrixes, that is, combining the nanomaterials with the antifouling materials. For example, polymers

with nanofiber structures have excellent antifouling property, and the surface charges can optimize the appropriate binding process. Further, the synthesis of nanomaterials-associated biosensors requires a cost-effective, reproducible, and scalable process. To achieve this a commercially viable product with reliable functionalization of materials is very important. Some detailed research is crucial to optimize some feasible methods like printing techniques, electrodeposition, and other solution-based processes like drop-casting, spray coating, and dip-coating.

In addition, the technology must focus on the development of novel materials with promising properties to solve the biocompatibility and immobilization problems. And need high concentration on developing new materials, design of multiarrays, miniaturization and flexible/wearable sensors. Moreover, future research direction and development appreciates more new findings; to avoid nonspecific reactions, to increase the signal-to-noise ratio, improve electron transfer rate, and better studies on the interface chemistry.

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Chapter 17
Nano-Adsorbents and Nano-Catalysts for Wastewater Treatment

Zeenat Sheerazi and Maqsood Ahmed

Contents

17.1 Introduction

Environmental conditions are very alarming all around us due to the anthropogenic activities disturbing the water bodies (Ray and Shipley 2015; Schwarzenbach et al. 2010). Even though anthropogenic processes are responsible for polluting water, natural processes also introduce some toxic metals into the water bodies due to weathering conditions, erosion of rock and soil, and rainwater (Wang and Mulligan

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A. Krishnan et al. (eds.), *Emerging Nanomaterials for Advanced Technologies*,
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2006). Water is the nectar for our life, but its quality is disturbed due to the contamination by industrial wastes, pesticides, harmful synthetic dyes and organic pollutants (pharmaceuticals, pesticide, phenols, fertilizer, plasticizer, detergent, oils, hydrocarbons etc.). Around the world more than 0.78 billion people face shortage of fresh and hygienic water. This causes serious infections and death of more than 200 million people every year, with 5000 to 6000 children deaths (Amin et al. 2014). Pollutant-removal techniques including biological treatment system, physicochemical, chlorination, ozonation, UV photolysis and ion exchange are not more effective for polluted water treatment (Amin et al. 2014). Due to enhancing nanotechnologies the role of nanomaterials in water purification attracted the attentions due to their nano size, large surface area, reusability, stability, electrical and optical properties (Lu et al. 2016; Prasad and Thirugnanasanbandham 2019). Various shapes of nanomaterials like nanowires, single and multi-walled carbon nanotubes (CNT), nano-colloids, carbon quantum dots (CQD), nano-membrane and films have been studied for diverse applications including wastewater treatment, due to their small size and large surface area (Fig. 17.1). These materials can be used in the form of absorbents for the capture of pollutants and catalytic degradation of larger organic molecules from polluted water (Khajeh et al. 2013). Metallic oxide nanoparticles including mono-metallic, bi-metallic and tri-metallic oxides are used in the form of absorbents and catalysts for wastewater remediation; the magnetic behaviour and presence of variable oxidation states make them efficient absorbents as well as catalysts (Ray and Shipley 2015; Khajeh et al. 2013). Nanostructural silica- and alumina-based materials were also studied in the form of nano-porous materials which provide accessible active sites. (Jadhav et al. 2019; Banerjee et al. 2019; Afkhami et al. 2011; Kalfa et al. 2009a). Polymer nanocomposite with hierarchical surface porosity is also an interesting material for the treatment of waste water (Zhao et al. 2018a). Moreover the nanomaterials can be functionalized with different types of

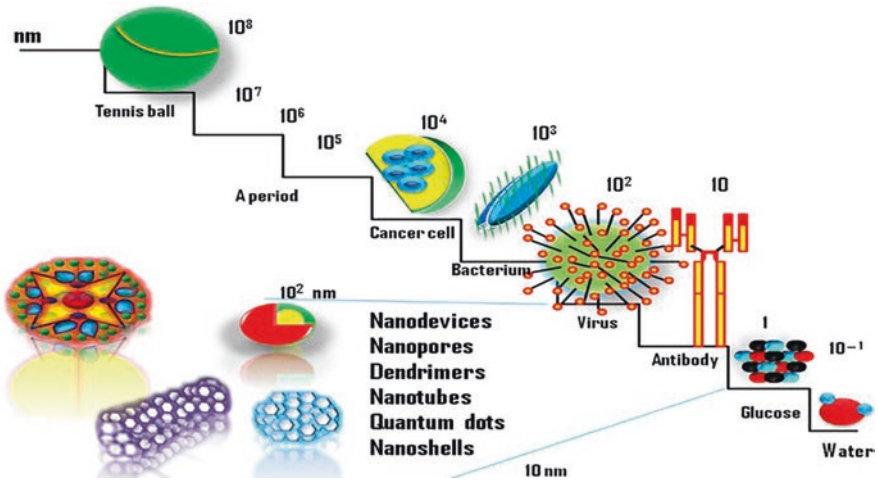

Fig. 17.1 Different morphologies of nanostructural materials

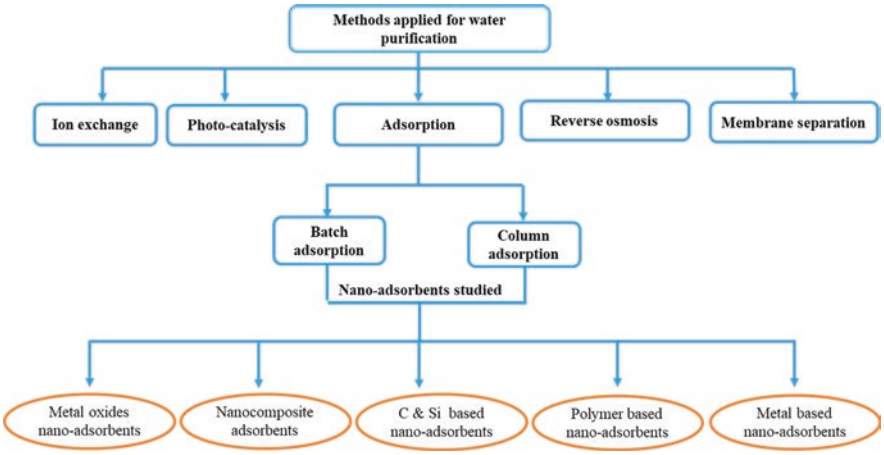

Fig. 17.2 Various chemical methods for waste water treatment and nano-adsorbents

organic functionalities possessing higher affinity for toxic metal ions (As, Cd, Hg, Cr etc.). Such materials include organo-modified nanostructural materials which can be functionalized via ex situ as well as in situ synthesis. The common methods used for the synthesis of metallic based nanoparticle involves co-precipitation, sol-gel and hydrothermal techniques. The nanoporous materials are commonly prepared through soft templating routes by using some surfactant and block copolymers as templates.

The most common methods applied for water purification are ion exchange (Akieh et al. 2008; Ismail et al. 2010; Qiu and Zheng 2009), reverse osmosis (Dialynas and Diamadopoulos 2009; Mohsen-Nia et al. 2007), electrochemical treatment (Hunsom et al. 2005; Deng and Englehardt 2007; Rana et al. 2004), membrane filtration (Qdais and Moussa 2004), photo catalysis and adsorption (Fu and Wang 2011). But the adsorption technique is the most recognised and convenient, as it does not require high amount of energy. The adsorption methods involve two different procedures viz. batch adsorption and column adsorption. The batch adsorption is carried out by adding the adsorbate into the sorbent solution under continuous agitation or stirring. The latter will be carried out through the continuous flow of contaminated water over fixed bed of adsorbent and is typically applied at industrial scale. Various chemical methods for waste water treatment and nano-adsorbents are depicted in Fig. 17.2.

17.2 Synthesis Approaches for Nano-Catalysts/Adsorbents

Most commonly the nanomaterials can be synthesised in two major categories viz. top to bottom and bottom to up approaches (Fig. 17.3). In top to down approach the bulk material is breakdown to nanoscale by mechanical process with uniform

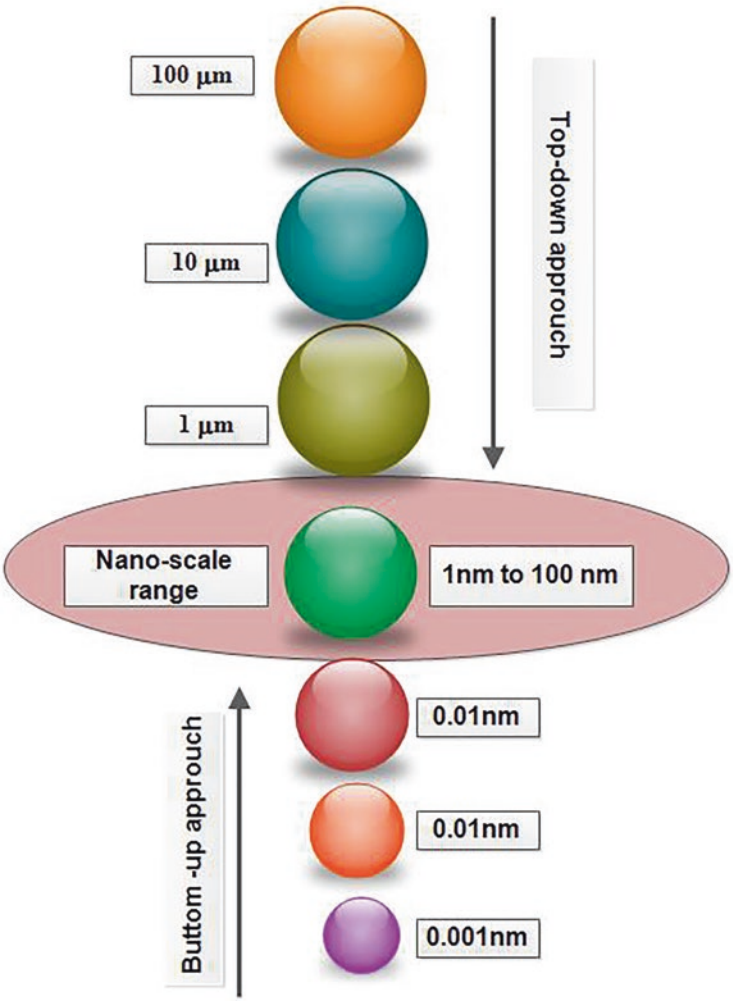

Fig. 17.3 Top-down bottom-up approaches for synthesis of nanomaterials

particle size and morphology. The latter involves the assembling of molecules and atoms to create various ranges of particles in nanoscales (Prasad et al. 2016). It is further divided into chemical, physical and biological methods. Among the three, the chemical method is more simplistic, low cost and quick in action. The chemical method is well established and more common, in which the nanomaterials are prepared through the interaction of molecules and atoms. It enables the easy functionalization of nanomaterials, which can be applied as adsorbents and catalysts in wastewater treatment. These chemical methods involve different synthetic chemistry (depicted in Fig. 17.5) viz. sol-gel, micro-emuslion, hydrothermal synthesis, Co-precipitation method, chemical vapour deposition (CVD) & Chemical vapour

synthesis (CVC), microwave and ultrasound-assisted synthesis (Devatha and Thalla 2018; Rane et al. 2018).

17.2.1 Sol-Gel Method

In sol-gel technique the colloidal solution called sol of the metal precursor or any inorganic species is formed through hydrolysis, followed by the condensation or formation of gel-like diphasic system containing both liquid and solid phases. The morphologies of these materials range from discrete particles to the polymer network range. Nanomaterials of different inorganic metals and their oxides like TiO_2, ZnO, SnO_2, CdSe, Fe_2O_3, ZrB_2, $GdVO_4$, Ta_2O_5, CeO_2 and nanoalumina are synthesised through sol-gel techniques and some of them are studied in the field of waste water treatment (Xiao et al. 2009; Sharma et al. 2008; Bayal and Jeevanandam 2012; Nautiyal et al. 2015; Reda 2010; Zhang et al. 2011; Chumha et al. 2014; Sreethawong et al. 2013). Variety of mesoporous silica nanoparticles (MSN) are synthesised through sol gel methods and studied for adsorption processes (Chen et al. 2018; Qin et al. 2018). Jie Chen et al. demonstrated the study of different morphologies of MSN synthesised through sol-gel and micro-emulsion method (Chen et al. 2018). The synthesis of MSN involves the soft templating route, in which surfactants are used as templates (Fig. 17.4). Mostly the silica

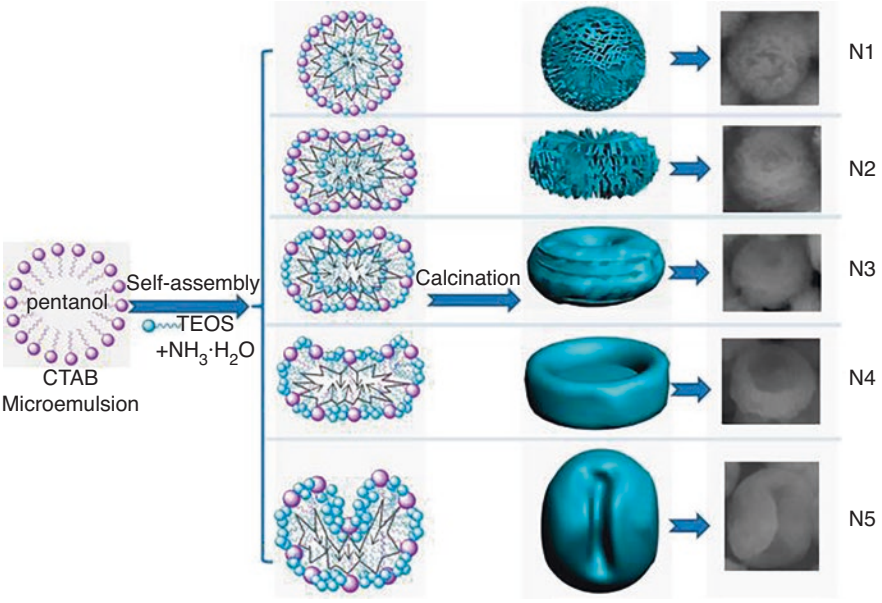

Fig. 17.4 Illustration of the synthetic procedure of MSNs with different morphologies. (Reprinted with permission from Ref. (Chen et al. 2018) Copyright (2020) American Chemical Society)

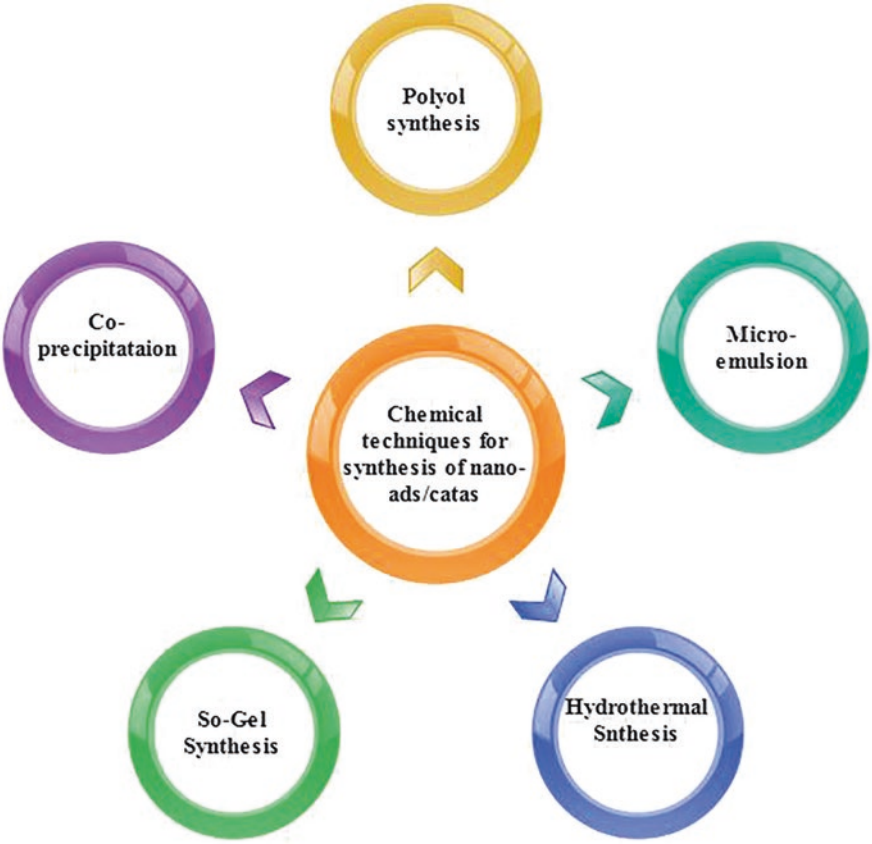

Fig. 17.5 Schematic representation of different techniques used for synthesis of nano-adsorbents and nano-catalysts through chemical method

precursors-tetraethylorthosilicate (TEOS) first hydrolysed and gets start condensing at different pH ranges. The surfactant/template is removed through calcination or solvent extraction methods. The same approach can be applied to other mesoporous materials by using their salt precursors with modified procedures.

17.2.2 Micro-Emulsion Method

Diameter range of 600 nm to 800 nm monodispersed spherical droplets of oil in water (o/w) or water in oil (w/o) depending upon the type of surfactant forming emulsion which is called as micro-emulsion system. Water in oil (w/o), also called as reverse micellar system, acts as a best reaction site for nanomaterial synthesis like Ag, Cu, CdS, Ni, Au, Rh, silica-CdS, Ag-Au, Pd-Au and Pd-Ag

nanoparticles. Other non-metallic nanomaterials of polystyrene (20–30 nm), cholesterol, rhodiarome, retinol, polyaniline, etc. can be synthesized through micro-emulsion technique. (Joshi and Kumar 2018; Wang et al. 2010a; Dhand et al. 2010).

17.2.3 Hydrothermal Synthesis

The process of crystallization under autogenesis pressure produced at higher temperature in the presence of water vapours is called hydrothermal synthesis. The synthesis is usually carried out in a stain less steel autoclave hydrothermal rectors, or any closed autoclavable container. Hydrothermal synthesis is a fast and facile process for the synthesis of different nanostructural materials such as Fe_3O_4, NiO, CuO, $CoFe_2O_4$ and ZnO (Zhao et al. 2007; Yang and Pan 2012; Guo et al. 2012; Choi et al. 2013; Cao et al. 2013; Behbahani et al. 2012; Maryanti et al. 2014). Guohong Qiu et al. demonstrated the microwave-assisted hydrothermal synthesis of α-Fe_2O_3 and studied the applications for As (III) removal from water (Qiu et al. 2011). Synthesis of various nanomaterials like Cu nanoparticles, hydroxyapatite/biochar nanocomposite, hydroxyl sodalite zeolite nanoparticles, Mn_2O_3 and $CoFe_2O_4$ were carried out through hydrothermal synthesis (Kumar et al. 2014a; Kumar et al. 2014b; Nassar et al. 2016; Abdelrahman et al. 2019; Hermosilla et al. 2020). These materials were studied for the removal of different contaminating agents from water. Microwave-assisted hydrothermal synthesis is also important for nanomaterial synthesis, which can be used for adsorption process and in catalysis.

17.2.4 Co-precipitation

In co-precipitation, continuous occurrence of nucleation, growth coarsening and agglomeration will take place during synthesis. Nucleation is the key step to take place and the product formed is usually the insoluble species under the condition of super saturation. Super saturation condition is mandatory to start precipitation, which are usually the result of following chemical reaction (Rane et al. 2018)

$$XAy + (\text{aqueous}) + YBx - ((\text{aqueous}) \rightarrow \text{AxBy}(\text{solid})$$

17.2.5 Polyol Synthesis

Polyol methods is the synthesis route for the preparation of a wide range of metal-based nanoparticles (Ag, Pr, Pt, Pd, Cu), metal oxides nanoparticles (ZnO, indium-tin-oxide; ITO, Gd_2O_3), magnetic nanoparticles and mixed metal

nanoparticles (Dhand et al. 2015). Polyethylene glycol is used as a solvent and a complexing and reducing agent at the same time, so the process is called as polyol process. Sharif Ahmad et al. (Ghosal et al. 2013) demonstrated the formation of nickel nanostructure using natural polyol and studied their dye adsorption properties. Nanoparticles of cuprous oxides were obtained in the forms of nanoboxes, nanocubes and nanospheres through polyol process by Lei Huang et al. (Huang et al. 2008).

17.3 Types of Nano-Adsorbents and Nano-Catalysts

A majority of inorganic adsorbents and catalysts belong to the transition metals and rare earth metals and their oxide forms. A few elements of main groups (like Si, Al, Mg) also play a role in the formation of active adsorbents and catalysts. The metallic oxides are well-studied nano-adsorbents in the form of mixed metal oxides (monometallic, bi-metallic, or tri-metallic oxides). In addition to metal oxides, pure metallic nano-adsorbents are also studied for their applications. Other adsorbents like surface-modified metal oxide, alumina, zeolites, and silica-based mesoporous materials are also good adsorbents for waste water treatment. Different forms of nano-adsorbents and nano-catalysts are described below.

17.3.1 Metal-Based Nano Adsorbents

Nanomaterials of transition metal are well studied in the various applications of catalysis, adsorption, and in the formation of semi-conductors and other devices. Due to the demands of efficient catalysts and adsorbents with paramagnetic behaviour for removal of harmful toxic metals and synthetic dyes from textile water, researchers focused on the transition-metal based nanomaterials for this application (Ge et al. 2012). Although number of transition metal ions are toxic in their ionic form like As(III), Cr (VI), Pb (II) and Hg (II) which contaminate water through their contamination but well design material is not soluble into water and work as adsorbents or catalyst. The introduction of organo-functionality onto the surface of nanomaterials also enhances the desirable activity of the material (Ge et al. 2012). Different types of metal-based nano-adsorbents with different structures and properties are discussed in the sections that follow.

17.3.1.1 Iron Oxide Nano-Adsorbents

Separation of adsorbents along with adsorbate from aqueous solution is a challenging task. The magnetically active forms of iron oxides nanomaterials (Fe_3O4 and γ-Fe_2O_3) act as excellent adsorbents for the capture of toxic elements, which

can be easily separated from solution. These nanomaterials used for the removal of different toxic heavy metals (viz. Cr, Co, Pb, Cu, As and Ni from water (Badruddoza et al. 2013; Lei et al. 2014; Tan et al. 2014; Shipley et al. 2010). Such materials can be synthesised in different forms like nanorods, nanoparticles, and nanotubes. Nanoparticles of magnetite (Fe_3O_4) are ideal nano-adsorbents for the capture of As (III) and As (V) from water (Shipley et al. 2010). Arsenic adsorption studies along with the effect of common containments present in water were carried out by Shipley et al. in (Shipley et al. 2010) through batch adsorption study. About 83 mg L^{-1} of arsenates were adsorbed within 1 hour by using 0.5 g L^{-1} magnetite nanoparticles as adsorbents at optimized conditions. In 2013, Roy et al. studied maghemite nanotubes (MHNT) as effective nano-adsorbents for Cu(II), Pb(II) and Zn(II) ion capture from water (Roy and Bhattacharya 2012). The nanotubes of γ-Fe_2O_3 were synthesised with microwave and were studied for adsorption kinetics (Roy and Bhattacharya 2013). The adsorption isotherm model (Langmuir and Freundlich) is used to study the adsorption capacity of adsorbents, and the Langmuir model showed good agreement to the observed data of the adsorption of metal ion onto the MHNT then Freundlich model (Roy and Bhattacharya 2012). Favourable adsorption study was done for different metal ions (Cu (II), Zn (II), and Pb (II) studied which are depicted in Table 17.1**.** Magnetite (Fe_3O_4) nano-rods were also studied as nano adsorbents by Karami in 2013 for the capture of Fe (II), Pb(II), Zn(II), Ni (II), Cd(II) and Cu(II) ions at lab scale with best fitted adsorption data with the theoretical models as shown in Table 17.1 (Karami 2013). When magnetite nanorods are compared with

Table 17.1 Various iron oxide nano-adsorbents studied for removal of toxic metal ions

Iron oxide nano-adsorbents	Shape and size of material (nm)	BET surface area (m^2g^{-1})	Targeted metal ions	Isothermal models	Sorption capacity	Ref.
Fe_3O_4	Nano-sphere, 19.3	60	As(V) As(III)	Langmuir q_m (mgg^{-1})	1.19 1.13	(Shipley et al. 2010)
Fe_3O_4, nano-rods	Rods, 55–65 Length 900–1000	–	Fe(II) Pb(II) Zn(II) Ni(II) Cd(II) Cu(II)	Langmuir q_m (mgg^{-1})	127.01 112.86 107.27 95.42 88.39 79.1	(Karami 2013)
γ-Fe_2O_3	Tubes, 10–15 Length 150–250	321	Cu(II) Zn(II) Pb(II)	Langmuir q_m (mgg^{-1})	111.11 84.95 71.42	(Roy and Bhattacharya 2012)
α-Fe_2O_3 (3D flower like)	Flower shape, 5000–7000	–	As(V) Cr(VI)	Langmuir q_m (mgg^{-1})	41.46 33.82	(Liang et al. 2013)
α-Fe_2O_3 (3D sphere)	Spheres, 37	31	Pb(II) Cd(II) Cu(II)	Freundlich qe mgg^{-1}	3.11 0.51 0.051 0.31	(Shipley et al. 2013)

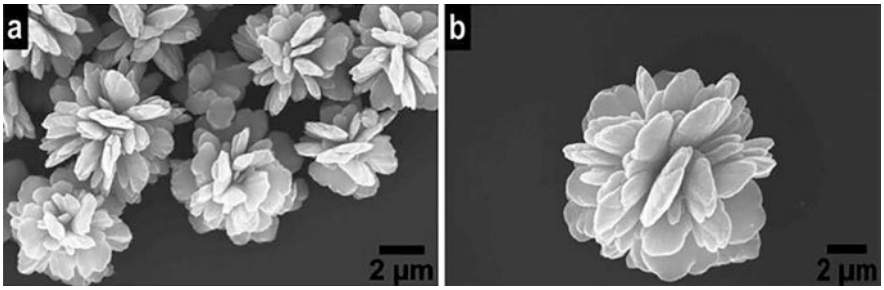

Fig. 17.6 SEM images of α-Fe_2O_3 micro-flowers after hydrothermal treatment at 150 °C for 12 h. (Reprinted from Ref. (Liang et al. 2013), Copyright 2020, with permission from Elsevier)

maghemite nanotubes, the former showed better adsorption capacity for Zn (II) and Pb (II) but exception for Cu, which might be due to the morphology of the nanorods (Karami 2013).

Nano-size hematite (α-Fe_2O_3) phase of iron oxide is a non-magnetic which is used in catalysis and environmental applications (Liang et al. 2013). Shipley et al. study the role of nono α-Fe_2O_3 for the removal of Pb (II), Cd ((II), Cu (II) and Zn(II) from aqueous solution (Shipley et al. 2013). The different adsorption parameters like pH, which affects the charge of adsorbent and temperature, were studied to elucidate the best absorption capacity. The surface chemistry of nano α-Fe_2O_3 depends upon optimized adsorption pH, which is attributed to the presence of –OH groups on the exterior surface of nano-adsorbents responsible for binding with toxic metals (Shipley et al. 2013). The isotherms models applied to the experimental data are in agreement with the observed conditions and are depicted in the Table 17.1**.** Hierarchical nano-structures of α-Fe_2O_3 with more surface area were studied by Liang et al. as adsorbents in order to achieve maximum adsorption capacity (Liang et al. 2013). The prepared structures are self-assembled and flower-like (SEM image shown Fig. 17.6), synthesised through hydrothermal treatment (Liang et al. 2013). Both the adsorption models, viz. Langmuir and Freundlich models, were studied in order to investigate the adsorption capacity of the flower-shaped nano α-Fe_2O_3 adsorbents.

17.3.1.2 Titanium Oxide Nano-Adsorbents

Titanium dioxide (TiO_2) has many applications of photo catalysis and photovoltaic, H_2 sensing, coatings and environmental applications for removal of pollutants (Bavykin et al. 2006a). Lao et at study the adsorption of arsenic by using TiO_2 at optimized parameters with 21 successive treatment adsorption cycles with regenerated TiO_2 (Luo et al. 2010). They study the adsorption kinetics through batch adsorption study which is fitted to pseudo second-order kinetic model (R value >0.999) and rate constant of 0.84 g mg^{-1} h^{-1}. Commercial TiO_2 nanoparticles were studied by Engates and Shipley et al. in 2011 for the adsorption of Pb(II), Cd(II) and

Table 17.2 Various iron oxide nano-adsorbents studied for removal of toxic metal ions

TiO_2 Nano-adsorbents	Shape and size of material (nm)	BET surface area (m^2g^{-1})	Targeted metal ions	Isothermal models	Sorption capacity	Ref.
TiO_2 nanoparticles	Nano-sphere, 8.3	185	Pb(II), Cd(II), Ni(II)	Langmuir q_m (mgg^{-1})	83.04 15.19 6.75	(Engates and Shipley 2011)
Layered protonated titanate sheets	Nano-sheets 2-15 nm thickness 0.78 nm interlayer distance	379	Pb(II)	Langmuir q_m (mgg^{-1})	366 mgg^{-1}	(Yang et al. 2008a)
$Na_2Ti_3O_7$ -T3	Nano fibres	321	Ba(II), Sr(II), Pb(II)	Sorption saturate capacity (mgg^{-1})	160.64 55.20 279.45	(Yang et al. 2008a)
$Na_{1.5}H_{0.5}$ Ti_3O_7 -T3(H)	Nano fibres	—	Ba(II), Sr(II), Pb(II)	Sorption saturate capacity (mgg^{-1})	130.44 49.94 244.26	(Yang et al. 2008a)
Titanate nano-flower	Flower shape, 600–100 nm	290	Pb(II), Cd(II), Ni(II), Zn(II)	Langmuir q_m (mgg^{-1})	304.3 168.6 88.05 98.1	(Huang et al. 2012)
Titanate nano-tubes	Tubes. 200 nm length, 7–10 nm outer dia.	230	Pb(II), Cd(II), Ni(II), Zn(II)	Langmuir q_m (mgg^{-1})	147.4 76.76 40.09 44.67	(Huang et al. 2012)
Titanate nano-wires	Wires shape 10 μm length, 40–240 nm dia	30	Pb(II), Cd(II), Ni(II), Zn(II)	Langmuir q_m (mgg^{-1})	106.09 47.55 24.83 27.66	(Huang et al. 2012)

Ni(II), and the results are depicted in Table 17.2 (Engates and Shipley 2011). The Langmuir adsorption model is well fitted to the process and indicates the monolayer adsorption on to the surface of TiO_2 nano-adsorbents, the adsorption efficiency of TiO_2 nanoparticles is more in comparison to bulk anantase TiO_2 (Engates and Shipley 2011). In addition to TiO_2, titanates are also useful as adsorbents for the removal of heavy metals from water (Kasap et al. 2012). Titanates in different forms like nano-sheets, nano-fibers fibers were also reported for adsorption process (Bavykin et al. 2006b; Lin et al. 2014; Yang et al. 2008a; Yang et al. 2008b; Bancroft et al. 1982). Huang et al. studied the titanate nanoflower, titanate nanotubes and titanate nanowires for the removal of Zn^{2+}, $Ni^{2+}$and Cd^{2+} using a ternary system (Huang et al. 2012). These three nanomaterials were synthesized through hydrothermal methods in alkaline condition which is followed by protonation in acidic

media (Huang et al. 2012). The adsorption study suggested the strong adsorption capacity of titanate nanotubes.

17.3.1.3 Cobalt Oxide Nano-Adsorbents

Nanostructural cobalt oxide with various structural morphologies has been synthesised by hydrothermal and solvothermal techniques (Nassar and Ahmed 2012; Ribeiro et al. 2018). The Co-based nanomaterials are found to be good agents for waste water remediation. M.Y. Nassar et al. prepared the cobalt oxide nanomaterials with different morphologies and studied the application for removal of organic dye (methylene blue dye). The material showed maximum adsorption of 99.19% for MB in 24 h (Nassar and Ahmed 2012). Surface functionalized nano-adsorbents with various organo-functionalities like amine and thiol is more interesting due to the grafting of proper and desirable active sites on to the surface of nanomaterials. Qurrat-ul-Ain et al. synthesised magnetic Co-Fe oxide nanoparticles (CoFeNp) and functionalized their surface with two separate amine functionalities (hydrazine and dodecyl amine) (Khurshid et al. 2020). After complete characterization, the material was carried out for adsorption of six different negatively charged azoic dyes, which include acid Orange 7, reactive Red-P2B, naphthol Blue Black, Acid Orange 52, reactive Orange 16 and amaranth. The experimental data showed the pseudo-second order kinetics, in which film diffusion was the dominant phenomenon compared to intra-particle diffusion. The composite of $CoFe_2O_4$ modified with tragacanth gum was prepared and studied for methyl orange (MO) and methyl red (MR) from waste water (Moghaddam et al. 2020).

17.3.1.4 Zinc Oxide Nano-Adsorbents

Zn oxide is not a much-studied material for adsorption; however it has more applications in photocatalysis and gas sensing. Its nontoxic nature and availability of surface hydroxyl groups makes it as good adsorbent for the removal of Zn(II), Cd(II), and Hg(II) ions from aqueous solution (Sheela et al. 2012). Nanomaterials are prepared through the precipitation method and calcined at 400 °C and carried out for batch adsorption study. The adsorption study is well fitted with the theoretical isotherm models; it is suggested that due to small hydrated ionic radii of Hg (II) and more electronegativity adsorption efficiency for Hg is more as compare to Zn(II), and Cd(II) ions (Sheela et al. 2012). ZnO hollow microspheres were prepared by Wang et al., and their adsorption study was compared with ZnO nanopowder and nano-plates (Wang et al. 2010b). Hollow microspheres showed better adsorption performance over ZnO nanopowder and nano-plates.

17.3.1.5 Mixed Metal Oxides Nano-Adsorbents

Synthesis of nanoscale mixed metal oxides like spinel (Wang and Kang 2012; Giri et al. 2002; Khedr et al. 2006), Ti-based bimetallic and trimetallic oxides (Galindo et al. 2007), In (III)-Sn (IV) oxides have many applications in electrical, magnetic and conducting properties. These bi-metallic and tri-metallic oxide nano-adsorbents were also synthesised through similar methods and studied for adsorption of heavy metal ions and synthetic dyes. Gupta et al. studied Fe-Ti mixed oxides for arsenic removal from ground water in West Bengal (India) and Bangladesh. Iron doped titanium oxide adsorbent was prepared by Lin Chen et al. in 2012 through precipitation method using $Ti(SO_4)_2$ and $FeSO_4$ salts (Chen et al. 2012). Adsorption study of the materials was carried out for removal of fluoride from drinking water which showed the adsorption capacity of 53.22 mg/g, obtained by fitting experimental data to the Langmuir isotherm model. It is suggested that Fe doped into the titanium oxide increases the –OH groups on adsorbent surface, which enhance the adsorption efficiency for fluoride (Chen et al. 2012). Mesoporous Ce-Zr mixed oxides were synthesised through salvo-thermal synthesis by Qi Li et al. (Su et al. 2015). These nanomaterials were studied for the removal of phosphate ions from water through batch adsorption study. The phosphate adsorption capacity is ~112.23 mg/g. The material can be regenerated after desorption by NaOH solution. Yaswanth K. Penke and co-workers studied the tri-metallic oxides (Mn-Al-Fe and Cu-Al-Fe) as nano-adsorbent for the removal of arsenic. XPS studies showed the redox behaviour of adsorbents and showed 75-90% adsorption of As (III) (Penke et al. 2019). Co-Fe oxide and many other mixed ferrites like $MnFe_2O_4$, $ZnFe_2O_4$, $MgFe_2O_4$, $NiFe_2O_4$, $CuFe_2O_4$, and $CoFe_2O_4$ have been studied by Hu et al. (2007) for the removal of Cr((VI) (Hu et al. 2007). Different forms of bi-metallic, tri-metallic and mixed oxides nano-adsorbents are summarized in Table 17.3**.**

17.3.1.6 Aluminium Oxide Nano-Adsorbents

Aluminium trioxide nanoparticles, Al_2O_3, are well-studied and efficient nano-adsorbents due to their large surface area. Afkhami et al. studied the adsorption of Pb(II) and Cr(III) ions on the surface of modified alumina nanomaterials (Afkhami et al. 2011). Kalfa et al. used nanoscale Al_2O_3 on single-walled carbon nanotubes for adsorption study of Cd ions. The material was prepared through sol-gel technique and mentioned to be a better absorbent for Cd in caparison to the single-walled carbon nanotubes (Kalfa et al. 2009b).

17.3.1.7 Magnesium Oxide Nano-Adsorbents

Nanoparticles of magnesium oxide (MgO) are useful for the removal different heavy metal ions. Different morphologies like microsphere were studied by Gupta et al. in 2015 for removal of heavy metal. Various nanostructures of MgO like

Table 17.3 Mixed metal oxide nano-adsorbents and catalysts studied for water purification

Nano-catalyst/ nano-adsorbent	Targeted metal ion	Method of preparation	Sorption capacity (%) Qe(mg/g)	Process	Ref.
$Ag\text{-}Sc_{0.01}Ti_{0.99}O_{1.99}$	RhB	PPM	90%	Photo catalytic	(da Silva et al. 2014)
TiO_2-Flakes	RhB	Sol-gel (Dip-coating)	73.2%	Photo catalytic	(Li et al. 2015)
FAP-TiO_2	Pb^{2+},Cd^{2+} Cr^{3+},Fe^{3+}	Solvothermal	99%	Adsorption	(Wang et al. 2020)
Nano- TiO_2	Cr(VI), Phenol	_	~99%	Photo catalytic	(Chi et al. 2019)
$Ti_3C_2/SrTiO_3$	U(VI)	Hydrothermal	77%	Photo catalytic	(Deng et al. 2019)
V_2O_5	MB	Hydrothermal	437	Adsorption	(Avansi et al. 2015)
CS-VTM	CR	Hydrothermal	99.1%	Adsorption	(Zhang et al. 2020a)
Ni-V_2O_5	RhB	Sol-gel	100%	Photo catalytic	(Rafique et al. 2020)
$MnFe_2O_4$	RhB	Sol-gel	90%	Photo catalytic	(Zhang et al. 2020b)
MnO_2@PmPD	Pb^{2+}	Oxidation	104.88	Adsorption	(Xiong et al. 2020)
OMS-2	U(VI) Eu(III)	Hydrothermal	348 106	Adsorption	(Yin et al. 2020)
FPL	M_O	Hydrothermal	833.33	Adsorption	(Natarajan et al. 2020)
Fe_2O_4/COP	AO, RhB	Solvothermal	107.11, 131.23	Adsorption	(Shakeri et al. 2020)
HFOR	p-ASA As(V)	Co-ppt	22 60	Adsorption	(Liu et al. 2020)
$CoFe_2O_4$@ɣ-Fe_2O_3	Cr(VI)	Hydrothermal coprecipitation	50	Adsorption	(Campos et al. 2019)

nanorods, nanotubes, and nanocubes are reported as nano-adsorbents for heavy metals. MgO nanomaterials were prepared and used for the removal of azo and anthraquinone reactive dyes from water by Gholamreza Moussavi et al. (Moussavi and Mahmoudi 2009).

17.3.2 Polymer-Based Nano-Adsorbents

In addition to the inorganic adsorbents, polymer-based nanocomposites are also well-studied nano-adsorbents due to their macromolecular structure and the variety of functional groups. These materials possess good physical properties, large

surface area, mechanical rigidity, and can be regenerated. These materials usually include, polyaniline, polystyrene and polyacrylic ester matrix. Compared to single polymers nano-adsorbents, dual polymers are more efficient for adsorption, due to their abundant surface functional groups (Wu et al. 2016). The combination of Polypyrrole (PPy) with PANI and polyacrylonitrile is found to be a suitable adsorbent for Co (II) (Javadian 2014a; Javadian 2014b; Wang et al. 2013). The adsorption study Co (II) on PANI/PPy polymer nanaofiber showed efficiency of 99.68% in 11 mins. The data are well fitted with Freundlich model and followed the pseudo-second-order kinetic model. Checkol et al. studied an efficient material consisting of poly (3,4 ethylenedioxythiophene)/polystyrene sulfonate (PEDOT/PSS) and the lignin (LG) for adsorption Pb(II) (Checkol et al. 2018). PPy/polyacrylonitrile core-shell nanostructures were also prepared and studied for Cr(VI) removal from aqueous solution (Wang et al. 2013). A variety of polymer-based nano-adsorbents including dual polymers, polymer-carbon composites, polymer silica composites, and polymer-metal composites are well studied and described in detail by Xiangke Wang et al. (Zhao et al. 2018b).

17.3.3 Silica- and Carbon-Based Nano-Adsorbents

Carbon nanotube in combination with other metals as support enhances the adsorption behaviour of adsorbents. Di et al. reported supported Ce in the form of CeO_2 on to the carbon nanotube and study its adsorptive behaviour for wastewater treatment (Di et al. 2006). The hydrated forms of these rare earth metals have high affinity for anions like fluoride, arsenate and phosphate (Zhang et al. 2003; Tokunaga et al. 1995). Carbon nanotubes were also used for supporting magnetic iron oxide by Gupta et al. (Gupta et al. 2011). The combined adsorptive behaviour of both the components in nanocomposite enhances the adsorption behaviour for Cr removal.

Silica nanoparticles are well-studied adsorbents for waste water treatment. They are also used for coating of metal oxides nanoparticles before their functionalization, with some organic functionality to improve adsorption. Bulk mesoporous silica like SBA-15, MCM-41, MCM-48, and HMS are found to be more superior adsorbents due to their large surface area, uniform pore size distribution and abundant hydroxyl groups. Their surface can be modified with various functional groups (like amines, thiol) to adsorb metal ions.

17.3.4 Nano-Catalysts for Wastewater Treatment

In addition to the adsorption of the toxic pollutants from water by nano-adsorbents, nano-catalysts are also play a role in polluted water remediation. Both the materials (nano-adsorbents & nano-catalysts) mostly have similar structure, composition, stability, surface area, and particle size, but differ only in their mode of action for

purification. Nano-absorbents capture the whole polluting agents (adsorbate) on to their surface through physiosorption or chemisorption. On the other hand nano-catalysts simply act as catalysts to make more toxic ions into less toxic ones, like reduction of nitrite and catalytic degradation of dye molecules into smaller fractions. Recently nano-sized Pd-Ag alloy was studied as nano-catalyst by J. P. Troutman et al. in 2020 and used for the reduction of nitrite in drinking water (Troutman et al. 2020). Nitrate is one of the most common pollutants present in ground water. It is harmful after ingestion and causes methemoglobinemia due to the formation of nitrite after the reduction of nitrate (blue-baby syndrome). Catalytic reduction of nitrite to N_2 gas or NH_3 is a promising route for the detoxification of nitrite ions. Titanium-based nano-catalysts are well used photocatalysts for the degradation of dyes. Polycarpos Falaras et al. in 2013 studied anion-doped mesoporous titania materials for the degradation of a hazardous material microcystin-LR (MC-LR) cyanotoxin pollutant in the presence of visible light (Likodimos et al. 2013). The materials were developed through sol-gel technique and co-doping of N and F anions (Likodimos et al. 2013). Rajender S. Varma and his co-workers studied and compiled the literature about green synthesis of nano-catalysts and their application in wastewater treatment (Nasrollahzadeh et al. 2020). There are many routes for the fabrication of bio-based chemicals to the nanotubes, nanowires etc. which are found to be excellent catalysts for reduction and degradation of water pollutant (Nasrollahzadeh et al. 2019a; Nasrollahzadeh et al. 2019b; Singh et al. 2016). Usually the metal salts precursors and plants or microorganisms are mixed and fabricated to develop nanostructures. The terpenoids, phenolic acid, carbohydrates, proteins, vitamins and alkaloids will work as capping reducing agents for the development of sustainable nanostructure (Prasad 2014; Bhuyan et al. 2015; Prasad et al. 2016, 2018; Srivastava et al. 2021). Metal oxide-based photocatalysts like mesoporous TiO_2 are also well-studied catalysts for the degradation of dyes present in water (Ahirwar et al. 2016). Most of the 3D metal-based materials are used as adsorbents and catalysts for wastewater treatment through adsorption and photo-degradation respectively. TiO_2 is a well-known photocatalyst used in the degradation of dyes present in water, due to their strong oxidizing properties (Lian et al. 2020). Most of the functionalized nonporous zeolites type materials studied for other catalytic activities can also be studied for adsorption as well as catalytic activities for wastewater treatment (Ahmed and Sakthivel 2017; Yadav et al. 2016; Ahmed et al. 2016). Bimetallic oxide-based nano-catalysts are summarized in Table 17.3.

17.4 Conclusion

The whole chapter presents the detailed study of nanomaterials' applications in waste water treatment. Varity of nanomaterials in different morphology, shape and size we studied as nano-adsorbent and nano-catalyst for the adsorption of various effluents from waste water are summarized in the current chapter. The different chemical techniques (viz. hydrothermal, co-precipitation and sol-gel) used for the

synthesis of nano-adsorbents and catalysts are stated with examples. Metal-based nano-adsorbents and nano-catalysts in the form of oxides, and bimetallic, and trimetallic oxides are discussed in details. Considerable work has been done to develop magnetic metallic oxides which were studied for the removal of toxic metal ions and are easy to separate from the water. The nano-types of such materials are very interesting due to the small size and large surface area. Moreover the porous silica, alumina and TiO_2 nanomaterials are also included in the chapter due to their potential application in metal ion capture and photocatalytic degradation.

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Chapter 18
Nano-Bioremediation Using Biologically Synthesized Intelligent Nanomaterials

S. Sakthinarendran, M. Ravi, and G. Mirunalini

Contents

18.1 Introduction

The total landmass present in the world accounts for about 13,003 million hectares. 37.6% of the total landmass is classified as an "agriculture area" by FAO (Marklund and Batello 2008). The use of synthetic fertilizer and pesticides in agriculture contaminate the soil affecting its health and fertility. For instance, urbanization and industrialization in China lead to the contamination of 19% agricultural soil (Zhao et al. 2014). Toxic elements like cadmium (Cd), copper (Cu), nickel (Ni), Zinc (Zn), etc. contaminate the soils, sediments, and groundwaters, posing a high threat to the

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environment and human health (Antoniadis et al. 2017; Sarkar et al. 2017; Niazi et al. 2018). The contaminants enter the soil system through various anthropogenic activities like spillages of pesticides and herbicides, industrial discharges, and discharges from service industries (solvent use, cleaning, and paint removal). Moreover, an organic compound such as trichloroethane (TCA), trichloroethylene (TCE), perchloroethane (PCA), etc.

According to WHO, survey data of 2015 reports about 494,550 deaths and 9.3 disability life due to long-term exposure to Pb. Even many young children's deaths have occurred when exposed to Pb-contaminated soil in countries like Nigeria, Senegal, and other countries (WHO 2018). Similarly, 35–77 million people got poisoned in Bangladesh due to soil contamination (Smith et al. 2000). These incidents show the importance and severity of the impact of soil contamination.

The focus on remediation of soil is the severity of risk based on different soil and human health contaminants. Remediation is done to preserve the limiting source (soil) for the future generation. Depending on the country, region, state, and local (community), the cleanup strategy must be employed. Soil contamination can also occur in nature, depending on the geochemical properties of source rocks, weathering process, volcanic eruption, etc. (Cui et al. 2018). Anthropogenic activities like agricultural practices, industrial production, military practices, mining, smelting operation, etc. add up toxic element concentration in soil. The toxic elements are collectively called as potential toxic element (PTE) (Hou and Li 2017).

The conventional methods of soil remediation could be categorized into physical and chemical methods. Physical remediation methods include excavation and removal, barrier system that prevents entry of contaminants to the soil, etc. Chemical methods include stabilization and solidification using chemical reaction agents. Similarly, biological remediation includes employing microbes for degradation or converting toxic elements to non-toxic ones Prasad and Aranda (2018). However, physical and chemical methods are not feasible and produces toxic residues like toxic sludge.

On the other hand, biological treatment takes its own time of action (Khan et al. 2018). To overcome these limitations, an urge for new sustainable technology is required. Nanotechnology is a promising field of science at the nanoscale level. It provides a sustainable technology for removing contamination of soil, thereby enhancing its health and maintaining soil fertility (Prasad et al. 2014, 2017). Nanomaterials are highly reactive, have high surface-to-volume ratio, and are smaller in size. These characteristics made these materials useful in situ remediations of soil compared to other traditional methods (Panpatte et al. 2016). The remediation mechanism is based on sorption, reduction, or chemical oxidation (Guerra et al. 2018). The remediation is of two types in situ and ex situ. The former treats the soil in the contaminated site, whereas the latter removes soil from the contaminated site and treats it externally outside its environment. Out of which in situ remediation was found to be feasible and effective.

18.2 Conventional Technology of Soil Remediation

18.2.1 Physical Methods

It includes soil washing, vitrification, encapsulation, electrokinesis, and permeable barrier system. We will see in brief about each technique.

18.2.1.1 Vitrification

Vitrification is a process of converting materials into a glass or glass-like substances. It could be applied as both in situ and ex situ methods. It employs heat to destroy organic compounds through pyrolysis or combustion and fusing inorganic metals into glass-like materials. These glass structures will be composed of oxides of silicon, boron, and alkaline earth metals. There are three heat treatment stages called first, second, and third heat generation (Reddi and Inyang 2000).

18.2.1.2 Electrokinetic Technique

This technique is suitable for an adequate grain soil system and effective in situ solutions. Electrodes are placed into the contaminated site, and a direct electrical current is applied that induces the movement of ions present in the soil towards the electrodes. Three principles are applied simultaneously: electro-osmosis, electromigration, and electrophoresis (Czurda et al. 2002). It can be used to remove organic as well as inorganic contaminants.

18.2.1.3 Permeable Barrier System

Usually, it is called pump-and-treat technology wherein groundwater is taken out of the aquifer, treating it in a water treatment plant, then back to the aquifer, or discharging it into the ground. This method was found inefficient with organic pollutants in groundwater. So, as an alternative method, the permeable wall was developed. Lower-density nonaqueous liquids will float on the water surface, and nonaqueous dense particles will settle down at the aquifer (Starr and Cherry 1994).

18.2.1.4 Encapsulation

It is a preventive measure taken to avoid further spreading of contaminants from the actual site of occurrence. For instance, bentonite is usually used as supporting slurry walls for the trench. Moreover, thin walls are a cost-effective way of encapsulation. A heavy steel beam is placed into the ground, which is vibrated with a high-pressure

jet. Similar advancements in techniques include sheet pile walls, bored pile walls, injection walls, artificial ground freezing, etc. (Philip 2001).

18.2.1.5 Soil Washing

It is a widely utilized technique for removing heavy metals and organic contaminants from the soil system. The main principle is selective categorizing fine contaminants, followed by solid/liquid phase separation of the remaining suspension. It does not directly remove contaminants but separates soil fraction containing high pollutants from low pollutant soil. The separation could be done using magnetic separation. The two primary steps are wet liberation and classification unit (Wilichowski 2001).

18.2.2 Chemical Methods

The chemical method includes precipitation, ion exchange, and membrane filter process.

18.2.2.1 Precipitation

In this technique, metal ions are dissolved with precipitant resulting in the formation of insoluble compounds. Further, these solid sediments could be removed using solid or liquid filtration techniques. Several materials are used as precipitating agents includes digested sludge, iron salts, calcium hydroxide, and aluminum iodide salts. It was found very effective against metal oxides (Bradl and Xenidis 2005).

18.2.2.2 Ion Exchange

It is a ubiquitous method for the removal of heavy metals. The basic principle behind this technique is an ion exchanger matrix with dissociable counter ions. The most common materials employ as matrices are polystyrene or polyacrylate, whereas condensation resins were made up of phenol and formaldehyde (Hahn 1987).

18.2.2.3 Flocculation

This method transforms the suspended colloidal particle into an easily separating form. Further, it can be removed using any mechanical means from supernatant or using flocculant. The main inorganic flocculation chemicals are ferric and ferrous salts, aluminum iodide salts, and calcium hydroxide (Lagaly 1986).

18.2.2.4 Stabilization

This is very effective in situ application, and it immobilizes or stabilizes, thereby reducing the mobility of contaminants. It is done by chemical/physical means. The stabilizing agents are directly injected into the contaminated site. These agents convert the toxic substance into less soluble, immobile, and less toxic (US EPA 1989).

18.2.3 Biological Methods

The most common biological approach is microbial remediation and phytoremediation of heavy metals contaminants in soil. However, the only limitation is that it takes its course of time to come into effect.

18.2.3.1 Microbial Degradation

Microbes like bacteria, fungi, actinomycetes, etc. In one way, the rhizosphere bacterial community has a close relationship with the root system, thereby forming a sheath, thus preventing toxic heavy metals (Inamuddin et al. 2021). Similarly, vesicular-arbuscular mycorrhizal (VAM) limits outside contaminants' uptake by plants (Paul and Clark 1996).

18.2.3.2 Phytoremediation

Plants have several mechanisms to sequester or stabilize the elements and prevent translocation into sensitive terrestrial portion. The plant takes up non-essential elements such as As, Cd, Na, Se, and Pb. Plants uptake of water and transpiration is an essential process (Ensley 2000). Simultaneously, photovolatilization of a volatile organic compound and certain metalloids is achieved through translocation and transpiration (Fig. 18.1).

18.3 Knowledge of Nanotechnological Application in Soil Remediation

18.3.1 Nanomaterials Used in Soil Remediation

Several types of nanomaterials could be employed in the remediation of soil. They are nanoscale: zeolite, zero-valent iron, iron oxide, phosphate, iron sulfide, carbon nanotubes, etc. Zeolite is employed as an adsorbent and catalyst for different

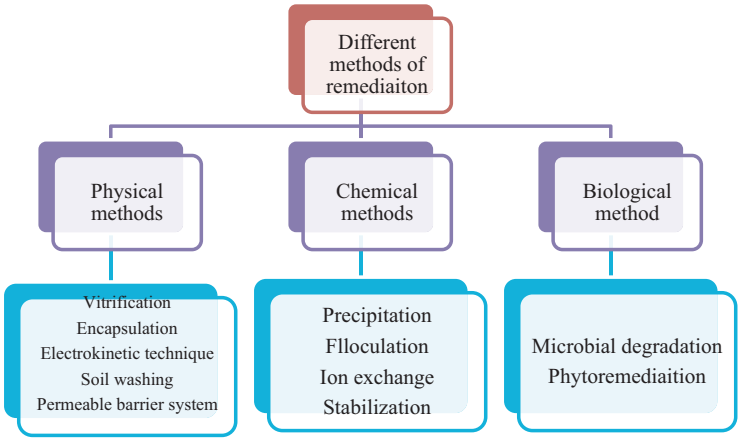

Fig. 18.1 Various methods employed in soil remediation

pollutants. These materials have a porous structure containing many cations making it readily exchangeable to other solutions. Zeolite application has provided a reduction in Hg uptake by some plants (Haidouti 1997). Then nanoiron oxide and nano-zero-valent iron oxide provides effective remediation while not having any secondary contamination. Since iron is already present in the soil, it is cost-effective and very effective against stabilizing heavy metals. This is due to their very high adsorbing capacity, which is being studied in a different context (Hua et al. 2012). Phosphate-based nanoparticles have a similar effect on pollutants and produce highly insoluble phosphorous compounds for absorbing heavy metal pollution. These particles were utilized in the soil amendment. Figure 18.2 depicts the various nanomaterials used in soil remediation.

18.3.2 Nano-Bioremediation of Organic Pollutants

Bioremediation is a practical, eco-friendly method of soil remediation using biological organisms as a tool for remediation (Kumar et al. 2021). It will be of double benefit when nanotechnology could be coupled with bioremediation. Nano remediation was utilized for chemical decontamination over the last two decades. However, integration in bioremediation is a new development, still at its infantry stage. Singh et al. studied the effect of stabilized Pb/Fe bimetallic nanoparticles on lindane contamination in soil followed by treatment using *Sphingomonas* sp. strain. It showed better efficacy in combining both techniques (Singh et al. 2013).

Nanomaterials enhance the availability of organic contaminants to biological agents. Similarly, altered membrane selectivity phytotoxic nanomaterials increases organic pollutants (Gong et al. 2018). Moreover, Le et al. 2015 studied the efficacy of bimetallic Pb/nFe on chemical oxidation of hexachlorinated biphenyls; further, it was degraded using *Burkholderia xenovorans* (Le et al. 2015). Similarly, De la

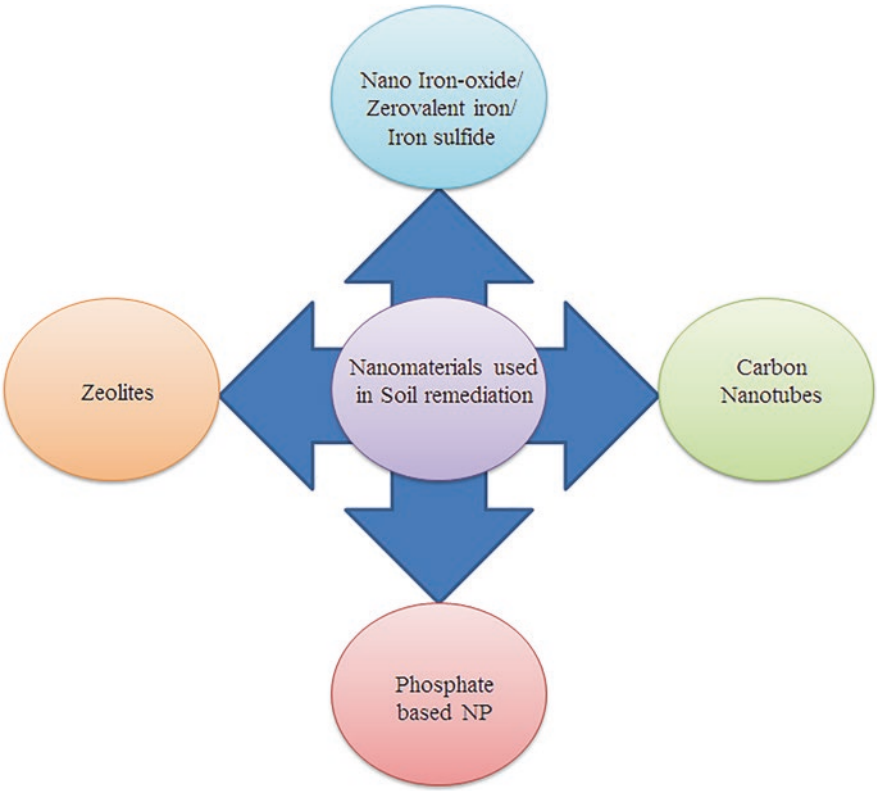

Fig. 18.2 Different nanomaterials utilized in soil remediation

Torre-Roche et al. also investigated DDT's accumulation by fullerene nanoparticles has increased the uptake of DDE significantly (De la Torre-Roche et al. 2012). Wu et al. also investigated the reduction of toxicity and translocation of polybrominated diphenyl ethers to Chinese cabbage by the application of Ni/Fe bimetallic nanoparticles. On the other hand, materials like carbon nanotubes harm *Chlorella vulgaris* grown in diuron-contaminated soil. Much work must be established to use this potential technique effectively.

18.3.3 Nano-Bioremediation of Inorganic Pollutants

Remediation of inorganic pollutants like heavy metals could be achieved by nano-bioremediation. Liang et al. showed a significant impact by nano-hydroxyapatite and nano- carbon black on lead phytoextraction by ryegrass (*Lolium temulentum*) (Liang et al. 2017). Hu et al. suggested that the accumulation of heavy metals in plants nanomaterials brings about a change in cell wall permeability (Hu et al. 2015). Different nanomaterials respond differently to various heavy metals and uptake of the same in plants (Gong et al. 2018).

18.3.4 The Fate of Nanoparticles Used in Soil System

Reports related to the fate of nanoparticles in water systems are more, whereas much work has not been done in the soil system. Nanomaterials deployed in the soil for various purposes interact first with soil components (organic or inorganic), and then depending on their nature, it undergoes physical, chemical, or biological changes (Darlington et al. 2009; Ben-Moshe et al. 2010). The most common physical changes in aggregation with the same type nanomaterials (homoaggregation) or aggregation with other soil constituents or pollutants (heteroaggregation). As a result, it reduces nanoparticles' mobility and behavior (Lowry et al. 2012; Batley et al. 2013). Soil organic matter also plays a vital role in behavior and the fate of nanomaterials by adsorption and stabilization. Even at a low concentration of 0.05 mg, L-1 of HS revoked the toxicity of nC60 (Lei et al. 2018). It also has an impact on the solubility and stability of NMs.

Since nanoparticles size is the minimal range, it can enter plants through osmotic pressure, cell wall pores, and capillary force. In most cases, the application of NMs over plants shows a positive result, but some plants also show a phytotoxic effect against NMs (Mazaheri-Tirani and Dayani 2020). The toxic effects of NPs could be observed in germination, biomass, and root elongation (Lin and Xing 2007; Racuciu and Creanga 2007; Lee et al. 2010). Similarly, it has a toxic effect on soil microbes too. Wu et al. (2020) showed carbon nanotubes' effect on functional genes and pathways of soil microbial communities, especially on carbon and nitrogen cycles. The toxicity of NMs is based on the concentration, nature, and synthesis process (Chen et al. 2019).

18.4 Green Synthesis of Nanoparticle

The very first essential step in nanotechnology is the synthesis of desired nanoparticles according to its target function. Nanoparticles could be synthesized through physical, chemical, and biological methods. There are numerous reports on the techniques of synthesizing nanoparticles. The most used physical approach includes evaporation-condensation, thermal decomposition, sputtering and sonication, etc. In comparison, chemical approaches include the sol-gel method, colloidal method, and chemical reducing technique using reducing agents.

These synthesis techniques could be categorized into the top-down method and bottom up methods. The former approach is made by etching nanoparticle from a substrate i.e., scaling down a bulk material to nanoparticles. In contrast, the other method is based on engraving particles onto a substrate, i.e., atoms are stacked to get a crystal plane, which is further arranged to get nanostructures since these methods use inorganic reagents that make them toxic to the environment and human health.

Therefore, an alternative method using bio-organism (plants extract, microbes, algae, secondary by-products like protein, lipids, etc.) was adopted for NP synthesis

(Prasad et al. 2016, 2018; Srivastava et al. 2021; Sarma et al. 2021). Green synthesis of nanoparticles makes use of eco-friendly, non-toxic, cost-effective reagents. So, the biological method of synthesis undergoes a bottom-up approach using reducing and stabilizing agents (Singh et al. 2011; Aziz et al. 2014, 2015, 2016, 2019; Joshi et al. 2018). Synthesis of NPs by using agro-waste should be employed to reduce the cost (Sangeetha et al. 2017). The feasibility of scaling it up to mass production will lead to waste utilization and reducing the production cost.

18.5 Intelligent Nano-Biosensors for Soil Remediation: An Innovative Approach

A biosensor is an analytical device that senses the biological changes and provides data into readable form. It comprises three crucial components, namely, detector, transducer, and bioreceptor (Dhole and Pitambara 2019; Singh et al. 2020). A biosensor at the nanoscale is called a nano-biosensor.

For the detection of heavy metals in the soil system, microbial cells can react to an available fraction of heavy metal ions, developed like luminescent bacterial sensors (Ivask et al. 2004). The application of intelligent nano-biosensors for environmental remediation is at the infantry stage. The concept behind intelligent nano-biosensors is they analyze the contaminated site with their biosensor capability and procure data, analyze it, and provide an apt solution to be employed in the site. For such a high-end device, more research must be taken to understand the soil system's pollutants. Then pollutant mediated changes in soil composition must be determined—similarly, nanomaterials' effect in various soil systems, its effect on soil microbes, and associated plants.

18.6 Conclusion and Future Perspective

Despite the promising potential of nanomaterials in application over environment and soil remediation, extensive research has been done in the development of new innovative technology for soil remediation. The limitation present in the current technology of remediation stresses nanotechnology shows higher results than conventional techniques. Since different nanomaterials react differently to pollutants, more research has to be done in understanding such effect at the same time to know about the fate of nanomaterials in the soil system. Extensive research should be done in understanding the fate of nanomaterials in the soil system and its toxic effects. Similarly, government bodies should implement regulations and guidelines for nanomaterials used in soil remediation. The effect of different nanomaterials in different soil systems should also be analyzed. So, green synthesized nanomaterials can be employed as non-toxic to the environment and a sustainable one. Combining nanotechnology strategies with bioremediation and biosensor in soil remediation is

beneficial and could be used for future remediation. Nanotechnology will provide effective remediation of toxic pollutants in a cost-effective, sustainable, and without much disturbance in ecosystem balance.

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Chapter 19
Recent Developments in Nanotechnological Interventions for Pesticide Remediation

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19.1 Introduction

In modern agriculture, pesticides are considered as an inescapable part for suppressing various flora and fauna pests in addition to prompt progression in urbanization and heavy industrialization that has ultimately urged to meet the demand for increase in agriculture yield to fulfill the needs of steady growth of population rate. Use of agrochemicals such as insecticides, herbicides, and fungicides kills the undesirable organisms (pests) along with some beneficial organisms existing in the ecosystem and also degrades the soil quality to a larger extent (Bhattacharyya et al. 2016). Moreover, pesticides tend to persist in the habitat for longer period causing serious issues like accumulation of undesirable residues, leading toxicity into the earth's stratum surface and also raising issues over food security using by the animals as well as the public. Worldwide, environmental protection and safety of public health has been considered as a pivotal issue and need to be addressed before time. Earlier classical methods have been used for removal of toxic wastes by chemical oxidation, adsorption, and biological oxidation, but these methods are time-consuming, with least cost effective. The emergence of nanotechnology in environmental sector has attained a great deal of interest and thus will be helpful for overall remediation through the application of nanoparticles (Prasad and Aranda 2018; Shash et al. 2019; Thangadurai et al. 2020; Saglam et al. 2021). The use of desired nanomaterials in environmental remediation with large surface-to-volume ratios act as sterling adsorbents, catalysts, and sensors thus in course increases the reactivity. Hence, there was utmost necessary for less time constraint as well as cost-effective method to remediate contaminated soil and groundwater at the hazardous sites and also breakdown to less hazardous products into the surroundings.

19.2 Background of Nanotechnology

During the period of 1980s, nanotechnology has come to the fore and gained popularity both in scientific and public domain having dimension sized ranging from 1 to 100 nm, where its unique phenomena enable novel applications. It basically deals with the use of nanomaterials in various scientific fields of biology, medicine, chemistry, physics, material science, engineering, etc. Currently the increasing efforts of using nanotechnology in the environmental sectors have improved the overall effectiveness of classical based remediation methods through the application of nanoparticles. With the constant development in technological tools, the implementation of nanotechnology in the field of detection of pollutants through techniques like

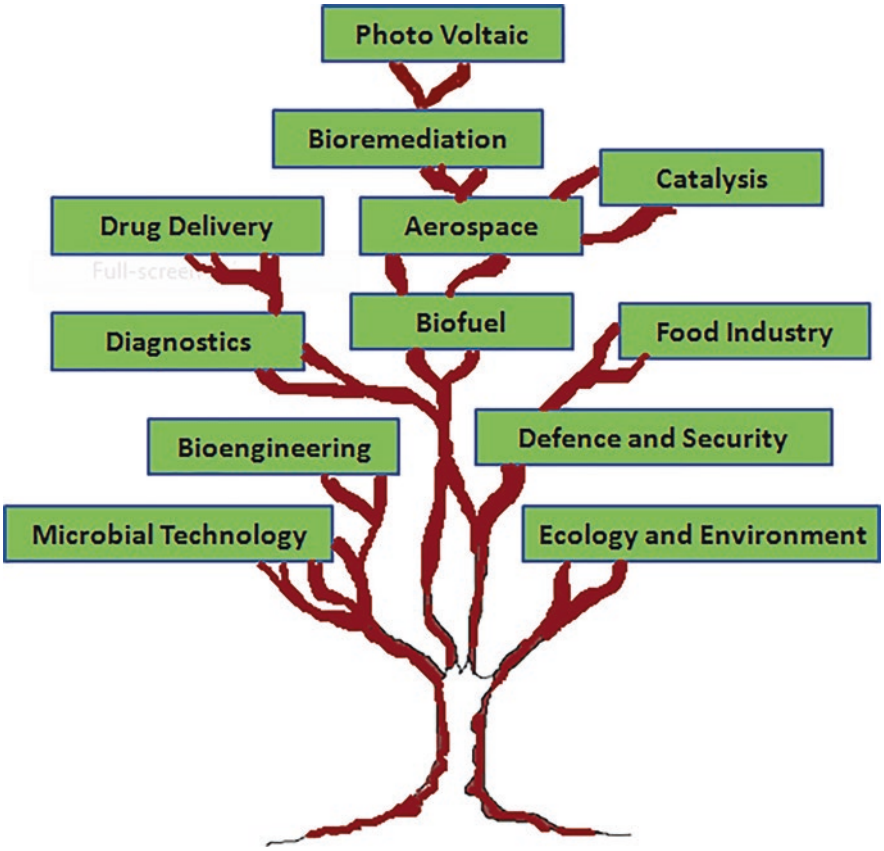

Fig. 19.1 Various branches of nanotechnology

surface-enhanced Raman scattering and electrochemical or optical detection is the need of the hour (Fulekar 2010; Tanwar et al. 2021) (Fig. 19.1).

19.3 Nanobiotechnology

In biotechnology, the knowledge and techniques of biology are applied to alter the molecular, genetic, and cellular processes to generate products and services that are being used in diverse fields from medicine to agriculture. Thus, nanobiotechnology is considered to be the unique fusion of two most progressive fields: biotechnology and nanotechnology where nanobiotechnology uses (nanoscale) biological starting materials. It has substantial potential for the programmed nano-/microfabrication of structured materials, to build tools for studying biological systems with specificity, better sensitivity, and a higher degree of recognition.

19.4 Nanomaterials

Nanomaterials has great potential in environmental remediation because of their large surface areas compared to their volumes (surface-to-volume ratio), thus acting as superior adsorbents and catalysts than other conventional tools within the range from 1 to 100 nm for efficient removal of hazardous chemicals and biological contaminants from the habitat. They can lead to very sensitive detection of pollutants to remediate the contaminants at a quicker rate with lesser hazardous by-products.

19.4.1 Nanoparticles in Pesticide Remediation

Nanoparticles exhibit a large number of special properties relative to bulk material; because of their specific size > than 100 nm; large surface area with exceptional parameters predominantly leads to a higher rate of detection of contaminants that allows to remediate these contaminants at a faster rate (Sun et al. 2006; Tosco et al. 2014). The utilization of zero-valent metals such as nickel, iron, and palladium has proved to be effective and better results in decontamination of toxic substances. Nanoparticles are synthesized by two approaches: The first approach is top-down synthesis thus involving the breakdown of bulk materials to nanoscale for obtaining nanoparticles, while the second approach is bottom-up synthesis involving the stacking-up of atoms and molecules of the bulk material mainly for the fabrication of nanoparticles. Now-a-days, the use of nanoparticles has been increased significantly by using countless nanoparticles for detecting, degrading, and removing contaminants and turn-up to be the most used in situ approach for remediation purpose (Ding et al. 2008). The major groups of NPs used for detection and degradation of pesticides are metal NPs, bimetallic NPs, and metal oxide NPs that have been frequently studied by the researchers.

19.4.2 Green Synthesis of Nanoparticles

In the past numerous years, nanoparticles synthesized by physicochemical techniques thus increase the accumulation of toxic, hazardous, and non-ecofriendly chemicals into the environment which impart non-lethal impacts on non-target organisms as well as on human population. With advancement of technology, the earnest need in synthesizing eco-friendly nanoparticles using non-toxic precursors having mild reactions and cost-effectiveness with environmental sustainability has help to emerge “green technology” by combining nanotechnology with green chemistry to exploit the potential of biological entities over physicochemical methods. Green synthesis approach provides a fast, easy, and eco-friendly nanoparticle production with environmental sustainability, simple, and reproducible approach with less hazards in the environment.

19.4.2.1 Bacterial Synthesis of Nanoparticles

Prokaryotes are comprised of single cell organisms such as bacteria that are considered as first choice for biosynthesis of nanoparticles due to their simplest structure and easy metabolism. The strong affinity for metals and its metal binding property by bacteria have helped in the synthesis of Au, Ag, Pt, Pd, Ti, nanoparticles, and so forth. The development of resistance mechanism like suppression and enhanced of influx system and efflux system, respectively, extracellular complexation, intracellular chelation, or precipitation and enzyme detoxification of metals (Silver 2003; Prasad et al. 2016) by bacteria after exposure to harsh metals and their metal ions have evolved in the large-scale synthesis of nanoparticles. Bacteria under the genus *Bacillus, Klebsiella, Lactobacillus,* and *Pseudomonas* fall under the category of nanoparticles by applying green technology. For instance, extracellular synthesis of nanoparticles by the member of Enterobacteriaceae (*Klebsiella pneumonia, Escherichia coli*, and *Enterobacter cloacae*) was first reported by Shahverdi et al. (2007). Similarly, silver nanoparticles were first synthesized by *Bacillus thuringiensis*.

19.4.2.2 Phytosynthesis of Nanoparticles

Plants possess the basic biological molecules such as carbohydrates, protein, and enzymes that have the immense potential to reduce metal salts for synthesis of nanoparticles. It is truly a one-step biosynthesis process where different plant extracts are employed due to their cost-effectiveness, easily scalable, safe to handle, less toxicity to overcome the drawbacks possessed by the conventional methods in synthesizing nanoparticles (Gurunathan et al. 2009; Prasad 2014; Srivastava et al. 2021). Biofabrication of nanoparticles by plant-based method can be easily available for large-scale production as compared to nanoparticles synthesized by microbe-based method since the latter rely more on the preservation of microbial culture that might generate toxic moieties which can be responsible for threatening both the environment and human population (Anuradha et al. 2015). Plant extracts are usually prepared from various parts such as extracts from plant leaves, juices of different medicinal plants, etc. are basically involved in mixing of plant extract with that of metal ions in a fixed ratio for synthesizing of nanoparticles. The nanoparticles are characterized by UV, XRD, and FTIR data analysis finally once they are synthesized (Table 19.1).

19.4.2.3 Nanoparticles Synthesized by Fungi and Yeast

Eukaryotic organisms such as fungi and yeast also come under the green synthesis approach of nanoparticles. Fungi has the potential to produce large-scale production of nanoparticles compared to prokaryotes (bacteria) because if the presence of various intracellular enzymes (Chen et al. 2009; Mohanpuria et al. 2008; Aziz et al. 2016, 2019; Prasad 2016, 2017; Prasad et al. 2018; Abdel-Aziz et al. 2018). Apart from monodispersity, fungi also help in the synthesis of well-defined dimensions of nanoparticles. The use of specific enzymes or metabolites; use of isolated

Table 19.1 Biosynthesis of nanoparticles from microbes and plants

Name of NP	Microorganism	References	Plant	References
Silver NPs	*Staphylococcus aureus* *Streptomyces* sp.	Kumar et al. (2011a, b), Alani et al. (2012)	*Sinapis arvensis* *Trigonella foenum-graecum*	Lam et al. (2018), Kavitha et al. (2013)
	Streptomyces naganishii *Brevibacterium casei*	Duran et al. (2011), Tripathi et al. (2015)	*Artemisia nilagirica* *Lantana camara*	Rasheed et al. (2017), Dimitrov (2006)
Gold NPs	*Rhodococcus* sp.	Yadav (2017)	*Abelmoschus esculentus*	Chaturvedi and Verma (2015)
	Klebsiella pneumonia	Balaji et al. (2009)	Angelica, Hypericum, Hamamelis Eucalyptus, Ocimum, Mentha	Subbaiya et al. (2014)
	Rhodopseudomonas capsulate	Park et al. (2011)	*Stevia rebaudiana*	Manivasagan et al. (2016)
	Rhodococcus sp., *Streptomyces* sp., *Streptomyces viridogens*	Ahmad et al. (2003a, b), Balagurunathan et al. (2011)	*Zingiber officinale*	Sinha et al. (2015) Pasca et al. (2014)
Iron NPs	*Shewanella oneidensis*, *Klebsiella oxytoca*	Narayanan and Sakthivel (2011), Binupriya et al. (2010)	Aloe vera, *Eucalyptus tereticornis*	Kumar et al. (2011a, b) Mishra et al. (2015)
	C. globosum	Elcey et al. (2014)	*Rosemarinus officinalis* Green tea	Kumar et al. (2012)
	E. coli, *Plerotus* sp.	Arcon et al. (2012) Kaul et al. (2012)	*Dodonaea viscose*	Kumar et al. (2012) Phumying et al. (2013)
Zinc NPs	*Lactobacillus*	Zhang (2003); Lee et al. (2008)	Aloe vera	Laokul and Maensiri (2009); Phumying et al. (2013)
	Streptomyces sp.	Raliya and Tarafdar (2014); Raliya and Tarafdar (2013)	*Nyctanthes arbor-tristis*	Taranath and Patil (2016)
	Candida albicans	Xu et al. (2005); Mazumdar and Haloi (2011)	*Nyctanthes arbor-tristis*	Jamdagni et al. (2016)

proteins instead of fungi culture has shown promising results in nanoparticle production. There are many reports regarding the ability of fungi to produce metal and metal oxides nanoparticles. The fungus *Verticillium* sp. is reported to reduce $AuCl_4$ ions and synthesis of Au nanoparticles on both the outer surface and the inner fungal cells with negligible reduction in the solution (Mukherjee et al. 2001; Shankar et al. 2004). *Fusarium oxysporum* have turn up for the extracellular synthesis of highly stable Au and Ag nanoparticles within the dimension range of 2–50 nm (Mukherjee et al. 2002; Ahmad et al. 2003a, b). The fungus *Aspergillus flavus* employed for the synthesizing of Ag nanoparticles wherein two proteins of 32 and 35 kDa are involved in the synthesizing process as well as gaining stability of synthesized Ag nanoparticles. Yeast (single-celled microorganisms) is also engaged in the synthesis of metallic nanoparticles (Ag and Au) by *Saccharomyces cerevisiae* regarded as more advantageous as compared to bacteria.

19.5 Mechanism Behind Nanomaterial-Based for Pesticide Sensing and Remediation

Pesticide detection, degradation, and finally removal from the environment basically involve two different type of chemistry: (a) homogeneous and (b) heterogeneous (Bond 1997). Thus, it is regarded as the fundamental method behind the chemistries for nanomaterials-based pesticide detection and removal, especially from water bodies.

19.5.1 Homogeneous Chemistry

This method first involves the nanoparticles diffused in water sample in presence of pesticide. The diffused nanoparticles then helps in the degradation or detection of pesticides present in water. The usage of most of the surface area, presented by the nanoparticles, is the fringe benefit of using this method. However, these nanoparticles are difficult to be removed from the water system, once they get diffused into it and might release toxic effects into the water system which can be a major concern of this method.

19.5.2 Heterogeneous Chemistry

This method involves the immobilized nanoparticles used on varied support materials before their use for detection of pesticides and remediation. Then these support materials are diffused into the water samples in presence of pesticide. The presence

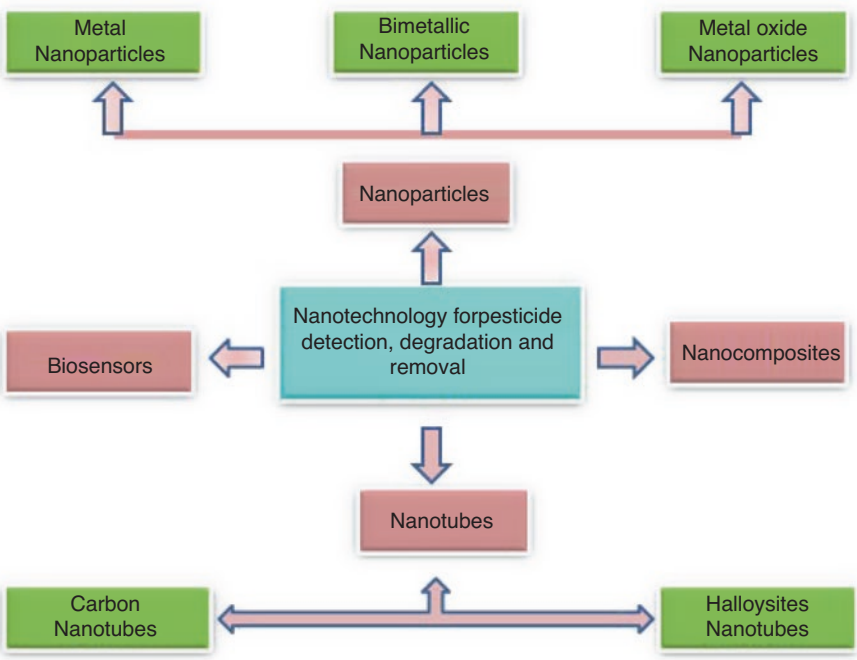

Fig. 19.2 Classification of nanotechnology-based approaches for pesticide sensing and detection

of immobilized nanoparticles into the support material helps in the detection and degradation of pesticides in the water system. The boon for heterogenous chemistry is the reuse of support systems for different water samples while detecting and degrading pesticides. The clump formation of nanoparticles is prevented through immobilization on solid supports are thus regarded as another benefit of using this method (Figs. 19.2 and 19.3).

19.6 Various Types of Nanoparticles for Pesticide Sensing, Remediation, and Elimination

19.6.1 Metal Nanoparticles

The NPs under the category of noble metals, namely, gold (Au), silver (Ag), platinum (Pt), and palladium (Pd) along with the transition metal nanoparticles like iron (Fe), copper (Cu), and zinc (Zn) have found limitless applications in environmental remediation. The incomparable surface chemistry of these NPs allows the redox reaction that takes place at the exterior of the nanoparticle thus playing a significant part in the decomposition of toxic pesticides to small-scale size and less hazardous pollutants (Street et al. 2014).

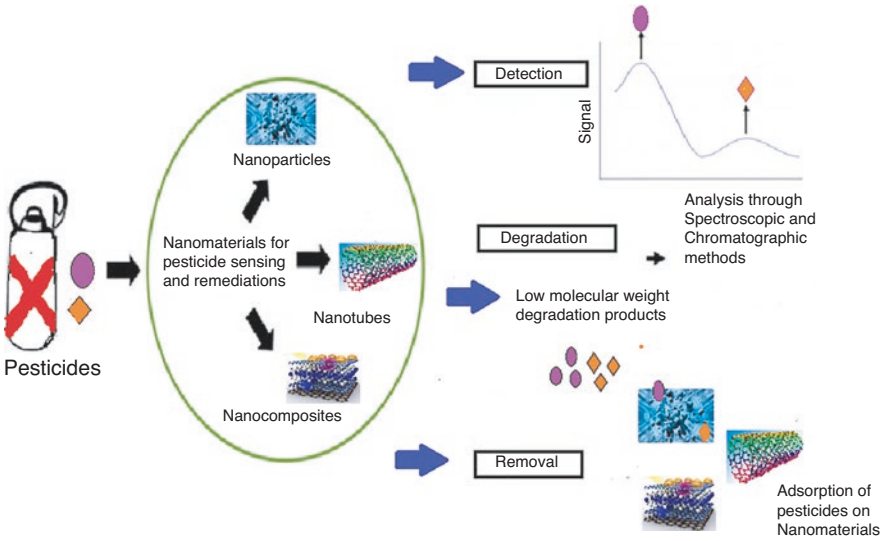

Fig. 19.3 Graphical representation of pesticide sensing, degradation, and elimination using nanomaterials

19.6.1.1 Gold Nanoparticles

From ancient times, gold has been regarded as a precious metal, and among the nanoparticles, gold is leading and has revolutionized the daily life. The AuNPs are familiar to have some properties like exhibiting various colors with change in size. The color change of AuNPs at different stages of agglomeration provides them to be a suitable visible material for analyte (Tsai et al. 2005). The sensitivity and specificity of AuNPs can be increased by their surface modification toward different pesticides. Sensors conjugated with AuNPs also help in the detection of organophosphates and organochlorines in the environment. The detection of DDT (organochlorine), by using AuNPs, is basically a colorimetric assay, where anti-DDT antibodies conjugate with AuNPs in the presence of DDT with various concentrations. The tested sample along with DDT blocks the anti-DDT antibodies followed by reduction of color intensity which is inversely proportional to the amount of DDT present in the tested sample.

19.6.1.2 Silver Nanoparticles

The AgNPs possess some specific properties of shape and size that enables their use in different fiber composites, biosensors and as antimicrobial properties (Rawtani et al. 2013; Prasad and Swamy 2013; Joshi et al. 2018). The optical properties of AgNPs with different sizes help in the sensing of pesticides. The surface modification of AgNPs similarly to AuNPs thus helps in increasing the sensitivity and

specificity for the pesticides detection. Generally, dipterex an organophosphate insecticide found to be contaminated in aquatic bodies is detected by using AgNPs capped with citrate. When immobilized acetylcholinesterase enzyme is present along with citrate-capped AgNPs, it forms pink color due to the occurrence of thiocholine from acetylthiocholine in the presence of the enzyme acetylcholinesterase. But, no occurrence of thiocholine or pink color development takes place when the organophosphate dipterex is present since it inhibits the acetylcholinesterase enzyme (Lia et al. 2014). Due to the presence of acetylcholinesterase enzyme, it allows the formation of thiocholine on the substrate. This enzymatic action helps in the conversion of yellow color solution of RB-AgNPs to grey color. At the same time, the fluorescence of rhodamine B dye was also unquenched. Whereas, due to the presence of pesticides, no color formation or fluorescence occurs in the tested sample (Luo et al. 2017). Thus, this method of detection of pesticides is based on both colorimetric as well as fluorescence assay.Similarly, a herbicide known as paraquat has also been detected by using citrate-capped AgNPs. It also helps in the detection of carbaryl, an insecticide present in the vegetables, fruits, and river water with the help of modified rhodamine B dye. Various pesticides such as paraoxon and thiram (fungicide) are detected by using AgNPs as active substrates in surface-enhanced Raman spectroscopy (SERS). The emission of Raman signals from the target pesticide that gets deposited on the nanostructure surface (in this case AgNP) is increased by using SERS, thereby helping to detect very low limits of pesticides in the tested sample (Wang et al. 2014; Tanwar et al. 2021).

19.6.1.3 Iron Nanoparticles

The importance of iron is well understood in environmental remediation due to its contaminant portability, adsorption property, and mainly breakdown of iron into two valence states, i.e., ferrous iron Fe(II) (water soluble) and ferric iron (III) (water insoluble). The rusting of iron is well known in presence of oxygen helps in the formation of iron oxide. Thus both iron and iron oxide nanoparticles are considered as convenient nanoparticles for environmental remediation. For instance, the degradation of the pesticide 2,4-dichlorophenol is being degraded by biosynthesizing FeNPs by means of adsorption. The split of the benzene ring on 2,4-dichlorophenol during the degradation process emerge in the formation of acetone and acetic acid as the starting products which are then detected on GC-MS (Guo et al. 2017).

The utilization of zero-valent iron nanoparticles (ZV-FeNPs) is considered as a useful technique for remediation of organochlorine as well as micropollutant from the environment. It has been reported that lindane, an organochlorine, has been degraded by using ZV-FeNPs. It was found that the organochlorine was degraded to a large extent by the particles post polymer stabilization thus raising the exposure period of the pesticide. Lindane degradation mainly involves dichloroelimination and dehydrohalogenation, and during this degradation phase benzene, chlorobenzene, and dichlorobenzene are regarded as the main products (San Roman et al. 2013) (Table 19.2).

Table 19.2 Nanomaterials used for detection of pesticides

Nanomaterial	Type of nanomaterial	Modification	Pesticide	Matrix	Detection limit	References
Metal nanoparticle	AuNPs	Conjugation with anti-DDT antibodies	DDT	Grapes, Cauliflower	27 ng/mL 0.65–	Lisa et al. (2009)
		Conjugation with IgG antibody	Kitazine	Tomato, Cucumber	2.44 mL/mL	Malarkodi et al. (2017)
	AgNPs	Capping with citrate	Dipterex	Water	0.18 ng/mL	Lia et al. (2014)
		Conjugation with Rhodamine B	Carbaryl	Tomato, Apple, River water	0.023 ng/L	Luo et al. (2017)
Metal oxide nanoparticle	SiO_2NPs	Immobilization of AChE and AuNPs	Paraoxon	Spiked pesticide solutions	500 nM	Luckham and Brennan (2010)
		Conjugation with anti-FNT and anti-CLT antibodies	FNT and CLT	Spiked pesticide solutions	0.25 ng/mL	Wang et al. (2013)
Nanotube	Carbon nanotubes	Coating with silica and immobilization of phthalocyanine ruthenium	FNT	Orange juice	0.45 mg/mL	Canevari et al. (2016)
		Immobilization of AgNPs	Dimethoate	Orange and lake water	0.01 mg/mL	Hsu et al. (2017)
	Halloysite nanotubes	Immobilization of TiO_2NPs	Parathion	Strawberry, celery, apple		Saraji et al. (2016)

AuNPs gold nanoparticles, *AgNPs* silver nanoparticles, *DDT* dichlorodiphenyl trichloroethane, *SiO_2* NPs silica nanoparticles, *AChE* acetylcholinesterase, *FNT* Feni-trothion, *CLT* chlorpyrifos methyl, *TiO_2NPs* titanium oxide nanoparticles

19.6.2 Bimetallic Nanoparticles

These nanoparticles consist of some interesting characteristics of combination of two metal nanoparticles in the interior of a single nanoparticle (Zaleska-Medynska et al. 2016). The utilization of bimetallic nanoparticles (BNPs) in the field of pesticides removal and degradation takes place by means of reduction by using Fe/Ni NPs (Liu et al. 2014). The degradation of the organophosphate, profenofos, takes place by using Fe/Ni BNPs as a catalyst. Here, nanoscale zero-valent iron (nZVI) particles act as a reducing factor for the pesticide degradation wherein Ni

safeguards the surface of nZVI particles from corrosion. Various studies have found the utilization of Fe/NiNPs, having nZVI particles for dechlorination of the herbicide sulfentrazone (Nascimento et al. 2016). In addition to this, the degradation of 4-chlorophenol takes place where superoxide radicals provide an effective mechanism for its degradation via bimetallic system having nZVI/Ni particles (Shen et al. 2017). Recently, chlorpyrifos, an organophosphate, where degradation is being carried out by green synthesized of Ag/CuBNPs where BNPs act as nano-catalyst that provides an environmental friendly route for water purification from pesticide contamination (Rosbero and Camacho 2017) (Table 19.3).

19.6.3 Metal Oxide Nanoparticles

This type of nanoparticle due to their superconducting nature is widely used for environmental remediation. These superconducting properties of metal oxide NPs come up with an effective and specific photocatalysis activity that has been applied in diverse research work for sensing and remediation of pesticides. Various types of metal oxide NPs are involved for pesticides sensing, degradation, and removal from diverse sources. These nanoparticles (NPs) are mainly silicon oxide (SiO_2), zinc oxide (ZnO), titanium oxide (TiO_2), and iron oxide (Fe_2O_3orFe_3O_4) have been taken into account.

19.6.3.1 Titanium Oxide Nanoparticles

TiO_2NPs have proved to be a promising candidate for metal oxide NPs due to their exceptional features, like photocatalysis, cost-effective, non-toxicity, and stability in connection with chemicals. They possess huge surface area for photocatalytic activity, thus increasing their consumption for pollutant remediation from the surrounding. It was reported that a study was carried out at Dindigul district in Tamil Nadu, where TiO_2NPs have been applied for chlorpyrifos and monocrotophos degradation present in pond and deep well water. The degradation of these pesticides was triggered by irradiation of the photocatalyst in presence of UV light. It was found that with increase in glow time, there was an increase in the photodegradation efficiency (Amalraj and Pius 2015).

Mesoporous TiO_2NPs is regarded as the most widely used mesoporous material due to their large surface area and intrinsic property. This NP was first synthesized by Antonelli and Ying using modified sol-gel method (Antonelli and Ying 1995). These NPs are used for the microextraction of six organochlorine pesticides, namely, hexachlororbenzene (HCB), *trans*-chlordane, *cis*-chlordane, o,p-DDT, p,p-DDT, and mirex. Fabrication of solid-phase microextraction fiber by using TiO_2NPs helps in the removal of these pesticides. TiO_2NPs helps in the degradation of carbendazim, a widely used fungicide, by doping with Fe and Si ions. Thus by doping, the photocatalytic activity of NPs has been increased resulting to a larger extent of degradation (98%) of the fungicide in presence of UV light (Kaur et al. 2016).

Table 19.3 Nanomaterials used for degradation of pesticides

Nanomaterial	Type of nanomaterial	Modification	Pesticide	Matrix	Mechanism of degradation	Degradation efficiency (%)	Reference
Metal nanoparticle	FeNPs	Immobilization with laccase	Chlorpyrifos	Spiked pesticide solution	Enzyme-based catalysis	99	Das et al. (2017)
		Coating with carboxymethyl cellulose	Lindane	Water	Dichloroelimination and dehydrohalogenation	95	San Roman et al. (2013)
Bimetallic nanoparticle	Fe/NiNPs	e	Profenofos	Spiked pesticide solution	Catalytic reduction	94.5	Mansouriieh et al. (2019)
		e	Sulfentrazone	Spiked pesticide solution	Dechlorination	100	Nascimento et al. (2016)
	Ag/CuNPs	e	Chlorpyrifos	Water	Catalytic reduction	e	Rosbero and Camacho (2017)
Metal oxide nanoparticle	TiO_2NPs	e	Chlorpyrifos and Monocrotophos	Pond and bore well water	Photocatalysis	>95	Amalraj and Pius (2015)
		Doping with Fe and Si ions	Carbendazim	Spiked pesticide solution	Photocatalysis	98	Kaur et al. (2016)
	ZnONPs	e	Methylparathion and parathion	Water	Photocatalysis	93	Sharma et al. (2016)
Nanocomposite	Graphene oxide and AG NPs	e	Chlorpyrifos, Endosulfan and DDE	Water	Catalytic dehalogenation	95	Koushik et al. (2016)

FeNPs iron nanoparticles, *Fe/Ni* NPs iron/nickel nanoparticles, *Ag/Cu* NPs silver/copper nanoparticles, *TiO_2NPs* titanium oxide nanoparticles, *ZnO NPs* zinc oxide nanoparticles, *AgNPs* silver nanoparticles, *DDE* dichlorodiphenyl- dichloroethylene, *Fe_3O_4 NPs* ferric oxide nanoparticles

19.6.3.2 Zinc Oxide Nanoparticles

ZnO NPs possess both distinctive chemico-physical nature, due to their specific size and high density at the edge of the surface. The surface functionalization of ZnO NPs increases their detection and catalytic properties and thereby engaged in pesticide remediation from varied samples. ZnO NPs act as nano-photocatalyst that helps in the degradation of methyl parathion and parathion present in water samples. These pesticides were basically degraded after irradiation of the photocatalyst with the UV light. It showed around 93% degradation of the target pesticides when carried out under optimum condition (Sharma et al. 2016).

ZnO NPs helped in the removal of permethrin, a broadly used neurotoxic pesticide in agriculture field that was removed from nearby water samples. This NP along with chitosan helps in bead formation for the effective removal of the pesticide. Highest removal efficiency was found to be 99% of the pesticide at neutral pH. The beads formation has proved to be a convenient one for water purification with 56% recovery after three cycles (Dehaghi et al. 2014).

19.6.3.3 Iron Oxide Nanoparticles

These nanoparticles mainly consist of maghemite (γ-Fe_2O_3) and magnetite (Fe_3O_4) particles having wide applications in pesticides remediation from varied samples. The basic concept of nanoparticles is the increase in the surface area to volume ratio remarkably thus the immobilization of iron oxide nanoparticles in different matrices helps in the sensing and degradation of the target pesticides. This perspective of involvement of iron oxide NPs for pesticide remediation thus increased by controlling the size, shape and surface properties of these NPs with both efficiency and specificity. Thus it plays an important role in the detection of various kinds of agro-inputs used in different sources. Glyphosate, a broad-spectrum systemic herbicide, is being removed from water system by using iron oxide NPs, entrapped in mesoporous silica where the immobilization increases greatly the surface area and the porous nature of the magnetic adsorbent (Fiorilli et al. 2017). The systemic fungicide, fenarimol, is being removed of post immobilization in palygorskite, a type of clay mineral by using iron oxide (Fe_2O_3) NPs thereby increasing the holding capacity of palygorskite for removal of the fungicide fenarimol. This method showed 70% adsorption rate for fenarimol, thus suggesting the broader use of iron oxide NPs for sustained removal of fungicide (Ouali et al. 2015).

19.6.3.4 Silica Oxide Nanoparticles

These are also known as silicon dioxide nanoparticles or nano-silica particles. They have some special characteristics of adsorbent; spherical, porous nature; as well as the increase in surface area which allow the extraction efficiency of varied pesticides from different sources. Sulfonylurea found in water samples are removed by

using silica oxide NPs post functionalization with N-methylimidazole. The process of functionalization helps in the enhancement of adsorption of polar pesticide on the surface of silica oxide NPs. Different types of organophosphates, namely, chlorpyrifos, methidathion, dicrotophos diazinon, mathamidophos, and malathion, have been extracted by using silica oxide NPs after co-functionalization with polar cyanopropyltriethoxysilane (CNPrTEOS) and non-polar methyltrimethoxysilane (MTMOS) and are finally analyzed by using HPLC or GC-MS (Ibrahim et al. 2013). Further, silica oxide NPs have been used by using various methods such as electrochemical, optical, and surface-enhanced Raman spectroscopy (SERS) for pesticides detection (Bapat et al. 2016). The enzyme acetylcholinesterase (AChE) binds with the silica oxide NPs that have been used for the detection of the pesticide paraoxon by using a colorimetric assay particularly known as "dipstick" assay. The detection of the pesticide at very low limits is thus increased by entrapment of AuNPs in silica oxide NPs along with the enzyme (Luckham and Brennan 2010). Similarly paraoxon can also be degraded by using enzymes such as organophosphate hydrolase and carboxyesterase that have been immobilized on mesoporous SiO2 NPs (Boubbou et al. 2012). Chlorpyrifos methyl (CLT) and fenitrothion (FNT) are detected by using antibody-tagged silica oxide NPs where monoclonal antibodies (anti-FNT and anti-CLT) isolated from mouse was found to link covalently with the silica oxide NPs for detection of pesticides (Wang et al. 2013). For detection of pesticides, SiO_2 NPs have been utilized with the help of optical, electrochemical, SERS, or fluorescence methods (Bapat et al. 2016); AChE immobilized SiO_2NPs used for detection of the paraoxon. Again, AuNPs entrapped in SiO_2 NPs along with the enzyme to increase the detection of the pesticide at very low levels (Luckham and Brennan 2010). Moreover, antibody-tagged SiO_2 NPs have been used for detecting fenitrothion (FNT) and chlorpyrifos methyl (CLT) where monoclonal antibodies from mouse (anti-FNT and anti-CLT) were covalently linked with the NPs for the pesticide detection (Wang et al. 2013). Recently, these type of procedures are regarded as a promising approach where silica oxide NPs are involved for degradation of broad range of pesticides using biotic system due to cost-effectiveness and eco-friendly nature which have attracted the attention among the researchers.

19.7 Nanocomposites

A nanocomposite falls under a broad range of materials that consist of a multiphase solid material that incorporates nanosized particles (i.e., metals, semiconductors) into a matrix having at least one dimension in the regime of nanoscopic size. Recently, several nanocomposite materials that include nanoparticles of metals, metal oxides, carbon nanotubes, plant-based nanocomposites, etc. with specific properties have played a major role for environmental remediation of pesticides more effectively from contaminated sites. Generally, nanocomposites express great surface area to large surface and volume ratio compared to normal adsorbents (Kamigaito 1991). Nowadays, graphene oxide (GO) and reduced grapheme oxide

(rGO) has been widely used for the production of nanocomposites by using various metal and metal oxide NPs for pollutants remediation. Nanocomposite with Fe_3O_4 NPs has been developed by using rGO for elimination of triazine (broad-spectrum herbicide). The presence of electrostatic interlinkage between nanocomposite and analyte is thus capable of pesticide removal with high adsorption (Boruah et al. 2016). Apart from this, rGO along with AgNPs are also used for the degradation of organophosphates and organochlorine pesticides. This involves a two-step mechanism where AgNP induce removal of halogen from pesticide followed on adsorption of the degradation product of the target pesticide (Koushik et al. 2016). Nanocomposites are also used to prepare montmorillonite clay (a very soft phyllosilicate group of minerals) by using hexadimethrine, a cationic polymer, to increase the efficiency of transduction for removal of a commonly used herbicide, 2-methyl-4-chlorophenoxy acetic acid (MCPA) (Gamiz et al. 2015). Thus, the utilization of nanocomposites works as a boon when it is combined with different materials, which signifies the improvement for the detection and degradation of various pesticides.

19.8 Nanobiocomposites

These are the noble class of composite materials which have great potential where nanofillers are used in biopolymer matrix of the nanocomposite system. Nowadays, bio-based products have shown promising results due to their sustainability in the environment. Biopolymer possesses hydrophilic nature that makes them efficient adsorbents for pollutant remediation from aquatic system. Recently, chitosan-based nanobiocomposite have grabbed more attention among the researchers due to their phenomenal characteristics of biodegradable and biocompatible. The intercalation process helped in the synthesis of Ag/chitosan nanobiocomposite where both chitosan and silver nitrate solution are mix together and followed by microwave irradiation (Saifuddin et al. 2011). Microwave irradiation is a method that uses “one-pot” synthesizing of metal NPs by using metal salts and solutions of polymer surfactants. When it is exposed to this method, silver nitrate reduction takes place for the formation of Ag NPs. Finally, synthesis of Ag/chitosan nanobiocomposite is obtained for the removal of atrazine (herbicide) from drinking water.

19.9 Nanotubes

A nanomaterial with long and hollow cylindrical shaped with length varying from nm to mm is usually defined as a nanotube. The diameter of this tube-form nanotubes ranges in nanometers of (~1–100 nm). Nanotubes functions as good adsorbents due to its different parameters such as big surface area, surface modification with high aspect ratio. Thus these parameters have enabled the use of nanotubes for

detection and degradation of pesticides from the contaminated sites. Based on the above based criteria, nanotubes are classified into carbon nanotubes (CNTs) and halloysite nanotubes (HNTs) that have attracted considerable attention among the researchers because of their unique properties and big surface area.

19.9.1 Carbon Nanotubes

Carbon nanotubes (CNTs) are believed to be promising material as building blocks that have better efficiency as compared to traditional adsorbents (e.g., activated carbon) due to the presence of mesoporous structure and high surface area consisting of different functional groups like phenol, carboxyl, and hydroxyl. They have higher efficiency in adsorbing large number of organic compounds and thus the process of adsorption takes place between the electrostatic attraction and formation of chemical bonds with an outer diameter ranging from 4 to 30 nm. The structure of CNTs depicts with hollow, ordered, graphene-based nanomaterial and bonded with sp^2 hybridization and acts as an exceptionally strong interaction. Some ideal properties of CNTs like thermal conductivity, high tensile strength, less weight, and high aspect ratio have not only limited their applications to electrical, electronics, sensors, and thermal devices but also attracted the researchers in the field of environmental nanotechnology (E-nanotechnology) for removal of recalcitrant from various contaminated sites. They are classified into two types:

(i) *Single-Walled CNTs (SWCNTs)*
Nanotubes with single sheet of grapheme shell is rotated up, to form a tube-form structure are known as single-walled CNTs (SWCNTs). It was first reported in the year 1993 (Iijima et al. 1993). The diameter of SWCNTs ranges less than 1 nanometer.

(ii) *Multi-walled CNTs (MWCNTs)*
Nanotubes with multi-walled sheets of grapheme shell consisting of concentric SWCNTs having an outer diameter and inner diameter of (50–80) nm and (5–15) nm, respectively, and spacings between the adjacent layers is of 3.4 *Å*. In the recent years, adsorption is considered as the most efficient and feasible technology for pollutants removal by transferring the required pollutant from water phase to solid phase (adsorbent) to collect the removal. It was found that MWCNTs are utilized as good nano-adsorbents to eliminate pesticide residues through solid phase extraction technique from tea and later on analyzed by using GC-MS/MS. The spiked pesticide residues in the tea samples are being removed and detected in GC-MS/MS and hence proved to be a skilled technique for pesticides removal.

Fenitrothion, an organophosphate insecticide, is being used in fruits, vegetables, rice, cereals, stored grains, etc. where the insecticide is determined by electrochemical detection with phthalocyanine ruthenium (RuPc); RuPc is being used as the catalyst for the redox reaction by using silica-coated MWCNT. The method behind

the detection of dimethoate, an organophosphate insecticide to kill insects and mites with oxidized MWCNTs capped with AgNPs, catalyzes the oxidation of ample red (AR)-hydrogen peroxide system into resorufin, a crystalline dye. So, in the presence of dimethoate, this oxidation reaction is inhibited (Hsu et al. 2017).

19.9.2 Halloysite Nanotubes (HNTs)

HNTs are naturally viable clay nanomaterial having different morphologies, such as tube-form, spheroidal with elongated tubes, the last being the most common among all the three. They exhibit large surface area with both positively and negatively charged from inner and outer surface respectively thus providing greater adsorption properties (Rawtani and Agrawal 2012). This adsorption capacity of HNT plays a major role in detection and degradation of toxic organic compounds from the environment. Due to their increase biocompatibility and lower cytotoxicity, HNT plays a major part in recent applications such as tumor cell isolation, as scaffolds for tissue engineering, novel drug, and gene delivery. Apart from all these, most importantly, the non-toxic effects exhibited by HNTs have been regarded as a boon into the environmental remediation by the replacement of toxic and expensive carbon nanotubes.

19.10 Nanobioremediation

Nowadays, bio-based sustainable remediation has gained a lot of attention due to its low risks by minimizing the subsidiary impacts of waste generation, consumption of natural resource, etc. But it was observed that bioremediation techniques are time-consuming and might have negative impact on the existing microorganisms if present at higher concentration. Basically, a single technology may not be sufficient for removal of recalcitrant from the polluted site that might be expensive and may not be efficient, high specificity, non-hazardous, and viable. This led to the combination of multiple technologies along with their applications for a single as well as effective remediation technology with less cost effective, high specificity, and better efficiency. Therefore, a promising integration of nanotechnology and biotechnology could overcome this limitation and emerged a more strong and sustainable remediation method known as nanobioremediation. It basically uses the applications of physico-chemical (fast, but expensive) and biological methods (cheap, but relatively slow) for biodegradation of soil and water contaminants to a low risk level and less toxic environment. It was found that nanoparticles used by plants, fungi, and microbes could enhance the microbial activity by removal of pollutants such as both organic and inorganic toxins and heavy metals from the surrounding (Singh and Walker 2006).

19.11 Biosensors for the Detection of Pesticides

Biosensor was first introduced by Cammann in the year 1977. Earlier pesticide residues are being determined in soil and water by using some sophisticated instruments like high-performance liquid chromatography and mass spectroscopy, liquid/gas chromatography. Since these approaches are regarded as highly efficient but at the same time require hardcore sample preparation, along with some highly qualified technicians for analyzing the samples. Therefore, great efforts are devoted for replacement of conventional methods with better sensitivity screening, low cost, and stability for detecting low levels of pesticides. Researchers have carried out rigorous efforts for the development of efficient, cost-effective, eco-friendly nanomaterial-based biosensors, which can detect the presence as well as concentration of organic compounds when present in limited or low amounts. A biosensor basically comprises of three parts: a component that recognizes the analyte and produces a signal, a signal transducer, and a reader device (Fig. 19.4).

19.11.1 Nanoparticle-Based Biosensors

19.11.1.1 Enzyme Biosensors

Here, enzymes are being used as identification component for detection of hazardous substances from both stratum and beneath of earth's surface with high accuracy and precision, high specificity and sensitivity, robustness, and safety. Through enzyme biosensor, information is not obtained regarding a particular pesticide; rather they provide detection of broad categories of pesticides. Since acetylcholinesterase is mostly inhibited by organophosphorous pesticides, hence it is regarded as the basis for enzyme biosensor. Acetylcholinesterase (AChE), butyrylcholinesterase (BChE), or urease is being used as biological receptors where they act as catalytic activity reducers for inhibition of enzyme-based biosensors for detecting pesticides is regarded as the basic mechanism behind the enzyme biosensor. In these reactions, several methods like amperometric, conductometric, and optical are employed for choline detection, the main reaction end-product. Hence, researchers have developed AChE-based biosensors where acetylcholine (ACh) is converted by

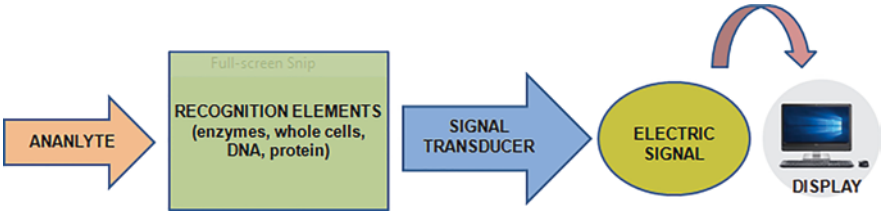

Fig. 19.4 Various parts of a biosensor

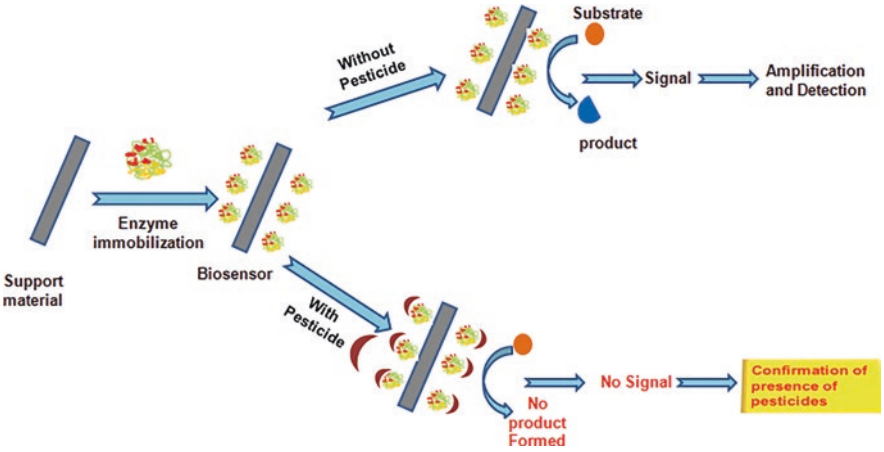

Fig. 19.5 Graphical representation of the mechanism behind pesticide detection using enzyme-based biosensor

AChE into acetic acid and choline (Ch) in presence of H_2O. The intensity of this reaction gives information about the detection of pesticides.

$$\text{Acetylcholine} + H_2O \xrightarrow{\text{AChE}} \text{Choline} + \text{Acetic acid}$$

Enzyme-based biosensors customize with different nanoparticles like quantum dots (QDs) and gold nanoparticles (AuNPs) are basically used for organophosphates, organochlorines detection in the environment. For instance, monocrotophos is being able to detect by this type of customized-based enzyme biosensors (Fig. 19.5).

19.11.1.2 Immunosensor

This type of sensor basically provides information regarding a specific pesticide, having high selectivity and sensitivity of antibody-antigen reaction. Conductimetric immunosensor helped in the detection of atrazine, by using antibodies labeled with NPs (Valera et al. 2008). Diuron, a substituted phenyl urea herbicide, was developed by an electrochemical immunosensor for its fast screening (Sharma et al. 2011). Fabrication of polystyrene substrate helps in the removal of low cost electrodes thus by modifying with Prussian Blue (PB)-AuNP film that helped in the enhancement of transfer of electrons in the domain of the gold electrode thereby increasing its sensitivity compared to unmodified gold electrodes.

19.11.2 Nanoparticle-Based Optical Biosensors

The use of nanoparticles has an important role in developing efficient optical biosensors for pesticide detection. Nanoparticles such as semiconductor QDs are frequently used in fluorescent sensing. These QDs or polymer nanoparticles are considered as highly photostable than a conventional fluorophore and thus allow high fluorescence quantum yields and also exhibit high sensitivity. Monocrotophos (organophosphate insecticide) can be detected through optical biosensor by CdTe as fluorescence probe (Sun et al. 2011). Recently, it was found that QDs-based fluorescence assays are able to detect several organophosphates and the activity of AChE (Saa et al. 2010; Chen et al. 2013; Yu et al. 2014; Zheng et al. 2011; Buiculescu et al. 2010; Garai-Ibabe et al. 2014).

19.11.3 Nanotube-Based Electrochemical Biosensors

The interaction between an analyte with an electrode (e.g., platinum, gold, silver, graphite) is usually measured in terms of potential or current for detection of electrochemical wherein various changes like chronoamperometry and chronopotentiometry cyclic voltammetry are observed by using abundant of techniques (Grieshaber et al. 2008). The use of nanoparticles such as modified carbon nanotubes have basically helped in enzyme electrodes, specifically electrochemical biosensor in various fields such as biosensing, biomedical engineering, nanoelectronics, and bioanalysis. Recently electrochemical biosensor has been developed by using CNTs for inhibiting the activity of AChE (Du et al. 2007; Oliveira and Mascaro 2011; Firdoz et al. 2010; Qu et al. 2010). This biosensor has shown promising results in terms of sensitivity and stability regarding pesticides monitoring in aquatic system.

19.12 Future Perspectives

The field of nanotechnology has great perspective in retransforming the previous used conventional techniques with high specificity, cost-effective, small-scale size, low detection limits and high sustainability in environmental remediation. In addition to these, utilization of various nanotechnology-based nanomaterials such as metals and metal oxides helps in increasing the removal of organic pollutants by means of reducing or oxidizing of metals along with functional groupings of chemical groups that can selectively detect the target pesticides from the contaminated sites. The use of nanoparticles such as AuNPs, TiO_2 NPs, ZnO NPs, AgNPs, and SiO_2 NPs together with nanocomposites and nanotubes like CNTs and HNTs helps to detect or sense pesticides when they are present at very negligible level. The

surface modifications of these nanoparticles help in the enhancement of both sensitivity and specificity for pesticide detection. For instance, ZnO NPs and nanotubes like CNTs and HNTs have proved to increase the removal efficiency by 99–100%. The practical applications of CNTs or magnetic composites should be explored more in the future. Biosensors are considered as superior candidate for pesticides recognition in complex samples. Enzyme inhibition-based biosensors have shown better results for detection of pesticides. The large-scale use of polymeric adsorbents has shown promising results in adsorption of metals and organic pollutants. Moreover, the capability of reuse and increasing the lifespan of these adsorbents should be investigated further to reduce the cost for pesticide remediation. Further, the understandings of nanotechnological applications in the bioremediation and nano-bio-interactions accelerate the development of nanopesticide. The wide use of the pesticide for the management of tea pest aggravates various concerns such as non-target toxicity to parasitoids and insect predators, development of resistance, and upsetting the ecological balance and heavy load of pesticide residue in tea leaves. Exploiting advantages of nanotechnological interventions and aligning it with green chemistry and environmental sustainability principles hold tremendous potential in combating tea plant pest. Recent report demonstrated alteration of the nonsystemic behavior of the pesticide ferbam on tea leaves by engineered gold nanoparticles (Hou et al. 2015). These finding open up new avenue of research and translational development in nanopesticide for an integral part of Integrated Pest Management (IPM) practices of tea plant.

19.13 Concluding Remarks

Nanoremediation has emerged as a new scope for environmental remediation from the field of nanobiotechnology that has immense potential for diminishing recalcitrants from the habitat to a more greenish environment. The effectiveness of nanoremediation has helped in the overall reduction of xenobiotics that has approximately reach to zero level in in situ nanoremediation due to cost effective, high competency as well as large-scale application compared to ex situ nanoremediation which needs to be workout for better results. The applications of various nanoparticles and biosensors having some specific characteristics of large surface area, high specificity, and small-scale size with quick response have helped to overcome the drawbacks for detection of pesticides at very low levels of detection in the environment over the conventional techniques. However, the toxicity of nanoparticles (carbon nanotubes, metals, and metal oxide NPs) cannot be denied completely because of their lethal effect on the significant proliferation over the microorganisms. Hence, more meticulous research is utmost necessary in this regard so that nanoremediation emerged as a promising tool in the future for contaminant remediation and also for better environmental sustainability.

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Chapter 20
Potential Applications of Nanomaterials in Agronomy: An African Insight

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20.1 Introduction

The green revolution which took place in the twentieth century saw the introduction of huge machinery in crop production such as tractors, ploughs, planters, and harvesters, as well as the significant use of inorganic nutrient sources in the soil. Notwithstanding the environmental and soil degradation consequences of the green revolution, as it relied on chemicals like inorganic fertilizers which only fed the crop and not the soil, it also resulted in significant improvement in crop yields and food security which was critical in feeding the growing world population. Due to the need for continued increase in food production per unit area to accommodate the ever-increasing world population, the twenty-first century has now seen a move towards sustainable intensification. The introduction of sustainable intensification is a concept that is related to increasing crop productivity in agriculture with limited or reduced impacts on the environment while maintaining the same or even higher productivity within the same area (Fraceto et al. 2016). As part of sustainable intensification, biotechnology is gaining momentum as the way forward in driving this concept where living organisms and their derivatives are utilized in increasing the efficiency of various processes linked to agriculture. From realizing that all matter is made up of atoms to the discovery of how all living organisms are made up of cells with various organelles inside, science has been inspired by nature, with most research driving towards the manipulation of matter and living organisms at their basic fundamental building structures. Through the exploitation of the various fundamental principles of nature, researchers are now able to control different physical, biological, and chemical properties at a nanoscale (Ghasemmezhad et al. 2019). This has led to the development of a new branch of science called nanotechnology, and this is seeing wide applications even in agriculture where nano-materials are now being used to power sustainable intensification and increase farmer's resilience and adaptation to climate change (Prasad et al. 2014, 2017a, b). With nano-technology being an emerging science, its applicability to resource poor African farmers is still limited. Our chapter presents some of the production challenges that are faced by these resource poor farmers, the nanotechnologies that are available in agriculture and provides a guide to where nanotechnology can be utilized under the African farming scenario.

20.2 African Smallholder Crop Production Challenges

20.2.1 Soil Fertility Management

Soils in much of Africa, where smallholder farming is practiced, are poor in quality and prone to rapid degradation. This setttlement of smallholder farmers on poor quality soils can be traced back to the colonial past, whereby Africans were forced to settle on marginal lands. Sandy soils, that are inherently acidic and low in

phosphorus (P) and zinc (Zn), predominate most smallholder farm lands in Africa (Mafongoya et al. 2006; Vanlauwe and Giller 2006). In commercial crop production, chemical fertilizers and composts play a major role in increasing yield. However, such is not generally the case in smallholder systems of Africa, where most farmers are resource poor. Thus, the poor soil fertility situation of resource poor farmers is exacerbated by continuous mono-cropping and removal of nutrients without any replenishment from either inorganic fertilizers or manures. Additionally, conventional farming practices such as overgrazing, intensive tillage, short-to-no fallow periods, lack of organic matter input, and limited crop rotation have been identified as further causes of soil degradation.

Poor soil fertility is long known to be a major reason why resource poor smallholder farmers abandon farming as a means of livelihood. It is also a component of the vicious cycle of poverty in African smallholder farmer communities. Barret and Bevis (2015) demonstrated a strong, self-reinforcing link between poor soil fertility and poverty, whereby, "poor soil constrained agricultural production and household capital, and low household capital constrained investments in improving soils." They recommended that interventions that provide poor families with inputs for improving soil fertility may all help break the soil–poverty cycle. It has often been suggested by various researchers that agronomical research on soil fertility improvement in African smallholder farmer systems may need to focus on alternative sources of nutrients to inorganic fertilizers for soil fertility improvement. Proposed nutrient sources include livestock manures, human waste, biomass transfer, cover crops, nitrogen (N)-fixing legumes, composts, and rock phosphates, among others. However, numerous challenges have also been observed regarding practical application of these alternative soil amendments.

Malnourished animals grazing on depleted veldts as those in resource poor smallholder communities of Africa will produce manures of poor quality, which are also difficult to collect as the animal's graze over vast areas. Similarly, organic sources for production of nutrient rich composts are scarce in resource poor communities and have at times been shown to stimulate harmful pests and diseases, especially under conservation agriculture (CA) (Chiduza and Dube 2013). For various ethical reasons, the acceptability of human wastes as soil fertility ameliorant may be contentious. It is accepted that not all legumes will fix N and at times require inoculation. Depending on the harvest index, legumes grown on poor soils may remove net amounts of N from the soil (Vanlauwe and Giller 2006). Since legumes require land, labor, and P fertilizer, the cost of legume N on poor soils may easily exceed that of purchasing N fertilizer. Rock phosphates are typically poor soluble, and this limits their applicability as they have to composted first before application (Vanlauwe and Giller 2006).

In the past two decades, there has been a research drive towards CA practices that encourage accumulation of SOM as well as prevent soil erosion for ameliorating soil fertility problems. The major principles of CA are minimum soil disturbance, crop rotation, and permanent soil cover through cover crops (Dube et al. 2012). Despite numerous efforts aimed at promoting CA by both government and non-governmental organizations, uptake of the CA technology in Africa remains low,

owing to various challenges in its implementation. As highlighted by Giller et al. (2009) in the heretic's review of CA, the lack of suitable no-till farming tools, pests and diseases, competing uses of crop residues in mulching, and animal feeding are some of the barriers to wide-scale CA adoption in resource poor smallholder farming systems of South Africa. Integrated soil fertility management (ISFM), which aims to increase food production through strategic combination of traditional and new technologies is the new approach being advocated for improving soil fertility in resource poor smallholder communities (Bekunda et al. 2010, Vanlauwe et al. 2015). It has been defined as soil fertility management practices/principles that include the use of fertilizer, organic inputs, improved cultivars/germplasm combined with various other crop production technologies, and the knowledge on how to adapt these practices to local conditions, aiming at maximizing agronomic use efficiency of the applied nutrients and improving crop productivity (Vanlauwe et al. 2010). To this regard, nanotechnologies present new opportunities yet to be explored for ISFM in resource poor smallholder farming systems.

20.2.2 Plant Pest Management

Apart from poor soil fertility, pests have been singled out by several researchers as another major cause of poor crop yields in smallholder farmer systems of Africa, including conservation agriculture systems (Chiduza and Dube 2013; Fanadzo et al. 2018). Pest and soil fertility management complement each other. Thus, the benefits of improved soil fertility may not be realized in the absence of good pest management and vice versa. Without adequate pest management, it may be wasteful to invest in soil fertility improvement. A plant pest is any organism that reduces the quantity, quality, or value of a plant grown for food, fiber, or recreation. The three major groups of plant pests are animal pests (such as insects, mites, other arthropods, and vertebrates such as birds and rodents), plant pathogens (such as fungi, bacteria, viruses and nematodes), and weeds. Of these, weeds, insects and plant pathogens have been identified are the main biological constraints faced by smallholder farmers. Economic losses caused by these pests do not only include the direct action of these organisms as they damage crops, but also indirect economic losses related to the costs of controlling the pest and environmental damage caused by pesticides.

In South Africa, weeding is identified as one of the activities demanding the most labor in smallholder farming (van Averbeke et al. 1998; Fanadzo 2007, 2010; Fanadzo et al. 2010). Most smallholder farmers are aware of the detrimental effects of weeds, but do not have the time or the means to control them especially where tractor mechanization has resulted in an increased area of land being cultivated. Owing to a history of poor weed management, soils of production lands of the resource poor smallholder farming systems typically have reservoirs of problematic weed seeds. In severe cases, weed problems have been known to cause abandonment of cropped fields (Fanadzo et al. 2010). Using smallholder irrigation schemes

in South Africa as a case study, Fanadzo et al. (2010) reported that there were no responses to N fertilization and irrigation owing to poor weed management. In the absence of adequate weed management, N fertilizer promotes weed growth more than crop growth. Because resource-poor smallholder farmers cannot afford herbicides and lack technical expertise for their use, they typically rely on hand hoes for weeding. Literacy rates are low, such that even where pesticides are made freely available, there is a general lack of technical knowledge on how to use them efficiently. There is drudgery through the many hours spend on hoe weeding and, in most cases, weeding is carried out by women and children (Giller et al. 2009). The move towards CA has presented more challenges with regard to pest management. Conventional tillage was useful for controlling not just weeds, but animal pests as well through exposing the pests to their natural enemies or directly by physical damage inflicted during the tillage process. Tillage was also used to bury crop residues that harbor plant pathogens into deeper layers of the soil where they cause less or no disease.

Labor shortages largely caused by rural–urban migration and shift from farming by younger community members into other activities means that hand weeding can be a daunting task. Thus, in many cases, labor is mostly family labor, comprising mainly of older people. The effect of HIV/AIDs has weakened the labor force, and the COVID-19 pandemic is likely to exacerbate the situation. Under irrigated crop production in South Africa, poor crop stands observed in farmlands have mainly been attributed to late weeding caused by shortage of labor (Fanadzo et al. 2010). Due to competing demands on family labor and the overlapping of the optimal times for weeding with other crop activities, there is a shortage of labor for hand-weeding at the optimal times. As a result, weeding is either not done at all or is performed inadequately or too late after the weeds have already reduced the crop yield potential. It is clear that herbicides have a major role to play in increasing agricultural production and improvement of rural welfare. The integration of herbicides into small-scale farmer pest management systems can minimize labor requirements and increase profitability. Recent developments in herbicide nanotechnology mean that herbicides may be applied in smaller proportions at a nanoscale, thus potentially reducing the costs and hazards associated with herbicide use (Bhattacharyya et al. 2016). These and other potential benefits of nano-technologies in pest management at the resource poor smallholder farmer level will be discussed in this book chapter.

20.2.3 Drought/Water Shortages and Management

Africa is experiencing extreme weather conditions due to climate change, and these include high annual rainfall variability and unreliability. Shifts in seasonal rainfall and temperature patterns have seen frequent droughts and major disruption of smallholder farmer livelihoods. For example, during the period 2015 to 2018, South Africa experienced one of the worst droughts in history, with a rainfall average of

403 mm in 2015, the lowest recorded since 1904. The extent of its severity was qualified as greater than the 1992 to 1993 drought, experienced by the entire region of the Southern Africa (Baudoin et al. 2017). Droughts can have devastating effects on smallholder farmer livelihoods and adapting to them is complicated because of the absence of a solution that can be suitable for a wide range of situations or problems. Compared to their large-scale commercial counterparts, smallholder farmers are more vulnerable to drought impacts, and they struggle to cope and adapt. Their capacity is restricted because of their limited or lack of access to water resources, finance, reliable markets, land, knowledge, managerial skills, and extension support.

It is suspected that as the continent is becoming drier overall, atmospheric temperatures are also rising. Hence, there has been a recent drive toward much research aimed at drought mitigation in smallholder farmer systems of Africa. Options proposed include rainwater harvesting, mulching, reduced tillage practices, and drought-tolerant cultivars, among others. These are referred to as "climate smart" agricultural technologies and include conservation agriculture (Ramanan et al. 2020). Rockstrom (2000) identified two broad strategies for increasing yields in dryland farming when water availability in the root zone constrains crop growth: (1) capturing more water and allowing it to infiltrate into the root zone and (2) using the available water more efficiently (increasing water productivity) by increasing the plant water uptake capacity and/or reducing non-productive soil evaporation. Practices used to achieve this include water harvesting, supplemental irrigation, deficit irrigation, precision irrigation techniques, and soil–water conservation practices. Generally, infield water management in smallholder farming is weak, partly due to the infield irrigation equipment which is inefficient, as inefficient, as well as the absence of proper irrigation scheduling. Lack of scheduling results in over- or under-irrigation depending on crop type and growth stage. There is a need for simple irrigation technologies that can improve water use efficiency in resource poor smallholder farming systems of Africa, where water is increasingly becoming a scarce resource.

20.3 Current Nanotechnologies in Agriculture

Production challenges such as extreme weather conditions, poor soil fertility, and plant pests and pathogens which cause extensive yield losses of between 20% and 40% per annum require innovative solutions that are not only cheaper by highly effective as well. Combining nanotechnology with current agricultural technologies such as climate smart agriculture could potentially significantly reduce production costs and boost yield especially for resource poor smallholder farmers. Already, there is a huge concern on the overuse of pesticides, which results in significant amounts being lost in runoff, drift, as well as causing pesticide resistance (Hayles et al. 2017). Nanotechnology can potentially play a significant role in building agricultural resilience to climate change, improved productivity, and food security (Venkatramanan et al. 2020). More specifically nanotechnology reduces the need

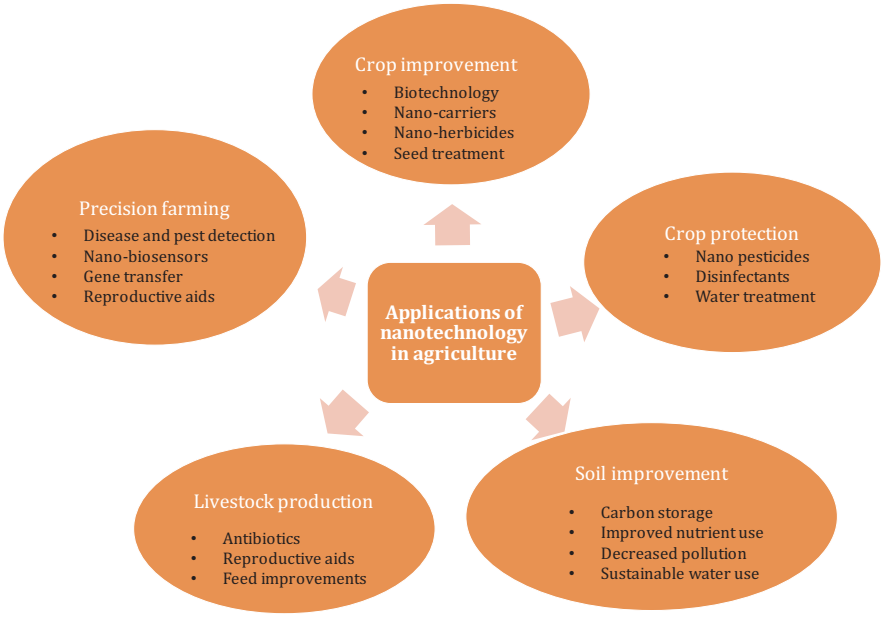

Fig. 20.1 Schematic diagram showing the potential applications of nanotechnology in agriculture. (Adopted from Dasgupta et al. 2014 and Shang et al. 2019)

and frequency for plant protection (Iqbal 2019) and improves crop and soil quality as well as nutrient and water use efficiency. Potential agricultural applications of nanotechnology are summarized in Fig. 20.1.

20.3.1 Nano-fertilizers

Any product with nanomaterials that are used to enhance nutrient use efficiency can be referred to as nano-fertilizers (Mikkelsen 2018). Nano-fertilizers are made by manipulating nutrients and minerals on a molecular level, typically amounts of mineral that is smaller than 100 nanometers (1 mm = 1,000,000 nm). Nano-fertilizers minimize environmental contamination and wastage by reducing the frequency and target application of fertilizer (El-Ramady et al. 2018). Compared to traditional fertilizers, nano-fertilizers have a higher surface area that increases their solubility and reaction capacity within the soil and can be designed to slowly release nutrients which limit leaching and result in more efficient plant nutrient uptake Cui et al. (2010). The small size of the particles increases their concentration per unit area, thus boosting chances of uptake/penetration into plants through roots and leaf surfaces. Furthermore, minimum to no energy is needed to move the nutrients from the soil into the plant's vascular system; therefore, the plant has more energy for other

growth processes. Other properties of nano-fertilizers are high solubility, controlled and timely release, stability, effectiveness, improved targeted activity by delivering desired concentration, and reduced toxicity with easy, safe distribution, and disposal (Pramanik et al. 2020). Researchers have put nano-fertilizers into three classes, (1) nanoscale fertilizer (nanoparticles that contain nutrients), (2) nanoscale additives (traditional fertilizers with nanoscale additives), and (3) nanoscale coating (traditional fertilizers coated with nanoparticles) (Rai et al. 2012, Mikkelsen 2018). Even though the nano-fertilizers technology is still in its infancy, various studies done show the potential of nano-fertilizers in agriculture. Most of the studies reported that nano-fertilizers improved crop growth, yield, and quality parameters of the crop, which resulted better food products for human and animals (Mahanta et al. 2019). Examples of nano-fertilizers include hydroxyapatite, ammonium-charged zeolites, nano-calcite ($CaCO_3$-40%) with nano-SiO_2 (4%), MgO (1%), and Fe_2O_3 (1%) and ZnO nanoparticles (Adhikari et al. 2015, Kah et al. 2018). For example, Marzouk et al. (2019) reported that applying zinc nano-fertilizer as a foliar spray improved the vegetative growth, fresh pod yield, pods physical quality, and nutritional value of two snap bean cultivars. Table 20.1 highlights some of the research that has been done on nano-fertilizers.

20.3.2 Nanopesticides

The green revolution indicated above resulted in the use of various chemical compounds for use in the control of pests and diseases in order to increase crop yields. This saw the introduction of chemicals like 2,4 D and glyphosate for the control of weeds, together with various insecticides, which all resulted in reduced crop competition and increased yields. However, the introduction of these pesticides also resulted in various environmental challenges such as death of bees and fish due to their excessive use. One of the critical drivers for the application of nano-technology is a reduction in the amount of pesticide needed to assure crop protection, which may be achieved by several ways such as by improved apparent solubility, controlled release, targeted delivery, enhanced bioavailability, increased leaf adhesion, and improved stability of the active ingredient in the environment (Kah et al. 2013). Nanopesticides are more effective than conventional pesticides because they have a more targeted delivery and effect. In addition, they pose less risk to non-target organisms and use less water and energy during the application of nanopesticides since they are required in smaller amounts and less frequently than the conventional pesticides. Consequently, nanopesticides reduce wastage and labor costs while sustainably increasing crop productivity (Sahu 2020). The application of nanopesticides involves smart delivery methods (nanoencapsulates and nanocontainers); controlled pesticide release; physical and biological changes in plant structures; and improved wettability and efficacy at reduced dosages (Khot et al. 2012). The use of Nanopesticides could complement current efforts to promote sustainable agriculture which entails minimized use of agro-chemicals in order to protect the environment (Bhattacharyya et al. 2016).

Table 20.1 Summary of research undertaken on nano-fertilizers in agriculture

Nanomaterial	Observations	References
Ferrous nano-oxide particles	Lipid and protein levels, fatty acids, Fe, Mg, Ca, and P, chlorophyll contents of Soybean (*Glycine max L.)* Seed were improved with an increasing in concentration of ferrous nano-oxide from 0 to 0.75 g L^{-1}, but the increase from 0.75 to 1 g L^{-1} resulted in a reduction all the parameters above	Sheykhbaglou et al. (2018)
Nano-KH_2PO_4	Shoot and root biomass increased under nano-KH_2PO_4 due to the high physiological efficiency of P in these organs. However, P uptake was lower in nano-KH_2PO_4 compared to KH_2PO_4.	Miranda-Villagomez et al. (2019)
Banana peel nano-fertilizer blend	Germination increased from 14% (control without nano) to 97% and from was enhanced from 25% (control without nano) to 93.14% for tomato plant and fenugreek, respectively	Hussein et al. (2019)
Nano chitosan-NPK fertilizer	Nano chitosan-NPK fertilizer compared to the control, significantly increased the harvest index, crop index, and mobilization index of the determined wheat yield variables, as compared with control. The number of days to maturity was reduced from 170 to 130 after treatment with nano chitosan-NPK fertilizer	Abdel-Aziz et al. (2016)
ZnO nanoparticles	The delayed and low germination of lentil seed was proportional with an increase in concentration of ZnO nanoparticles from 25 μg mL^{-1} to 200 μg mL^{-1}	Mahanta et al. (2019)
Iron oxide nanoparticles	The study showed that significant increment of plant height (37 cm), leaf area (45.4 cm^2 /plant), number of symbodial branches per plant (15.1), seed cotton yield (14.9 g/pot), and boll weight (3.5 g/boll) were increased due to foliar application of magnetite nanoparticles	Kanjana (2019)
Nano-TiO_2	An increase in nanoTiO_2 treatment from 0.25–4% increased spinach the plant dry weight, chlorophyll formation, ribulose bisphosphate carboxylase/ oxygenase activity, and the photosynthetic rate	Zheng et al. (2005)
Fe nano-oxide (Fe_3O_4, N1) and Mg nano-oxide (MgO, N_2)	Bulk density increased with increase in Fe from 0% to 5% while it decreased increase in Mg levels	Bayat et al. (2018)

20.4 Mycosynthesis of Nanomaterials

Mushrooms are the group of fungi with characteristic fruiting bodies that are large enough to be seen by naked eyes. They have been used as food and medicine in many parts of the world for a long time (Kamalebo 2018). Besides their use as food and medicine, mushrooms have also been used in bioremediation (using mushrooms to detoxify contaminated soil) and myco-filtration (using fungal mycelium to remove biological contaminants from surface water passing directly into sensitive watersheds). Nanotechnology has of late been growing significantly with promising

applications in the medical, electronics, photonics, and catalyst industries. Metal nanoparticles (NPs) can be synthesized by physical, chemical, hybrid, and biological techniques (Khanna et al. 2019). Biological techniques have been of interest due to the potential of the NPs produced through these techniques in the production of antimicrobial materials, catalysts in biological labeling, gene therapy, and DNA among others uses (Adeeyo and Odiyo 2018). Biological agents such as plants and fungi including mushrooms have been used successfully for synthesis of metal NPs (Balakumaran et al. 2016; Prasad et al. 2016, 2018; Srivastava et al. 2021; Sarma et al. 2021).

The use of edible and medicinal mushrooms to synthesize metal NPs, a process known as mycosynthesis, has however demonstrated to be advantageous over other biological techniques due to their high tolerance toward heavy metals and their potential to secrete large amount of enzymes that are essential for reduction of metal ions into their nano-forms (Prasad 2016, 2017; Prasad et al. 2018; Abdel-Aziz et al. 2018). Furthermore, fungi provide relatively quick and ecologically "clean" metallic NPs compared to the use of other biological entities (Shah et al. 2015). The process of mycosynthesis involves the extraction of various phytochemicals which include polyphenols, flavonoids, terpenoids, and high-low molecular weight proteins participate in the formation of metallic nanoparticles upon reduction of their precursor salts and stabilization of the NPs in a complex redox-mediated process. The basic principle behind mycosynthesis is the reduction of metal ions into their NPs, and as the reduction takes place, the biomolecules aggregate with the metal ions to form nano-sized corona (Patil et al. 2019; Aziz et al. 2016, 2019). Due to the complexity of the process of mycosynthesis, there is extensive research being undertaken in this field biological synthesis of nanoparticles by evaluating various fungi as highlighted in Table 20.2.

20.5 Potential of Nanotechnologies in African Smallholder Agriculture

As highlighted above, most of the African resource poor farmers' soils are now degraded with poor physical properties, reduced organic matter content, and limited biological activity which greatly reduces the resilience of these farmers in the face of a changing climate. The main challenge that these farmers often face is that of poor soil quality measured by their very low organic matter, reduced water holding capacity, and poor nutrient retention capacity. Furthermore, due to the mono-cropping introduced to most of these farmers, African farmers tend to face serious yield-reducing competition from pests and diseases. Nanotechnology is quite novel to propose for the resource poor smallholder African farmers, but we propose some of the technologies that can be critical to research on for adoption by these farmers in the near future.

20.5.1 The Soil

Nanotechnology promises to offer quicker and cheaper solutions to reverse soil degradation under the African soils and soil improvement through use of nanotechnology can be at a macro- and micro-level. At a macro-level, the nanoparticles strengthen soil structure and modify the pore fluid, while at a microscale the nanoparticles influence the colloidal properties and nature of the soil (Ozin et al. 2009). A study by Aminiyan et al. (2015) showed significant improvement in soil structural stability after applying nanozeolite, zeolite, and plant residues. In

Table 20.2 Selected current research focusing on the use of mushroom species in the mycosynthesis of metal nanoparticles (NPs)

Mushroom species used and nanomaterial synthesized	How nanomaterial was synthesized	Nanomaterial characterization	Nanoparticle use	References
Ramaria botryti – **Silver–gold composite nanoparticle**	Aqueous solution of polysaccharide extracted from fruit bodies mixed with chloroauric acid tetra hydrate and silver nitrate solutions	Change in color of the solution from yellow to reddish violet and Ag@AuCNPs was confirmed by UV–vis spectroscopy, where a peak at 506 nm was observed	Antioxidants and antibacterial assays as well as catalytic activity toward the reduction of 4-nitrophenol	Bhanja et al. (2020)
Ganoderma lucidum - **Silver nanoparticles**	Ethanol extract of powdered mushroom fruit bodies was obtained by using a microwave process. The extract was diluted using distilled water then 15 mg of $AgNO_3$ salt was mixed with the mushroom extract then placed on a magnetic stirrer system for the reduction of Ag+ ions to Ag0	Transparent solution changed to a brown-reddish color. UV-vis spectrum exhibited a broad absorption peak between 400–460 nm which indicates the existence of Ag NPs. TEM images showed Ag NPs are spherical with a diameter range of 15–22 nm	Antioxidant, DNA cleavage, and antibacterial activities	Aygün et al. (2020)

(continued)

Table 20.2 (continued)

Mushroom species used and nanomaterial synthesized	How nanomaterial was synthesized	Nanomaterial characterization	Nanoparticle use	References
Fomitopsis pinicola - **Titanium oxide and silver nanoparticles**	Aqueous solution of powdered fruit bodies were mixed with $AgNO_3$ and TiO_2, respectively.	UV-visible spectroscopy showing diffraction lines corresponding to (111), (200) and (220) planes indicating the presence of Ag NPs. FTIR spectroscopy determined the presence of mushroom biomolecules. SEM used to analyzed synthesized TiO_2 NPs and Ag NPs. TEM used to determine size and shape of the synthesized TiO_2 NPs and Ag NPs	Antibacterial and anti-proliferative properties	Rehman et al. (2020)
Pleurotusdjamor- **Titanium dioxide**	Aqueous extract of fresh fruit bodies mixed with TiO_2	UV–Vis spectrum of TiO_2 NPs showed maximum absorption at 345 nm. EDX pattern confirmed the purity of TiO_2 NPs	Antibacterial, anticancer, and mosquito larvicidal activity	Manimaran et al. (2020)
Flammulina velutipes - **Silver nanoparticles**	Aqueous extract of fresh fruiting bodies mixed with mixed with chloroauric acid	Change in color from light yellow purple color UV–vis spectrometer	Catalyst for decolorization of methylene blue	Rabeea et al. (2020)
Pleurotus giganteus - **Silver nanoparticles**	Aqueous solution of fresh fruit bodies were mixed with $AgNO_3$	UV–Vis spectroscopy surface plasmon resonance peak around at 420 nm	Antimicrobial and α-amylase inhibitory activity	Debnath et al. (2020)

(continued)

Table 20.2 (continued)

Mushroom species used and nanomaterial synthesized	How nanomaterial was synthesized	Nanomaterial characterization	Nanoparticle use	References
Agaricus bisporus - **Gold nanoparticles**	Chloroauric acid heated on a magnetic stirrer hotplate from 80 °C to 100 °C in a 250-ml flask then aqueous solution from fresh fruit bodies was added.	The EDX spectrum confirmed the identity of the nanoparticles as being that of gold	Degradation of Azo dye	Dheyab et al. (2020)

addition to soil structural stability, application of nanozeolite significantly increased soil organic carbon in soil aggregates. This finding indicated the potential of nanozeolite in soil carbon sequestration, hence reducing loss of carbon to the atmosphere. Under African systems, one of the main limitations to improved soil quality is their lack of soil organic matter, and this tends to reduce soil biological, chemical, and physical properties and thus their productivity. Several researchers have proposed technologies such as conservation agriculture and application of animal manures as a way of increasing soil organic carbon. However, all these technologies proposed require addition of huge quantities of organic matter to the soil over several years to accrue positive soil quality benefits. For example, Nyambo et al. (2018) determined that addition of high rates of up to 200 t ha^{-1} biochar is required for improved soil bulk density, soil organic carbon, aggregate stability, and microbial biomass carbon, and this may not be feasible for full field application especially under smallholder farmer setup. In another study, Aminiyan et al. (2015) showed that the application of nanozeolite improved the concentration of soil organic carbon in light and heavy fractions, which also play significant roles in soil stability. In addition, nanozeolites play critical roles in improving the water-holding capacity of soil which could be very critical in dry areas. Padidar et al. (2015) reported a significant reduction in wind erosion with use of nanoclay. This was attributed to improved dry aggregate stability after applying nanoclay. What is critical to observe is that nanotechnology offers a much more feasible and faster method of improving African farmers' soil quality relative to the current technologies being promoted. However, since this technology is high tech and very new, there is need for research that can practically evaluate the feasibility of these nanomaterials in actually increasing soil quality, as such information is lacking. With other researchers reporting that some nanoparticles do not contribute to the soil organic carbon themselves, but rather affect the organic matter decomposition rates, research also evaluate the combination of nanomaterials, and the current organic agriculture-based systems will also be important.

20.5.2 The Crop Yield

To African farmers, weeds and pests present their greatest nemesis to achieving higher yields even with increased fertilization. What is interesting is that most of the African farmers have not adopted the use of pesticides in their conventional substance farming systems. Though still far-fetched, nanotechnologies still offer a twenty-first century opportunity for increased yields among these farmers. The use of nanotechnology is proposed to have the ability to reduce the dosages of herbicides and insecticides that are needed to achieve similar results, which has cost-saving effects to these farmers whilst reducing the environmental effects of these insecticides. This research on the potential of such improved technologies is still very limited from an African perspective, and if the resilience of these farmers is to be improved in the face of a changing climate, there is a need for research in this area.

20.6 Socioeconomic Implications of Nanotechnology on Agriculture

There are many goods (nanoproducts) on the market that are produced using nanotechnology capabilities, or that are nanotechnology-based, ranging from foods, cosmetics, household appliances, computers, cellular phones, medicines, textiles, ceramics, construction materials, sports equipment, and military weapons. In food, nanotechnology is used in product packaging, nutritional supplements, and agricultural production. As such, the types of nanotechnologies are diverse; hence their application in agriculture is wide. However, researchers in nanotechnology and agriculture emphasize that the broad application of nanotechnology is aimed at resolving the current challenges of sustainability, food insecurity, and climate change (Pasiri et al. 2014). As such, nanotechnologies are being promoted as new source of key improvements for the agricultural sector through reduction of the amount of sprayed chemical products by smart delivery of active ingredients, minimize nutrient losses in fertilization, and increase yields through optimized water and nutrient management (Pasiri et al. 2014). Furthermore, nanotechnology-derived devices are also being explored in the field of plant breeding and genetic transformation.

Despite these potential advantages, nanotechnology applications in the agricultural sector are still comparably marginal and have not yet made it to the market to any large extent in comparison with other industrial sectors. This has led to deficiencies in data sets related to adoption of nanotechnology thereby posing challenges on credible economic evaluation of the economic impact of nanotechnology to the economies and the society. Some economic researchers have suggested that nanotechnology could be a new post-industrial economy emerging, which is shaped by nanoscience (Canton 2015). The NanoEconomy is based on manipulating matter on demand, thus fundamentally changing the products, services, markets, channels, jobs, and supply chains that we know today (Canton undated).

The limited availability of nanotechnology data in the market has weakened the economic research output in this area. As such, Canton (undated) points a gap in knowledge by highlighting that there is no economic theory sufficiently well developed to understand the impact of nanotechnology and science on the economy. There is reliance on technology adoption theories, which may fail to give credible information in situations where the technology is new, and data is limited. However, evolutionary economic models might provide a useful context for explaining the impact of core technologies and sciences that create economic change. In this instance, economic change may be described as the movement of capital, the invention of new products and services, the emergence of new markets, and the production of wealth (Canton undated; Musee et al. 2010). In addition, the formulation of new economic opportunity such as job creation and investment potential would be characteristic of these economic changes as well. Competitive advantage may also be an outcome. The basis of this approach to evolutionary economics is the recognition that core technologies represent economic shifts impacting on agricultural markets, customers, as well as both upstream and downstream industries. There is often a convergence of technologies that end affecting communities. It is the convergence of these technologies that create the most significant economic changes. It is becoming clear that as nanoscience becomes the next core scientific advancement, it also may represent the next evolutionary economic shift in the societies.

Although there is need for continuous research on actual as well as potential risks associated with nanotechnology, some research highlights some concerns of the technology. For instance, Musee et al. (2012) argued that the toxicity of nanoparticles affects both human health and other forms of biological organisms in the environment. This is because the increasing accumulation of nanoparticles in ecosystems with potential for transfer to higher organisms through the food chain may result in exposure of humans through foods such as fish, bacteria, earthworms, and snails and vegetables, among others (Musee et al. 2012). The fact that nanoparticles can move along the food chain, the extent to which consumers should be vigilant for possible toxic effects of engineered nanomaterials should be emphasized. Although potential health and environmental risks of nanomaterials are scientifically documented and numerous uncertainties remain, the public funds dedicated to evaluating these risks are extremely low, especially in Africa. Furthermore, the African context is unique in that there is a challenge to balance the need to use technology to fight hunger and poverty while are at the same time mitigating the adverse effects of such technology to the society. The current lack of information and supervision of nanotechnology, in the African economies has also posed a serious regulatory challenge of the technology in Africa and some parts of the globe; hence some activists call for precautionary regulatory frameworks (Musee et al. 2012). It is important to note that the uncertainty about nano-related risks has not impeded the introduction of nanotechnology products into the market. Globally, most nanotechnology research and policies put in place have been largely geared toward accelerating nanotechnology introduction into the markets with only very limited consideration of precautionary approaches to address the potential risks of this emerging technology (Royal Society and the Royal Academy of Engineering 2004).

20.7 Conclusion

Nanotechnology is an emerging field from an African perspective, when it comes to its applications in agriculture where most subsistence farmers are still using green revolution technologies. Our chapter however gives an insight on technologies that are being developed elsewhere in other developed countries and indicates where these technologies can benefit the resource poor African farmers. What is critical for a start is to promote research that looks at the soil quality improving capabilities and functionality under the African context. Furthermore, nanotechnology techniques that improve the efficacy of current pesticides can be critical in reducing their cost and environmental effects, making the aspect of sustainable intensification a reality. From an African perspective, there is a need for intensive research if nanotechnology is to be adopted by the resource poor farmers in this twenty-first century; otherwise, this may remain a pipe-dream.

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Chapter 21
Nanomaterials for Wastewater Remediation: Resolving Huge Problems with Tiny Particles

Ambikapathi Ramya, Periyasamy Dhevagi, and S. S. Rakesh

Contents

21.1 Introduction

Water is the prime requirement for the endurance of animals and human beings. The earth is covered by 70% of water, and only 2.5% is clean water. Water is utilized for domestic purpose and numerous industrial activities being discharged enormous quantity of untreated wastewater into water bodies. Besides, farming activities consume a range of fertilizers, pesticides and insecticides which reach water bodies through run-off.

In general, the microorganisms, inorganic and organic materials, cause water contamination. The inorganic pollutants consist of metals like Pb, Hg, Cd, Cr, etc., and the organic pollutants consist of agricultural pesticides, pharmaceuticals, textile wastes such as dyes, personal care products, household wastes like detergents,

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phenolic compounds and halogenated and aromatic compounds. Discharge of these pollutants in the lakes, rivers and/or drinking water resources leads to serious environmental issues like water pollution, water scarcity and health risks (Saleh 2015). According to the World Health Organization (WHO), up to 12 million people are affected by consumption of polluted water every year.

In present decades, water treatment techniques have turn into a considerable attention worldwide in increasing fast growth of industries and ecological contamination (Geise et al. 2010; Sharma et al. 2019; Yahya et al. 2018). Removal of pollutants from water is most important for the developing countries and some of the techniques are employed for the water treatment. Among, various wastewater treatment technologies, nanotechnology acquire several advantages owing to its unique physicochemical properties. Oxidation, adsorption and degradation are the nanotechniques used for the removal of contaminants which persist in the polluted water. Chemical oxidation and advanced oxidation are efficient processes for the removal of organic contaminants in water. The oxidants used in the chemical oxidation process are ozone, chlorine, chlorite, hydrogen peroxide, etc. Fenton process is one of the advanced oxidation process (AOP) which degrades the organic contaminants from water by redox reactions, dehydrogenation and electrophilic addition. AOP does not eliminate the byproducts completely during the treatment which leads to health risk to humans (Feng et al. 2013; Celiz et al. 2009).

Adsorption is a critically significant method to remediate pollutants from the polluted water, and it is an economic method. The efficiency of the adsorption depends on the nature of adsorbate, adsorbent and condition of the operation. The mechanism of adsorption generally attributes to electrostatic, π–π and Van der Waals interactions. Activated carbon, carbon nanomaterials, metal organic frameworks, clays and zeolites are used as the adsorbent (Yu et al. 2016). This remediation mechanism can be applied in water treatment nanotechnology to eliminate a number of contaminants. Hence, this chapter highlights sources of wastewater, properties of various nanomaterials, mechanism of nanoremediation and efficiency of nanomaterials used for target pollutants in wastewater.

21.2 Sources of Wastewater

Organic contaminants in waster ecosystem cause serious issues in the environment. In addition to the organic contaminants, heavy metals in water also lead to the health issue to the living organism. The pharmaceutical products are also identified in surface and groundwater ecosystem. The personal care products and endocrine disrupting compounds are high volatile and high polar in nature. Due to this intractable and persistent nature in the environment, these compounds does not undergo the degradation process (Archer et al. 2017; Tijani et al. 2019; Snyder et al. 2003).

The world population is increasing day by day, and so the world faces the lack of food. Pesticides play a significant part in the production of crops and vegetables, and it includes fungicides, herbicides, insecticides, etc. To control the pest in

farming, more than a million tons of pesticides have been prepared each year. Usage of pesticides in farming leads to fast transfer of pesticide residue to the water bodies and penetrated into food chain. In farming countries, water pollution due to pesticides are incredibly frequent, and it is hazardous to human beings. Consumption of water affected by pesticide causes organ damage, cancer, reproduction effects, nervous system damage and also birth defects. The famous pesticides are organophosphate, organochlorine, *N*-methyl carbamate, arsenic-containing fungicides, chlorophenoxy, nitrophenol, pentachlorophenol, rodenticides and fumigants (Milne 2018).

Organic dyes are the most common organic pollutants obtained from textile, plastic, construction, leather, food industries, cosmetics and paper industries. It was anticipated that above 15% of dyes (approximately 400 ton/day) were liberated into the water body during the dyeing process (Garcia et al. 2007; Vanhulle et al. 2008). These are synthetic organic compounds which have the mutagenic and carcinogenic effects (Tang et al. 2016). The azo dyes, for instance, methylene blue and rhodamine B, are commonly used in the recent decades. These organic dyes are nondegradable naturally (Chen et al. 2011; Mirzazadeh and Lashanizadegan 2018; Han et al. 2015). Methylene blue causes eye and skin irritation and also respiratory tract irritation upon contact during the consumption (Jain et al. 2007; Kumar and Kumaran 2005). In addition, usage of detergents has increased in our daily life, and it affects the water ecosystem. These detergents are classified as cationic detergents like quaternary ammonium cations; anionic detergents like linear alkylbenzene sulfonates; and non-ionic and zwitterionic detergents. The general industrial chemicals like aromatic compounds and bisphenol A cause many health issues during consumption (Sui et al. 2011).

The water contaminated with heavy metals shows high density and atomic weight as high as five times than pure water, and these metals naturally occur via different sources. Heavy metal sources including soils, rocks and volcanic explosion and other anthropogenic sources including mining actions contaminates the water bodies. Arsenic (As), chromium (Cr), lead (Pb), mercury (Hg), cadmium (Cd), copper (Cu) and nickel (Ni) are some of the common metals which cause heavy metal contamination in water. Amongst all the heavy metals, arsenic and chromium are the principal reasons of water contamination by both natural and anthropogenic sources. According to the World Health Organization (WHO), arsenic is classified as group 1 human carcinogenic substance. Consumption of arsenic-polluted water leads to various types of skin diseases such as hyperpigmentation, hyperkeratosis and cancers like kidney, skin, lung and bladder (Khare 2016; Singh et al. 2015; Halem et al. 2009).

21.3 Mechanism

Elimination of contaminants present in wastewater can be done by photocatalysis, and the catalyst used for the degradation process in photocatalysis is known as photocatalyst which alters rate of the reaction only. After the completion of degradation process, the catalyst can be recovered and reused. During the photocatalytic activity, the following reactions are taking place in the remediation of contaminants in the water body:

- The contaminants transferred are adsorbed on the surface of the catalyst.
- The photonic activation and decomposition of the adsorbed contaminants.
- Desorption of the reaction product.
- Reaction products are eliminated from the surface of the catalyst.

$$e^- + O_2 \rightarrow O_2^{\cdot -}$$
$$O_2^{\cdot -} + 2H^+ + 2e^- \rightarrow OH^{\cdot} + OH^-$$
$$h^+ + H_2O \rightarrow OH^{\cdot} + OH^+ / OH^{\cdot}$$
$$OH^{\cdot} + OC \rightarrow CO_2(g) + H_2O(l) + \text{Other}$$
$$e^- + OC \rightarrow OC^- \rightarrow \text{Degradation products}$$
$$h^+ + OC \rightarrow OC^+ \rightarrow \text{Degradation products}$$

where OC organic contaminants.

The photocatalytic degradation of pollutants present in water can be carried out with the use of photons, electrons and catalyst (Fig. 21.1). The photocatalytic degradation of materials such as dyes, heavy metals, organic pollutants, microplastics, etc., engages the photons, catalyst and electrons. These were engaged the individual energy stage in the atom. Depending upon the atoms, every individual energy state was divided into several energy levels. The energy bands are formed depends on close energy state. Atom filled with electrons by donation of the energy and

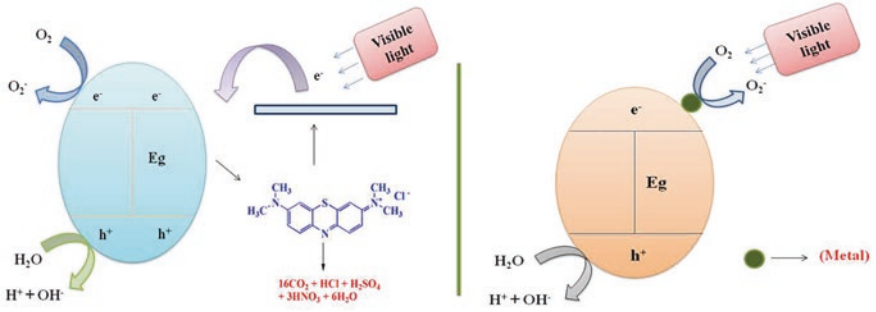

Fig. 21.1 Photocatalytic mechanism of nanomaterials

conductivity band was created. This action can be done by photocatalyst, and then the different factors were contributed in the important parts of photocatalytic activity. The electrons are energized to conductance band from valence band in the presence of sunlight. The assortment of the photogenerated n-type and p-type from nanoparticles prohibited beneath sunlight gives enhanced time of charge transporters and additional proficient redox properties (Nivetha et al. 2019).

21.4 Remediation

Nowadays, wastewater obtained from industrial sources are treated by different processes, and they have the capability to remediate the contaminants. There are numerous methods that have been adopted for the wastewater treatment such as phytoremediation, bioremediation, etc. But these methods have some disadvantages like inefficiency, regeneration, waste products, weak selectivity, etc. To overcome these demerits, alternate method must be needed. Hence, nanotechnologies play a pivotal role in wastewater treatment processes. Adsorption and degradation process is considered as the most significant process in the water purification. The degradation efficiency of contaminants relies on several factors like source of irradiation, adsorbent dosage, contact time, effect of pH, temperature and nature and type of the

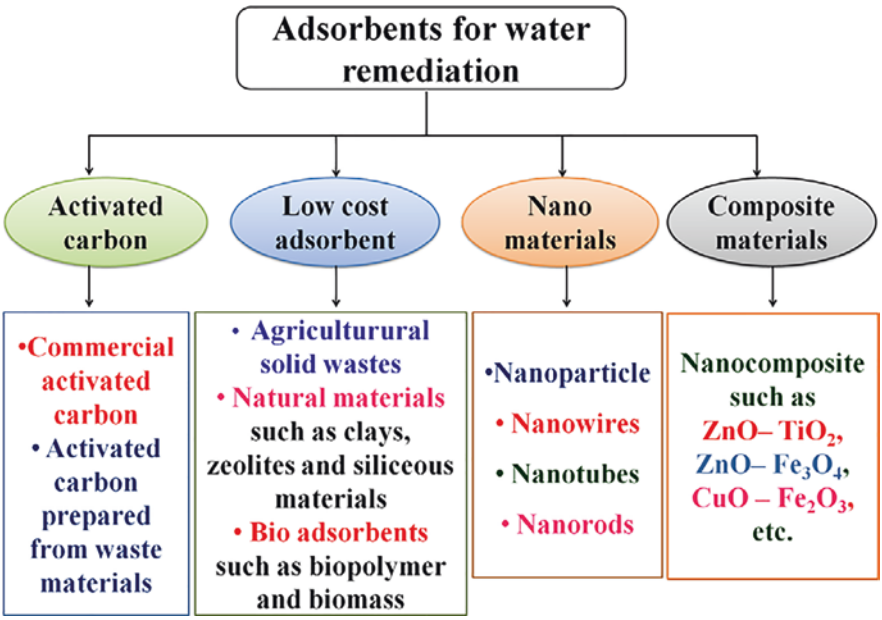

Fig. 21.2 Nano-adsorbents for wastewater remediation

catalyst used in the wastewater remediation. Some of the important nano-based materials are depicted in Fig. 21.2 for wastewater remediation.

21.4.1 Magnetic Nanomaterials

The application of various nanomaterials and its degradation efficiency in pollutant remediation were depicted in Tables 21.1 and 21.2.

21.4.1.1 Zero-Valent Iron Nanoparticles

Zero-valent iron (ZVI) nanoparticles have been widely considered and applied for the wastewater treatment (Fig. 21.3). Owing to the ease of oxidation, high reactivity, non-hazardous nature, economic, plenty, synthesize easily, bioavailabilities and large surface area, it is used in wastewater treatment processes (Zhu and Chen 2019; Zhang 2003). The ZVI is used to eliminate the organic pollutants, polychlorinated biphenyl, organic chlorinated solvent and heavy metals present in wastewater. It is used as catalyst in the degradation and oxidation of organic pollutants transferred to hydrogen peroxide in presence of dissolved oxygen. From ZVI, two electrons are transported repeatedly to reduce the hydrogen peroxide into the water. In addition, the hydroxyl radicals are produced, and it has the ability to oxidize the organic pollutants during the permutation of hydrogen peroxide and Fe^{2+} (Fenton reaction). It has the standard redox potential value 0.440 V and shows that it can eliminate the halogenated compounds via reductive dehalogenation (Fu et al. 2014; He and Zhao 2007). It quickly removes hazardous non-aqueous phase liquids like halogenated partially volatile compound, halogenated volatile material and non-halogenated partially volatile materials to non-hazardous materials in polluted water.

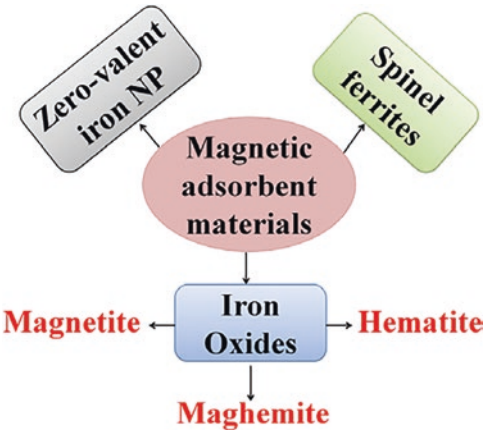

Fig. 21.3 Iron-based nanomaterials for wastewater remediation

Table 21.1 Degradation efficiency of various nanomaterials in pollutant removal

S. no	Material	Pollutants	Degradation efficiency and time	Reference
1	ZVI NPs	Amoxicillin	86.5% & 25 min	Zha et al. (2014)
2	ZVI NPs	Methylene blue	72.1% & 30 min	Hamdy et al. (2018)
3	ZVI NPs	Pb(II)	95% & 1 h	Ahmed et al. (2017)
4	ZVI NPs	Cd(II) Cu(II) Pb(II) Ni(II)	71.4% 100% 99.9% 96.6%	Danila et al. (2018)
5	ZVI/kaolinite	Acid black 1	98% & 2 h	Kakavandi et al. (2019)
6	ZVI/peroxymonosulfate	Tetracycline	88.5% & 5 min	Cao et al. (2019)
7	Cu	Safranin Carbol fuchsin Malachite green Methylene blue	92% 94% 97% 85%	Dlamini et al. (2019)
8	CuO-Fe_2O_3	Rhodamine B	100% & 1 h	Alp et al. (2019)
9	ZnO	Ag(I) Pb(II) Cr(VI)	97.92% 85.18% 43.34%	Le et al. (2019)
10	ZnO	Cd Cu Fe Pb	99.03% & 1 h 97.39% & 1 h 100% & 1 h 97.64% & 1 h	El-Dafrawy et al. (2017)
11	ZnO	Crystal violet dye	90% & 2 h	Franco et al. (2019)
12	ZnO	Dibenzothiophene	97% & 3 h	Khalafi et al. (2019)
13	ZnO MWCNT ZnO/ MWCNT	Reactive blue 203	85.4% & 20 min 19% & 20 min 99.1% & 20 min	Bagheri et al. (2020)
14	TiO_2/$CoFe_2O_4$	4-nitrophenol	94% & 35 min	Ibrahim et al. (2019)
15	Fe_3O_4/TiO_2/SiO_2	Methylene blue	98% & 2 h	Abbas et al. (2016)
16	Fe_2O_3/$BiVO_4$	Methylene blue and rhodamine B	100% 20 min	Wen et al. (2019)
17	$MgFe_2O_4$-TiO_2@GO	Methylene blue	100% & 5 h	Kaur and Kaur (2019)

(continued)

Table 21.1 (continued)

S. no	Material	Pollutants	Degradation efficiency and time	Reference
18	Cu Fe_2O_4/graphene oxide	Acid orange 7	95% & 50 min	Ayazi et al. (2016)
19	$ZnFe_2O_4$/AgI	*E. coli*	100% & 1 h 20 min	Xu et al. (2018)
20	TiO_2-CdS/reduced graphene oxide	Methylene blue	97.5% & 20 min	Kassaee et al. 2011
21	Reduced graphene oxide/ TiO_2	Methylene blue	92% & 2 h	Kireeti et al. (2016)
22	TiO_2/graphene oxide	Phenol	99.3% & 8 h	Pizarro et al. (2015)
23	Ag–TiO_2	Chloramphenicol	100% & 30 min	Shokri et al. (2013)
24	Fe–TiO_2	Metronidazole	97% & 2 h	Malakootian et al. (2019)
25	Zr–TiO_2	Bisphenol A	100% & 1 h 20 min	Gao et al. (2010)
26	Cu–TiO_2	Naproxen sodium	87% & 6 h	Hinojosa-Reyes et al. (2019)
27	Multiwalled carbon nanotubes (MWCNT)	Phenol, anti-inflammatory and nonsteroidal drugs, polychlorinated biphenyls	80–99%	Hu et al. (2015)
28	CNT	As(V)	80%	Peng et al. (2005)

In aqueous solution, zero-valent iron nanoparticles undergo oxidation readily either by oxygen or react with subsurface component which is occurring naturally leading to low reactivity and surface passivation. The reaction circumstances like pH, strength of ions, initial concentration of pollutant, method of synthesis, stabilizing agent used during the synthesis, medium for oxidation either air or water, and time play a crucial role in the degradation of organic contaminants. ZVI nanoparticles have some disadvantages as follows:

(i) Passivation – Owing to the less active iron hydroxides formation on ZVI nanoparticles surface during the reaction
(ii) Aggregation – Owing to the Van der Walls and magnetic force and also formation of less active small particles
(iii) Poor retrievability
(iv) Potential health and environmental risk – Because of bioaccumulation (Lu and Astruc 2020)

Table 21.2 Various nanomaterials and its adsorption capacity in pollutant removal

S. no	Material	Pollutant	Adsorption capacity (mg/g)	Reference
1	EDTA-GO	Pb(II)	479 ± 46	Clemonne et al. (2012)
2	MWCNT	Magnetic carbon Methylene blue	149 399	Ma et al. (2012)
3	MWCNT	Pb(II) Cd(II)	97.08 10.86	Li et al. (2003)
4	Chitosan	Pb(II)	398	Qi et al. (2004)
5	Graphene sand composite	Cr(VI)	2859.38	Dubey et al. (2015)
6	Nitrogen-doped magnetic CNT	Cr(III)	638.56	Shin et al. (2011)
7	MnO_2-MWCNT	Cr(III)	99.01	Tian et al. (2014)
8	TiO_2	Cd(II)	29.28	Sharaf El-Deen and Zhang (2016)
9	TiO_2	Cd Cu Ni Pb	120.1 50.2 39.3 21.7	Mahdavi et al. (2013)

21.4.1.2 Iron Oxide

Iron oxide nanoparticles have existed in different structures like maghemite, hematite and magnetite (Fig. 21.3). These iron oxide nanoparticles acquire polymorphism which includes temperature-induced phase transition (Cornell and Schwertmann 2003). Owing to the strong magnetic property, porosity and precise surface area, iron nanoparticles displayed tremendous properties in adsorption process (Huang and Chen 2009; Nizamuddin et al. 2019).

Hematite (α-Fe_2O_3) is an n-type semiconductor, and it has the band gap value of 2.1–2.2 eV, and it has paramagnetic phase at Curie temperature (T_c = 682.85 °C). According to JCPDS file No. 33-0664, it has trigonal crystal structure which belongs to R-3c space group and unit cell parameter $a = b = 4.9865$ Å, $c = 13.5016$ Å (Rozenberg et al. 2002). Crystallinity, particle size, cation doping, exchange interactions and subparticle structure influence the magnetic properties of the hematite. Not only the size and shape of hematite but also the nature of the dopant plays a vital role to increase the adsorption properties and lead to the efficient catalyst in the wastewater treatment (Tadic et al. 2019). Owing to poor conductivity and low efficiency of separation, its photocatalytic activity is controlled (Zhang et al. 2017). During visible light irradiation, it absorbs approximately 43% of light which helps to degrade the effluent from the polluted water under light source (Santhosh et al. 2019). Kang et al. (2019) reported that hematite-based material can enhance the degradation efficiency of rhodamine B in the presence of photocatalyst. Chen et al. (2019) reported the admirable degradation kinetics of antibiotics such as

ciprofloxacin, norfloxacin, sulfadiazine and tetracycline under solar light irradiation in the presence of $AgBr/Ag_3PO_4$@natural hematite as a photocatalyst. The rate constants of antibiotics are 0.16, 0.19, 0.34 and 0.10 min^{-1} for ciprofloxacin, norfloxacin, sulfadiazine and tetracycline, respectively.

Magnetite (Fe_3O_4) is nothing but a combination of ferrous and ferric ions, different to all other metal oxides. Magnetite divulges both p-type and n-type semiconductor with low band gap energy of 0.1 eV. According to JCPDS file No. 19-0629, it has a cubic inverse spinel structure which belongs to Fd3m space group (Okube et al. 2012). Owing to high surface energy, it is not stable in the aqueous environment. Surface functionalization generates the stability of the magnetite, and it increases the efficiency of elimination of pollutant. It can be used as adsorbent to remove the heavy metals from the polluted water compared with other adsorbents. Fan et al. (2019) tried to eliminate the lead from lead-containing solution using carboxymethyl-cellulose-immobilized magnetite nanoparticles, and it shows that the utmost adsorption capability of lead ion was attained at 152 mg/g.

Maghemite (γ-Fe_2O_3) has an analogous crystal arrangement to magnetite, and it has cubic structure. Because of high magnetization saturation, it is broadly employed as an appropriate adsorbent in wastewater treatment (Wu et al. 2015; Leone et al. 2018). It reveals ferromagnetic nature and more stable in aqueous environment. It is more superior adsorbent for heavy metal than magnetite due to small size and high specific surface area (Martinez-Boubeta and Simeonidis 2019). Rajput et al. (2017) reported the removal efficiency was found at 59.2 and 25 for lead (II) and copper (II), respectively, in the presence of maghemite.

21.4.1.3 Spinel Ferrites

Spinel ferrites have the general formula MFe_2O_4, where M represents the divalent metal ions with ionic radius ranging between 0.6 and 1 Å. Examples for divalent ions are Cu, Ni, Mg, Mn, Co, Zn, Cd, etc. (Ashour et al. 2014). These are magnetic semiconductors which are widely used in the field of water treatment. Depends on nature, sharing of cations and synthesis method, the properties and application of spinel ferrites varies (Fig. 21.3). The attractive band gap makes the spinel ferrite a more efficient catalyst in heavy metal removal and increases the ability of photodegradation. Owing to biocompatibility, magnetic behaviour and chemical stability, spinel ferrites and its composites are utilized in wastewater treatment. Aromatic nitro compounds are identified as common pollutant in agricultural and industrial wastewater owing to their stability and solubility in water which can be efficiently degraded by photocatalytic activity of spinel ferrites.

21.4.2 Transition Metal Oxide NPs

21.4.2.1 Titania

Titanium oxide (TiO_2) is a semiconductor material which acts as photocatalyst under ultraviolet light. The electron present on the surface of substrates is transported to the conduction band. The various effluents present in the water can be degraded using titania because of its stability, abundance and less hazardous (Shakeel et al. 2016). Owing to the intrinsic properties like wide band gap (3.2 eV) and low quantum yield, the use of titania in water treatment was limited under visible light (Upadhyay et al. 2014; Qin et al. 2015). To induce the solar efficiency the nanomaterials are undergoing modification. During contact of catalyst with light sources, it produces electron and hole pairs. The electrons and hole pairs move around to the surface of the catalyst, and the redox reaction occurs for absorbing the pollutant (Fujishima et al. 2008; Di Paola et al. 2012). Transition metal or non-metal supporting is one of the tactics to decrease the band gap of titania which stimulates the photocatalyst under different light sources or direct sunlight radiation. Titania thin films and titania-decorated alumina showed high efficiency in the remediation of creatinine and methylene blue dye. Titania nanoparticles have the ability to degrade the highly hazardous materials such as antibiotic and chemotherapeutic doxorubicin present in water. Titania nanorods, nanobelts, nanowires, nanotubes, nanomembranes and nanofibers have been used to remediate the wastewater. Titania doped with other metals such as silver, iron, copper, zirconium, etc. improved electrical, catalytic and optical properties.

21.4.2.2 Copper Oxide

Copper oxide nanoparticles have been employed for the wastewater treatment owing to its incredible optical, superconductive, electrical, magnetic and thermal properties and also its low cost, low toxicity and abundance. The monovalent copper oxide nanoparticle is a p-type semiconductor with the narrow band gap of 2.0–2.5 eV. Copper oxide nanoparticles have the affinity to adsorb molecular oxygen to proliferate photogenerated electrons. Yadav et al. (2021) tried to remove the organic dyes such as Congo red (CR), methylene blue (MB), methyl orange (MO) and methyl red (MR) from the water using copper oxide nanoparticles. The increasing order of degradation efficiency was found to be MO > MB > CR > MR. Husein et al. (2019) synthesized copper nano-adsorbent for the removal of pharmaceutical pollutants from real wastewater samples. Ibuprofen, naproxen and diclofenac were identified as pollutants in real water samples. The removal capacities were calculated as 36.0, 33.9 and 33.9 mg/g for ibuprofen, naproxen and diclofenac. Dlamini et al. (2019) collected three different samples such as coal mine water, domestic wastewater and Mzingazi river water. Copper nanoparticle showed 85 and 76% removal efficiency of phosphate and sulphate from coal mine water, respectively.

The removal efficiency was found at 80, 89, 63, 62 and 64% for phosphate, total nitrogen, nitrate, aluminium and sulphate, respectively, in domestic water sample. The removal efficiency was found at 92 and 52% for phosphate and total nitrogen in Mzingazi river water, respectively.

21.4.2.3 Zinc Oxide

Zinc oxide nanoparticles are a semiconductor material which acts as better photocatalyst in the removal of organic dyes. It is an n-type semiconductor with the band gap value of 3.37 eV. Owing to the non-hazardous nature, effective adsorption properties, good thermal, mechanical and chemical properties and zinc oxide nanoparticles can be employed for the elimination of organic and inorganic nanomaterials (Mustapha et al. 2020). It has the admirable UV and visible light adsorption and reflective properties, and it has high surface activity due to its large number of active adsorption sites. The wavelength and intensity of light source is more important, owing to the essential characteristic of the material in photocatalytic reaction. The catalyst used for the wastewater treatment not only eliminates the chemicals but also eliminates the microbial contaminants present in water. Photocatalytic inactivation of microbes was a tedious process, and the process differs with concentration, physiological state and kind of microbes. The morphology, nature and concentration of the catalyst influence the rate of microbial inactivation. Anusa et al. (2017) removed the heavy metals such as Cu(II), Pb(II) and Cd(II) using zinc oxide nanoparticles at different pH from simulated industrial wastewater. The removal efficiency of Cu(II) at pH = 2, 4, 6 and 8 was 99.15, 99.25, 100 and 100%. The removal efficiency of Pb(II) at pH = 2 was 63.61 and at pH = 4, 6 and 8 was 77.47%. The removal efficiency of Cd(II) at pH = 2, 4, 6 and 8 was 87.05, 96.50, 98.05 and 97.85%.

21.4.3 Carbon-Based Nanoparticles

21.4.3.1 Carbon Nanotubes (CNTs)

Currently, carbon-enriched materials such as carbon nanotubes, graphene oxides, activated carbon, carbon fibres and biochar are used as adsorbents in water purification. CNTs have π–π conjugative structure with hexagonal arrays, and every carbon atom has sp^2 hybridization. It is hydrophobic in nature (Gupta et al. 2013). Carbon has the capability to form carbon to carbon long chains due to its binding ability in both straight and complex branching which facilitates double or triple bond formation and collection of atoms in different geometrical arrangements (Mubarak et al. 2014). Because of non-hazardous and high adsorption property, carbon-based nanomaterials have been broadly used for the elimination of heavy metals present in water. Electrostatic communication, ligand replacement, surface complex formation and adsorption–precipitation within metal ion and functional groups present in

surface of carbon nanotubes (CNTs) are the steps followed in the mechanism of elimination of heavy metals in water. Due to the higher surface area to volume ratio of CNTs, the absorption property will be increased (Ruthiraan et al. 2015).

Multiwalled carbon nanotubes (MWCNTs) were synthesized by chemical vapour deposition, and the synthesized MWCNTs which has been found in between the width 60 and 70 nm range revealed the 100% efficiency in the removal of Cd(II) at pH = 10 and 12 with 0.5 mg/mL from 100 ppm metallic solution. The pH plays a vital role in the elimination of heavy metals. The heavy metals can be removed easily in the acidic condition. In the case of basic pH, the metals form precipitate because of the hydroxide formation. The MWCNTs shows the higher efficiency in the elimination of heavy metals in water, but its efficiency depends upon the pH of the reaction (Bhanjana et al. 2017).

Carbon microspheres can be utilized for the elimination of chromium, nickel and copper. Magnetic carbon nanomaterials have been employed for the elimination of heavy metals. MWCNTs-incorporated ZVI nanoparticles have been used in the removal of arsenic in the pH ranging between 6 and 7. During the oxidation in water, ZVI forms Fe^{2+} and Fe^{3+} hydroxides and leads to the formation of arsenic complexes, and these complexes can easily be eliminated from the water because the precipitation is taking place (Alijani and Shariatinia 2017).

21.4.3.2 Graphene Nanomaterials

Graphene have been obtained from graphite, and it acquires good electrical and mechanical properties and also it shows better thermal conductivity with honeycomb network structure (Aghigh et al. 2015; Chatterjee et al. 2015). It exists in various forms such as graphene oxide and reduced graphene oxide which are used for the removal of heavy metals (Gao et al. 2011). Graphene oxide (GO) is an oxidative product of graphene, and reduced graphene oxide (r-GO) is a reduction product of graphene oxide. GO have different oxygen functional group, while r-GO can be changed by functional groups, for instance, hydroxyl, amine and carboxylic acid group with more structural imperfection than graphene. To enhance the adsorption nature of GO, different kinds of functional groups are added to modify the GO. Due to the high surface area with fine chemical constancy, GO and r-GO are used for the wastewater remediation. The mechanism of heavy metal elimination from water using graphene-based nanomaterials depends on the electrostatic interactions and surface metal hydroxide. Based upon the surface area and surface charge, the interaction is taking place. Surface area is directly proportional to adsorption ability which is straightly with respect to particularly tunable morphology of the GO-supported nanomaterials. GO-supported metal oxides increase the ability of elimination of heavy metals in the water because of the increase of metal oxide's electronegative charge over the GO (Ghorbani et al. 2020).

21.4.4 Nanomembranes

Filtration and membranes are extremely efficient methodologies for purification water and remediation of wastewater. The remediation includes elimination of heavy metals, inorganic ions, organic pollutants such as dyes, pesticides, pharmaceutical products, etc. and bio-based products like microorganisms (Zhang et al. 2018). Reverse osmosis is the process which is used to purify the water and desalination of seawater till now. In between ultrafiltration and reverse osmosis, there is a process called nano-filtration, using membranes that have been employed for the wastewater treatment and desalination of seawater. Nanomembrane filtration is a very efficient method for wastewater treatment. It can be divided into inorganic and organic membranes in which zeolite, silicon dioxide and 2D graphene-based nanomaterials are inorganic membranes and organic polymer-based nanomaterials belong to organic nanomembranes (Liu et al. 2014; Pedrosa et al. 2019; Huang et al. 2014). The organic polymer membranes consist of natural polymer such as chitosan, cellulose acetate and synthetic polymeric membrane such as polyacrylonitrile, polyurethane, polyamidoamine, polysulfone, polyethersulfone, polyvinyl alcohol and polyamide. The efficiency of membranes mainly depends on the structure and weight of the molecule, pore size and volume, polarity, hydrophilicity and hydrophobicity (Cyna et al. 2002; Ahmad et al. 2008; Bonne et al. 2000; Tepus et al. 2009).

21.5 Conclusion and Future Prospect

The universe is in need of advanced water treatment technologies to get freshwater for drinking and agricultural purposes. Nanotechnology mutiny will play a crucial part in resolving the difficulty of increasing demands of freshwater and disseminated water recycle. Nanomaterials are attractive material which is used for water treatment because of its fascinating physicochemical properties. Engineering nanomaterials like nanoadsorbents, photocatalysts, nanomembranes, etc. provide the prospective for new water treatment technologies, and it can be adapted to precise applications in the removal of pollutants from contaminated water. Owing to their distinctive properties such as high reaction rate, high surface area-to-volume ratio, increased surface associated behaviour (antimicrobial properties and catalysis), high conductivity and self-assembling property on substrate, nanomaterials show high efficiency in the removal of pollutants. Nanomaterials can act as catalyst to purify the water under ultraviolet light source and freely existing sun irradiation. Nanomaterials can be used to eliminate harmful organic pollutants, microplastics and microbes via catalysis using ultraviolet and solar irradiation. A nanomembrane (semi porous membranes) is used to convert hard water into soft water by blocking monovalent and bivalent ions present in water body. In future, nanotechnology plays a fascinating role in water treatment, water monitoring, etc. that can effectively stop an extensive assortment of contaminant present in water together with

affordability and ease of operation. There is no debate that nanotechnologies play a vital role in the field of wastewater treatment because of its unique nature.

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Chapter 22
Impact of Nanomaterials on Waste Management: An Insight to the Modern Concept of Waste Abatement

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Contents

Abbreviation

CNT	Carbon nanotube
NP	Nanoparticle
nZVI	Nonzerovalent iron

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22.1 Introduction

Wastes stance a solemn menace to society. In order to meet the over increasing economic demands, all the countries of the world have been trying to increase their production for both industrial and domestic sectors, generating huge amount of wastes which are the prime reason for contaminating and polluting the natural environment (Ganguly and Chakraborty 2020a). However, such environmental encumbrance can be reduced through less conservation of resources, reduction of chemical use and energy. Wastes emerged from different industrial and agricultural sectors include solid wastes, wastewaters and air contaminants. The harmful impact of such pollutants can be reduced through control of production, emission and effective management of wastes (Boldrin et al. 2014). Therefore, it has appeared to become a challenge for the entrepreneur to ensure a green environment despite huge production demand of commodity. Nanotechnology has proven to be a most emerging trend in the field of green engineering as it involves the utilization of minuscule particles having distinct structural, magnetic and electrokinetic properties that enable better removal of contaminants through adsorption (Vázquez-Núñez et al. 2020; Rizwan et al. 2014). Such functionalities reduce energy consumption and facilitate a sustainable environment (Bhushan 2017; Poole Jr and Owens 2003; Paul and Robeson 2008).

Nanotechnology is apprehensive with the realm of imperceptible diminutive particles and is governed by different underlying principles of physics and surface chemistry. It involves the production of materials in the form of a nanometer or one billionth of a metre (Dasgupta et al. 2017). The technology gains its attention after the development of AFM (atomic force microscope) which allows the manipulation and relative comparison at the atomic scale (Brar et al. 2010). Such particles pose a high surface area to the mass ratio which impacts significantly over physical, chemical, biological and mechanical characteristics. Bolyard et al. (2013) estimated a huge rise in the production of nanomaterials from 1000 tons (2011) to 58,000 tons (2020). The presence of such unique properties led to better adsorption with the different types of contaminants. Nanotechnology can be employed as both in form of in situ or ex situ waste management strategies. In situ strategies implies the development of reactive barrier utilizing non zero-valent iron nanoparticles (nZVI), magnetic nanoparticles, etc. in the flow of contaminants generated from ordinary waste management techniques (Thomé et al. 2015; Singh et al. 2020). Ex situ strategies involve the utilization of photocatalytic degradation and other filtration processes such as ultrafiltration, reverse osmosis, nanofiltration, etc. which are based on adsorption property of nanoparticles (Andrade et al. 2015; Crane et al. 2015). Nanomaterials are often used in the preparation of membrane matrix which helps in greater removal of contaminants through adsorption (Huang et al. 2019; Jiang et al. 2017). Such methodologies are also used in the removal of heavy metals from the canals or streams carrying wastewater and thereby help in cleaning of water as a part of sustainable environment through the reduction, recycling, reusing and other hazardous materials (Madhura et al. 2019; Mubarak et al. 2014). Different

engineered nanoparticles proved their efficiency by displaying different biophysical properties such as adsorption, photocatalytic degradation, nanofiltration, etc. which limits the consumption of reactants and imparts better conversion of waste into value-added products. Therefore, nanoparticles-supplemented waste management technologies can mitigate a wide range of environmental problems through the reduction of different organic, inorganic and nonpoint source pollutants through the development of nanocoated membranes, environmental sensors, etc. (Fan et al. 2016). The unique properties of nanoparticles lead to huge implementation in the context of waste management which has urged expansion along with modification of existing nanotechnology such as the development of different types of carbon nanotubes (single-walled CNTs, multiwalled CNTs, hybrid CNTs), graphenes and magnetic NPs alongside the improvement of technologies such as nanobioremediation, nanofiltration, etc. (Kim and Kwak 2007). Nowadays nanoparticles like nZVI, silver, CNTs, etc. are used in food products, cosmetics, textiles, etc. and therefore get impinged with our daily life. Recently, increased application of different engineered nanoparticles in the management of wastewater streams and industrial wastes further leads to contamination of the environment. Therefore, there is a multitude of sources by which the minuscule particles get contaminated with the environment (Boldrin et al. 2014; Le et al. 2015). Owing to their physical and chemical properties, these substances can get easily intermixed with the environment. Such disposal to the natural environment causes severe toxicity to the environment and explicitly damage life forms. Several types of research have been done concerning the impact of nanomaterials on human health and the environment. All of these ecotoxicological studies have generated information for the prevention of the overproduction and overuse of nanoparticles (Lee et al. 2008). Therefore, the present study has expposed different ways and means for the application of different nanoparticles in light of remediation of contaminants in different areas of waste management and also highlight the risk imposed by such implementation towards a sustainable green environment.

22.2 Nanomaterials in the Remediation of Toxic Chemicals and Heavy Metals

Industrial discharge has been estimated to around 10 million tons per year across the world which includes the discharge of several toxic chemicals such as dibenzofurans, dibenzo-p-dioxins, etc. posing severe cytotoxicity and interact with different biotic and abiotic environmental factors (Ganguly and Chakraborty 2018, 2020a). Several research methodologies had been proposed in context to sludge abatement, but the application of NPs has appeared to be most effective among other methodologies as it increases the rate of degradation, reduction of heavy metal content, etc. in order to maintain ecosystem health (Fig. 22.1). Different parameters of nanomaterials such as size, shape, surface area, surface coating, etc. play a pivotal role in

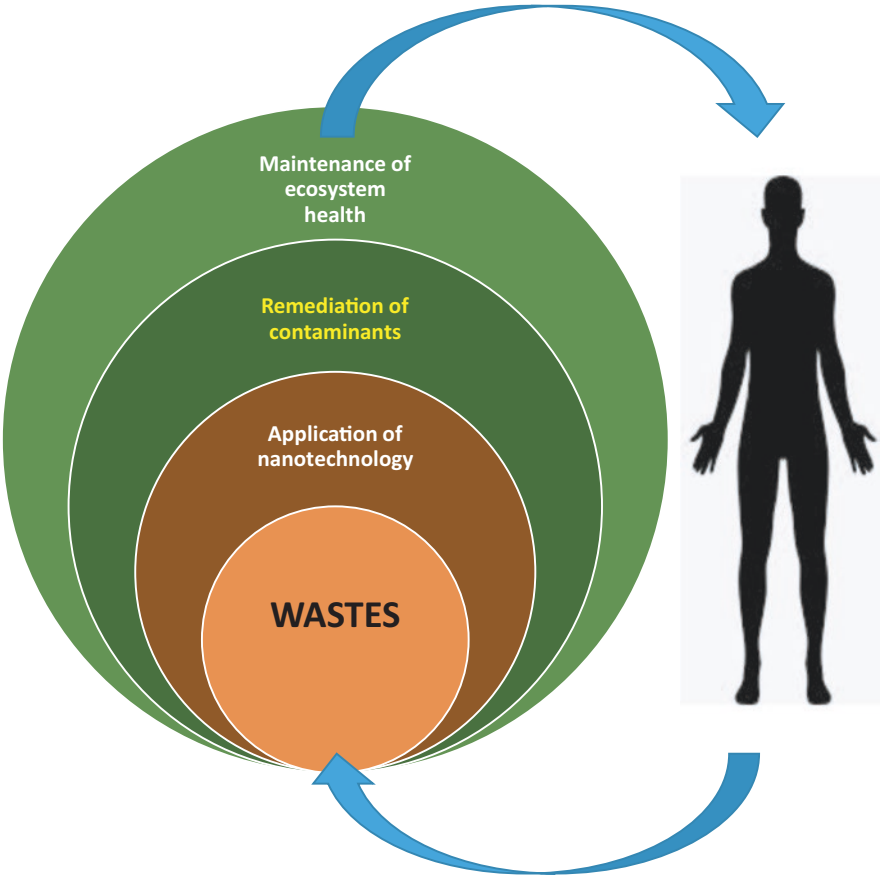

Fig. 22.1 Schematic representation of human-manipulated waste management using nanotechnology

bioremediation depending upon some external features such as media, pH, temperature, etc. of the contaminated environment. During the last couple of decades, several forms of nanomaterials have gained importance such as (i) dendrimers, (ii) carbon-based nanomaterials, (iii) single enzyme-linked nanoparticle, etc. (Crespilho et al. 2006; Rizwan et al. 2014). Nanomaterials are often conjugated with the membrane and are used in contaminated air or water streams for remediation of different hazardous materials using the process of adsorption or absorption. For example, activated carbon plays an important role in the treatment of non-point source pollution; different fullerenes, carbon nanotubes (CNTs), are found to adsorb benzene compounds and polycyclic aromatic hydrocarbons (PAHs) from the contaminated environment (Shan et al. 2009).

However, adsorption properties of different types of CNTs depend upon morphology, structure, etc. and also upon different physiochemical properties such as hydrophobicity, polarizability, etc. However, an adsorption affinity depends upon

π-π (donor-acceptor) electron interactions (Vázquez-Núñez et al. 2020). Similar interactions are also found for graphene sheets. Such properties contribute for the development of maximum adsorption affinity for nitroaromatics. Multiwalled CNTs play an immense role in the adsorption of different aromatics such as benzene, cyclohexane, toluene, nitrobenzene and metal ions such as Pb^{+2}, atrazine, etc. from the contaminated environment (Lu et al. 2005; Wang et al. 2000; Yan et al. 2008). Similar evidences are also found in the case of iron nanomaterials for remediation of organics and inorganics. nZVI is widely used in the removal of Ba^{+2}, As^{+3} and different types of humic acid compounds (Celebi et al. 2007). A number of steps have so far been undertaken such as lignocellulose-based anion removal media which entails nanocoating technology for better removal of halocarbons, sulphur, phosphorus and different environmental toxins. Micellar-enhanced filtration (MEF) proved its potential role in the removal of Cu^{+2} from groundwater (Thomé et al. 2015). Due to the specific surface characterization, nanomaterials can reach a certain depth and help in the removal of organochlorine pesticides, polychlorinated benzene organics (Table 22.1). nZVI nanoparticles are found to be effective in remediation of arsenic, chromium, lead, etc. Ferragels are much more efficient for removal of heavy metal ions. Poly acrylic-supported nZVI has proved its efficacy in the removal of chlorinated hydrocarbons from soil and groundwater. The name "Dendrimers" derived from the words "dendri" meaning the branch of the tree and "meros" which means part of a tree. These are branched polymers made of several smaller subunits consisting of the central core, interior radial symmetry and terminal branch cell. These macromolecules have void spaces that allow them to interact with several metal ions which help in wastewater and dye treatment industries.

22.3 Nanotechnology in Wastewater Treatment

Water pollution has posed real threat to the very existence of mankind as water alongside playing supportive roles, represents the most essential components for human survival. Therefore, the supply of high-quality water with low-cost technology appears to be a global concern. Several innovations had been made for better treatment of wastewater. Owing to better adsorption, magnetic and photocatalytic properties, amendment of nanotechnology proved to be a promising tool of modern wastewater management strategies (Baruah et al. 2016; Madhura et al. 2018; Prasad and Thirugnanasanbandham 2019).

The application of nanoparticles helps in the reuse of water which results in the regular supply of recycled water in agricultural and other industrial sectors. Such infrastructural developments are also associated with proper distribution networks which can reduce energy consumption especially for developing countries which suffer from trepidations about the hasty worsening of water quality and immense pressure for pure production of water to meet environmental standards and good

Table 22.1 Commonly used nanoparticles in remediation of organic contaminants

Organic contaminants	Use of ENM	Removal ability (mg/g)	Citation
Chlorobenzene	TiO_2 combined with bentonite nanocomposite	0.2	Mishra et al. (2017)
Trichloroethane	Biochar hybridized Fe^{+2} or Ni^{+2} nanoparticles	20	Li et al. (2017)
	Multiwalled CNTs	0.35	Ma et al. (2011)
Dichlorobenzene	CNTs	30.8	Peng et al. 2003
	Graphitized CNTs	28.7	Peng et al. 2003
	TiO_2 nanocomposite		Salamat et al. (2017)
Hexachlorocyclohexane	nZVI	0.23	Li et al. (2007)
Rhodamine B	NiO_2 nanoparticles	2.5	Suo et al. (2013)
	nZVI nanoparticles	87.72	Shi et al. (2017)
	CNT membrane		Wei et al. (2014)
	Gold nanoparticles	40.3	Xiong et al. (2010)
	TiO_2 nanocomposite	6	Wang et al. (2000)
Methyl orange	TiO_2 nanoparticles hybridized with silver	135	Yang et al. (2013)
	TiO_2 nanoparticles hybridized with tin oxide	38	Yang et al. (2013)
Azo dye black	nZVI nanoparticles	299	Shu et al. (2007)
Methylene blue	Hybrid of graphene oxide with iron oxide nanocomposite		Deng et al. (2013)
	Graphene oxide nanoparticles	84	Fan et al. (2013)
	TiO_2 nanoparticles	50	Kim and Kwak (2007)
	Manganese oxide nanoparticles	68	Chen and He (2008)
	Graphene oxide filters		Hou et al. (2013)
	Silver hybrid TiO_2 nanoparticles	135	Yang et al. (2013)
Orange II	Gold/zinc nanoparticles	35	Cho et al. (2012)
Naphthalene	Single-walled CNTs	8	Moradi et al. (2012)
Guaiacol	TiO_2 nanoparticles	49.7	Peiro et al. (2001)

(continued)

Table 22.1 (continued)

Organic contaminants	Use of ENM	Removal ability (mg/g)	Citation
Phenol	TiO_2 nanoparticles	37.6	Peiro et al. (2001)
	MnO hybridized peroxymonosulphate nanoparticles	62.5	Saputra et al. (2013)
	Ruthenium oxide hybridized peroxymonosulphate nanocomposite	125	Muhammad et al. (2012)

ENM represent engineered nanomaterials used in different treatment

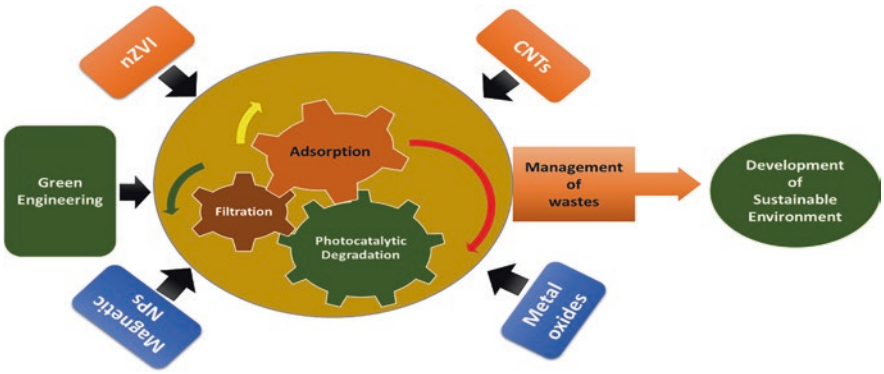

Fig. 22.2 Represents the role of nanoparticles in green engineering for the development of sustainable environment

public health (Han et al. 2009; Girginova et al. 2010). Such a situation caters to the need for development of high-performance water treatment technologies. The use of nanotechnology proves to be an easy method as it can target a wide array of pollutants. Such innovations are mainly based on four concepts such as adsorptive elimination of pollutants; decontamination of microbes; photocatalytic degradation; and filtration technology (Fig. 22.2). For example, nanoparticles prepared from silver are widely used as filters for wastewater treatment (Zhao et al. 2017). Furthermore, nanoparticles prepared from titanium oxide and fullerenes are used as photocatalytic degradation which disinfects different microbial populaces (Han et al. 2009; Goutam et al. 2018). Such technology favours substantial qualitative enhancement of wastewater.

Adsorbents in nanoscale have played an important role in adsorbing different organic and inorganic complexes from the aqueous environment. Nanoparticles with small size with large active surface area functionalize the property of adsorbing contaminants from the environment. Several carbon-based nanotubes, fullerenes and graphenes have good thermal stability demonstrate excellent adsorbing capacity of several organic contaminants from the environment (Deng et al. 2013; Jiang

Table 22.2 Commonly used nanoparticles in remediation of inorganic contaminants

Inorganic contaminants	Use of ENM	Removal ability (mg/g)	Citation
Lead	nZVI	1667	Zhang et al. (2013)
	Magnetite nanoparticles	77	Fan et al. (2013)
	Zirconium oxide nanoparticles	320	Hua et al. (2013)
	Multiwalled CNTs	66	Zhou et al. (2014)
	Manganese ferrite nanoparticles	69	Ren et al. (2012)
Cadmium	ZnO nanoparticles	217	Khezamia et al. (2017)
	nZVI	67	Zhang et al. (2014)
	Graphene oxide	91	Deng et al. (2013)
	Zirconium dioxide nanoparticles	215	Hua et al. (2013)
	Multiwalled CNTs	22	Vuković et al. (2010)
Copper	nZVI	340	Zhang et al. (2014)
	Manganese hybridized ferrite nanoparticles	61	Ren et al. (2012)
	Multiwalled CNTs	39	
Cobalt	nZVI	172	Uzum et al. (2008)
	Bentonite magnetic composite	22.73	Chen et al. (2011)
Mercury	Magnetite nanoparticles	17	Girginova et al. (2010)
	nZVI	80	Yan et al. (2010)
Arsenic	Cerium oxide nanoparticles	14	Zhong et al. (2007)
	Aluminium oxide nanocomposites	140	Wu et al. (2012)
	nZVI	As(III) = 36; As(V) = 29	Wang et al. (2014)
	Zirconia dioxide nanocomposites	As(III) = 95; As(V) = 85	Luo et al. (2013)
	Multiwalled CNTs	As(III) = 1.7; As(V) = 0.2	Ntim and Mitra (2012)
Nitrate	Carbon nanosheets	140	Tofighy and Mohammadi (2012)
Phosphate	Graphene oxide nanocomposite	18	Zong et al. (2013)
	Aluminium oxide nanocomposite	60	Wu et al. (2014)

ENM represent engineered nanomaterials used in different treatment

et al. 2017). The integration of magnetic nanoparticles and CNTs reflects the removal of inorganic metal ions (Huang et al. 2019; Cao et al. 2020) (Table 22.2).

The adsorption of CNT depends upon the functional nature of adsorbate such as the presence of phenolic, carboxylic and lactone groups which increase the rate of adsorption and are proved to be efficient in wastewater treatment (Ma et al. 2011).

The CNT has proved their efficiency in the removal of hydrocarbon components from petroleum and water in several higher magnitudes than commercial polycarbonate membranes and therefore widely used in wastewater purification. Hybridization of calcium alginate with carbon nanotubes had increased the removal of Cu^{+2} from solution (Singh et al. 2012; Mubarak et al. 2014).

Earlier studies had revealed the role of carbon-based nanoparticles in the removal of organic pollutants (Yu et al. 2014; Matsumura et al. 2018; Jabbari et al. 2016). Different nano network polymers had been developed to increase the rate of mineralization such as poly (ethylene) glycol-modified urethane acrylate (PUMA) which had increased bioavailability of phenanthrene molecule in water (Riaz and Park 2020).

The 3D sponge-like CNT played a significant role in the adsorption of dichlorobenzene and showed an easy recovery from the contaminated aqueous environment (Camilli et al. 2014). It was demonstrated that the presence of chlorine groups favoured the adsorption of chlorobenzene by both CNTs and graphenes (Balamurugan and Subramanian 2013; Pasti et al. 2018). However, graphene has been proved to be much more effective in comparison to CNTs owing to economic feasibility, and it provides two basal planes for adsorption of contaminants (Shan et al. 2009).

Another aspect of wastewater treatment is the removal of heavy metals in which different magnetic nanoparticles such as magnetite, maghemite and iron oxide particles play the significant task of remediation (Chen et al. 2011).

Recently, innovations have been made over the development of membranes impinged with nanomaterials for the treatment of wastewater coming out from industrial and agricultural wastes. Different types of filtration processes such as nanofiltration, ultrafiltration and reverse osmosis are performed for the treatment of wastewater which involves purification of water and removal of the organic contaminants (Braeken et al. 2006; Frank et al. 2002). Several fabricated alumina-coated ultrafiltration membranes had been developed for the removal of synthetic dyes. Ericsson et al. (1996) demonstrated that nanofiltration could effectively remove organic matter and different microbiota such as viruses, bacteria, etc. (Ericsson et al. 1996; ven der Bruggen and Vandecasteele 2003). The ultralow pressure reverse osmosis process coupled nanofiltered membranes endowed with hydrophilic and hydrophobic ultra-filtration membranes and is highly used for desalination of brackish water. Such innovations also proved to be useful for the removal of organic and inorganic contaminants (Hassan et al. 2000; Ozaki et al. 2000). However, supplementation with dendrimers enhanced the removal of different metal ions along with complex organics at low cost in comparison to conventional ion exchangers (Christen 2004). Nanofilter membrane is widely used to filter the outlet stream of the food processing industry. Such industries release dense slurry-type water enriched with starch materials. Nanofiltration can filter out the dextrose from other oligosaccharides and thereby prepare purified glucose solution.

Although different opinions exist on the remediation mechanism of CNT and nanofiltration which are mainly based on electrostatic interactions, concentration gradient and pressure difference over charged membrane, both the technologies

work hand in hand for qualitative enrichment of wastewater (Andrade et al. 2015; Frank et al. 2002). The elimination of contaminants (both organic and inorganic) is determined by properties of membranes which include porosity, membrane charges, etc. along with properties of contaminants such as hydrophobicity, ionization potential, etc. which altogether strengthen the operating conditions of membrane system (Riaz and Park 2020; Wei et al. 2014).

22.4 Nanomaterials in Solid Waste Management

Valourization of wastes plays an immense role in the conversion of wastes into value-added products. Several technological innovations have been made to undermine wastes and their toxicity to the surrounding environment (Ganguly and Chakraborty 2020b). Therefore, several bioconversion methods have been adopted to decrease the environmental burden of several organic wastes and to increase potentially value-added products.

Among different mechanical processes, enzymatic or catalytic breakdown of wastes are supposed to have played an immense role as a process of waste abatement (Ezeilo et al. 2017; Ganguly and Chakraborty 2018). But it suffers from shorter lifetime owing to their higher rate of oxidation; rendering catalyst inactive after a certain time.

Therefore, enzymes are immobilized over inert support to improve enzyme stability, recovery and inhibition (Cipolatti et al. 2016; Chen et al. 2017). In such a context, nanomaterials are thought to render better roles such as gold nanoparticles-silica nanocomposite serves as a novel enzyme immobilization matrix owing to its higher surface area, biocompatibility and electrical conductivity (Pingarrón et al. 2008; Thangaraj and Solomon 2019). Significance relies on the development of polyamidoamide (PMAM) dendrimers with cobalt hexacyanoferrate-modified gold nanoparticles which alternate with polyvinyl sulfonic acid layers on indium tin oxide electrodes and immobilize glucose oxidase which plays a contributing role in wastewater treatment (Crespilho et al. 2006; Akin et al. 2010). Such innovations face the question of the reusability of an enzyme. Therefore, magnetic iron-based nanoparticles are used with the enzyme for better separation of reactants and products (Yazid et al. 2016; Vaghari et al. 2016). Such nanoparticles proved to be very useful in facillitating the functioning of enzymes such as trypsin and peroxides which render them much more stable, economical and efficient.

Another important aspect involves the removal of toxic and carcinogenic dye pollutants using several technologies such as photocatalytic degradation, adsorption, etc. which help remediation of environmental contaminants. Owing to the large surface area, efficiency of nanoparticles such as Fe_3O_4 can be enhanced in adsorption process and thereby can undertake in better way for removal of toxic dye which pose a high adsorption range for acid green, crocein orange G, etc. (Salamat et al. 2017; Ahmed et al. 2013). Nanoscale zerovalent iron (NZVI), with doses ranging between 0.16 and 0.33 g/L, has revealed an adsorptive capability of

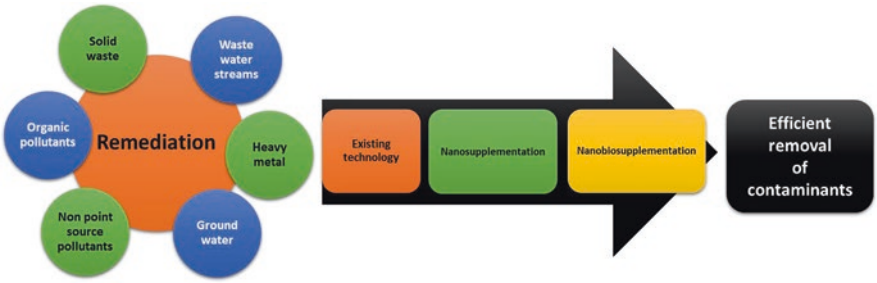

Fig. 22.3 Represent the applicative role of nanotechnology and its advances in remediation of environmental contaminants

609.4 mg/g for C.I. Acid Black 24 (pH 4–9; Initial conc. 25–100 mg/L; time 15–30 min) (Shu et al. 2007). Adsorbent prepared with nano-chitosan can be utilized to remove Acid Green 27 (Ragab et al. 2019).

The incineration process plays an important role in the debasement of solid wastes as it involves a greater rate of degradation and minimal landfilling and performed as a potential source of energy (Ganguly and Chakraborty 2020a). But such techniques release toxic dioxin and severely contaminate the surrounding environment. Therefore, the admixture of wastes along with nanoparticles proved to be much more efficient and eco-friendly (Fig. 22.3).

Nanoparticles exhibit a property of photocatalytic degradation and by the process can be a part of effective measure in the remediation of dyes (Adeleke et al. 2018; Raliya et al. 2017; Ahmed et al. 2013; Roy et al. 2022). As for example, the roles relating to the photocatalytic degradation of Acid Orange 7, Reactive Orange 16, Malachite green, etc. using nanoparticles prepared from TiO_2.

Upon UV stimulation, nano-TiO_2 harvests electron-hole pairs which led to the development of photodegradable TiO_2 nanocomposite (Lin et al. 2017; Nazarpour Laghani and Ebrahimian Pirbazari 2017). For the augmentation of work efficiency, modifications of TiO_2 have been installed with the addition of polystyrene or polyvinyl chloride support which enhanced the adequate dispersion and support eco-friendly management of wastes. Such utilization of polystyrene and polyvinyl chloride also reduces the detrimental effect of such pollutant or "white pollution." The photocatalytic degradation of PVC/TiO_2 nanohybrid proved to be a good alternative to landfilling (Yang et al. 2010).

22.5 Integration of Nanotechnology with Bioremediation

Another aspect of remediation is the utilization of different plants, animals or microbiota for the eradication of contaminants which is termed as bioremediation. Manipulation of wastes with biological organisms results in a greater reduction of both types of organic and inorganic pollutants (Murakami et al. 2006; Prasad et al. 2021). Nowadays, several attempts have been made with the integration of

nanomaterials and bioremediation technologies for the effective elimination of contaminants. Nanomaterials enhance the process of bioremediation as they facilitate microbial growth or upregulate different microbial enzymes which promotes the process of elimination of different organic pollutants (Prasad and Aranda 2018; Borah et al. 2022).

However, such integration gives promising results upon proper environmental conditions, nature of pollutants and type of nanoparticles. Nano-bio-treatment of nZVI with *Sphingomonas* sp. was able to show good results in the elimination of polybrominated diphenyl ethers (Kim et al. 2012). The bacterial group showed promising growth in nanomaterial solution and therefore is very helpful in the remediation of contaminants from polluted sites. Such preparation along with the addition of biosurfactant and electrokinetics elements have been successful in the remediation of nitrate ions, heavy metals, polychlorinated biphenyls and organic chlorines (Fan et al. 2016).

Bioremediation studies have demonstrated that bacteria and plants are capable of immobilizing metals which transformed both organic and inorganic contaminants. During recent years, there are some promising positive results of the combined use of NMs and bioremediation technologies to eliminate contaminants from the environment. Nanoparticles prepared from Pd/nFe and in conjunction with *Burkholderia xenovorans* were used in dehalogenation of Aroclor 1248 (Le et al. 2015). Earlier studies had revealed its efficiency in terms of reduction of toxicity of polychlorinated benzene compounds (Bhattacharya et al. 2016; De Lima et al. 2012). However, the efficiency of such nano-compounds suffers some limitations as several humic acids undergo competition with the pollutants for surface binding sites of nZVI. Similar degradation of chlorophenols was noticed using *R. rhodochrous* immobilized with magnetic nanoparticles (Hou et al. 2013). It involves the bioconversion of compounds into chlorocatechols through the upregulation of microbial genes Cat A, Cat B and Cat C, and it also enhances the degradation of aniline compounds (Matsumura et al. 2018).

Such a nano-combined bioremediation of polychlorinated benzenes had been noticed for CNTs with *Arthrobacter* sp. However, a high concentration of CNT prevents the rate of biodegradation and the growth of microbiota, but low concentration favours microbial growth and expression of different bioremediation genes. The polyvinylpyrrolidone-coated iron oxide NPs in the combination of *Halomonas* sp. demonstrate remediation of heavy metals such as Cu^{+2} and Pb^{+2} (Cao et al. 2020). CNTs also favour the breakdown of azo dyes in the presence of electron-withdrawing groups such as sulphanilamide which facilitate the breakdown of the azo bond.

Although nano-bio-remediation plays an important role in the context of elimination of contaminants, the application of such materials in the natural environment should be made under proper surveillance. There are several shreds of evidence depicting that nanomaterials do not support bioaugmentation; it decreases the diversity of natural microbes and reduces the natural enzymes present in the environment. However, several instances support such change in the early phase of treatment which again regains in later phases due to the resilience property of the ecosystem. Thus inadvertent utilization of nanomaterials should be checked to maintain a sustainable environment and ecosystem health.

22.6 Risk Assessment

Several regulations based on the monitoring of the scope of applicabilities and efficacies of nanoparticles by different authorities such as Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH; Europe) and Toxic Substances Control Act (TSCA; USA) have been undertaken to prevent unintentionally or overuse of nanomaterials (Brar et al. 2010). For example, the production of CNTs has been limited or under termination because of their acute toxicity to the environment. The toxic potential of nanomaterials depends on the nature of nanoproducts. Many research studies have advocated with regard to the reduction of the persistence of nanomaterials in the process of any biological or physical transformation in the natural environment. Such release of nanoparticles takes place during a different phase of waste management processes such as the collection and recycling of solid waste, waste incineration and land disposal (Ganguly and Chakraborty 2020a). Therefore, several recommendations have been made regarding risk assessments of nanoparticles based on the rate of exposure and hazard potential to prevent the overproduction of nanoproducts as they impart severe harm to flora and fauna of the environment (Fig. 22.4). Nanoparticles such as multiwalled CNTs, zinc oxide, zinc, etc. inhibit root development and germination of seeds in lettuce, cucumber, radish, etc. (Lin and Xing 2008). Such phytotoxic effects were much more prominent for nonfunctional CNTs. The bioavailable concentration of Cu^{+2} nanoparticles shows toxicity to wheat plants (*Triticum* sp.*)* and mung bean plants (*Phaseolus* sp.) (Lee et al. 2008). However, earlier studies had revealed a shift in soil microbiome structure upon contamination with silver, gold and Cu nanoparticles. Owing to the nanodimension, such particles become immobilize as they enter the minute spaces

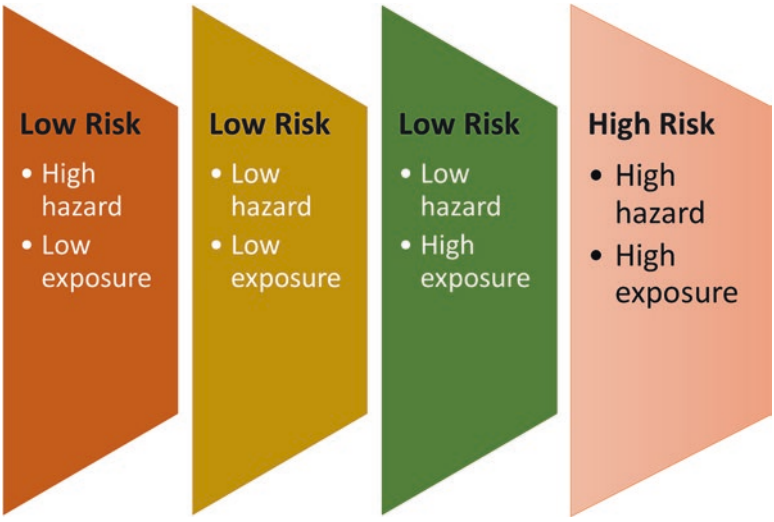

Fig. 22.4 Risk assessment of nanomaterials upon exposure to environment

between soil particles and get embedded within the soil matrix. The extent of sorption depends upon the nature of nanoparticles and soil conditions. Other instances such as contamination of graphenes in soil diminish the number of fast-growing bacteria and soil arthropod resulting to alteration of the ecosystem. Organic matter such as the presence of different humic acids interact with the nanoparticles and modify the kinetics of sorption. Similarly, the presence of high organic load also favours the sorption kinetics of nanomaterials among sludge water. The earlier studies had reported the role of organic carbon in the sorption potential of nanoparticles (Ahmad et al. 2001; Gunasekara and Xing 2003).

Nowadays, nanomaterials are engineered to produce different products in order to enhance the qualitative enrichment of the products and are termed as engineered nanomaterials (ENM). Such high usefulness of products results in the generation of contaminants in the nano-dimension and is often termed as "nanowaste". Such leaching of nanoparticles occurs from the manufacturing process of nanoproducts, nonfunctional or end-of-life nanoproducts and waste materials contaminated with NPs. Owing to their dimension, surface area, electrokinetic properties, solubility, etc., their exposure poses toxicity to the natural environment, and the future consequences are presently impulsive. Therefore, different ecotoxicological researches are required to predict the fate of such molecules for the development of a sustainable environment. Hence, production and reuse of nanomaterials should be done concerning ecosystem health so that hazardous effects can be mitigated.

22.7 Recent Trends and Future Outlook

Nanotechnology including application of nanomaterials along with some innovations played a pivotal role in context of waste management. Several considerable research developments have been amended which are based upon integration of nanotechnology specifically nanobiotechnology for effective remediation of contaminants with an aim to maintain ecosystem health. Nanobiotechnology is an evolving technology which involves the development of different nanofluids, nanoproteomics, nanobiomembrane, nanobiosensor, etc. For better functionalization, special efforts are constantly being made over coating procedures for better impregnation of nanoparticles (NPs). Progress is observed in field of application of biomolecules for the improvement of nanoproduct functionalization. Utilization of amyloid protein or milk proteins in fibrillary form help in better remediation of metal ions. Membrane coating using cellulose polymers are prepared along with implementation of bacterial species proved to be a better tool in removal of environmental contaminants. Different features of living organisms are used for better functioning of nano-assisted membranes. Several forms of mixed matrix membranes such as nanoparticle entrapped membranes are now being regularly used in effective removal of industrial contaminants. For example, utilization of different types of lipid biomembranes for effective removal of metal ions and different organic contaminants. Development of aquaporin-based biomimetic membranes functions better in comparison to conventional membranes through enhanced reverse osmosis

and elaborately used in desalination applications. Furthermore, development of nanofibrous webs through electrospinning technology along with microbial supplementation plays a pivotal role in removal of wastewater contaminants (Wendorff et al. 2012). Such technology is highly efficient over existing nanotechnology owing to better porosity, surface area and economic feasibility. Engineering of microbial fuel cell (MFC) technology with microbial population and nanoparticles such as CNTs are also playing a promising role in remediation of organic or inorganic contaminants and help in derivation of energy (Hou et al. 2016). Therefore, different innovations have been made for better removal of environmental pollutants through nanotechnology. Although development of nanobiotechnology alongwith the use of nanofibers have been rendering valuable services to remediate pollutants, disposal of such nanocompounds further increases the concern towards "nanowaste". However, adequate ecotoxicological research should be done for the utilization of such products, and their adequate disposal through proper planning and execution will lead to the maintenance of ecological integrity.

22.8 Conclusion

Different types of nanoparticles along with its differential utilization in different forms such as nanocoated membrane, photocatalytic degradation, etc. play a very significant role in the context of waste management. These minuscule particles play a major role in the remediation of different organic and inorganic contaminants from the environment. However, in the milieu of waste treatment such as water streams or in solid waste treatment, these particles get admixed to our natural environment and sometimes become detrimental roles threatening the structure and functioning of the ecosystem health. Therefore, overproduction and overutilization can impart negative effects which marked it as a "necessary evil". Therefore, utilization of nanoparticles demands the development of some comprehensive ideas and ecotoxicological researches so that one can pursue research for the generation of qualitative products to achieve the target of having a greener environment in the foreseeable future.

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Chapter 23
Applicability of Emerging Nanomaterials in Microbial Fuel Cells as Cathode Catalysts

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Contents

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23.1 Introduction

Innovation in this technological era has amalgamated different streams of science as an answer to the future world. With depleting fuel resources, the urge for alternative energies, particularly in the areas of renewable energies, is continuously looking for different sustainable technologies as an alternative. One such "green" approach is microbial fuel cell (MFC), which is a microbial powered electrochemical device for bio-electricity generation. The employed microbes oxidize organic feeds at the anode and release electrons and protons that eventually travel towards the cathode (Hosseini and Ahadzadeh 2012; Han et al. 2018; Pattanayak et al. 2019). At the cathode, these incoming electrons and protons get accepted by a particular substrate of interest that finally reduces to form a product. In total, the microbes generate electrons and protons by organic feed oxidation, where cathode catalysis is used to capture the liberated electrons and protons to form a specific product from reduction. For example, oxygen reduction into water is a commonly catalysed process at the cathode that captures the incoming electron and protons in the reaction (Logan et al. 2006).

This process of catalysis is however quite complex. It deals with various aspects of recombining substrates and their feasibility at the reaction site. Substantial investigations in the areas of cathode catalysis have been conducted, where platinum (Pt) is the most commercialized catalysts used in oxygen reduction reaction (ORR). However, it lags in many aspects of prolonged applicability. Major limitations like poisoning, limited availability and high cost are some of its major setbacks (Pattanayak et al. 2020a; Kumar et al. 2018). As a substitute, wider studies on low-cost cathode catalysts have also been conducted that can efficiently conduct the oxygen reduction reactions (ORR) in the process.

In the rigor, several transition metal oxide-based catalysts such as V_2O_5, carbon-supported nickel-phthalocyanine/MnOx, GO-Zn/Co, Spinel-type Cu/Co, and Ni/Co-oxides, α-Fe2O3/polyaniline, Cu_2O/RGO and polyaniline/β-MnO_2 materials have been tested as cathode catalysts in MFCs (Noori et al. 2018; Tiwari et al. 2017; Tang and Ng 2017; Papiya et al. 2019; Li and Zhou 2018; Zhou et al. 2018; Ayyaru et al. 2019). Titanium dioxide (TiO_2) is another widely studied nanomaterial because of its ample availability, higher electro-activity, chemical durability and eco-friendliness (Pattanayak et al. 2020a). The particle shape and size of metal oxides are generally regulated by the conventional hydrothermal process, which is widely employed for their preparation. Modified carbon electrodes, such as carbon blacks, carbon fibre, carbon felt, carbon nanotubes (CNT) and carbon papers have also been duly applied in bio-electrochemical systems for wider applications (Yang et al. 2019). Recently, graphene oxide (GO) has been proved as a high-performance material because of its enhanced specific surface area and mechanical stability (Pattanayak et al. 2019; Papiya et al. 2019). Apart from that, modifications like doping metals in the electrodes, providing conductive polymer (CP) matrix to nanoparticles, etc., have also shown higher electron transfer efficiency in fuel cell operation. Therefore, it has been suggested that the incorporation of specific nanocomposites

in the electrode structure or coating with efficient electro-active nanomaterials can enhance the electrochemical process in the system.

The chapter here encompasses the oxygen reduction efficiency of these nanomaterials in MFCs, majorly as a cathode catalyst. The larger surface area of nanocatalyst serves as an advantage for higher electro-catalytical activity, which ultimately improves the power generation and stability in the system (Khurmi and Sedha 2008; Kirubakaran et al. 2009). Having a prospective role in treating wastewater and generating bio-electricity in MFCs, there are several factors that require serious outlook, primarily in the domains of hydrogen yield, purity and overall efficiency of the system. There are ample opportunities particularly in the areas of electrode and catalyst development that can largely influence the electrical conductivity, stability, power density and overall cost economics of the system. In effect, designing this nanomaterial-based electrode setup offers a promising tool for enhancing the systemic efficiency, where a comprehensive illustration about how influential these nanomaterials are in practical usage is discussed in detail in this chapter. Hopefully, this will endow a broad insight into the recent advances and ongoing alterations in the areas of oxygen reduction and cathode catalysis.

23.2 Basic Principle and Architecture of Microbial Fuel Cell (MFC)

In principle, MFC can be a single- or dual-chambered system, comprising anode and cathode areas, where a proton exchange membrane (PEM) separates these two segments for individual operation. At the anode, microbial oxidation of organic feed occurs, where the employed electrogenic microbes finally liberate electrons and protons in the process (Bosch-Jimenez et al. 2017; Gnana et al. 2014). The released protons get internally transferred towards the cathode via PEM, where it meets the externally transported electron through an external circuit. A reducing agent (oxygen) takes up the incoming electron and proton in presence of a cathode catalyst and finally gets reduced into water. The overall process results in organic feed degradation and bio-electricity generation from the system (Nandy et al. 2016). This can be a single-chambered MFC with an air cathode or a dual-chambered system with anodic and cathodic compartments separated by a polymer electrolyte membrane (PEM) as a barrier (Fig. 23.1).

The whole circuit gets completed by oxygen reduction into water molecules as represented by the reaction (Peera et al. 2021):

$$\text{At anode}: \ C_6H_{12}O_6 + 6H_2O \xrightarrow{\text{Microbes}} 6CO_2 + 24H^+ + 24e^- \quad \left(E^\circ = -0.428\text{V} / \text{NHE}\right) \tag{23.1}$$

$$\text{At cathode}: \ O_2 + 4H^+ + 4e^- \rightarrow 2H_2O \quad \left(E^\circ = 0.805\text{V} / \text{NHE}\right) \tag{23.2}$$

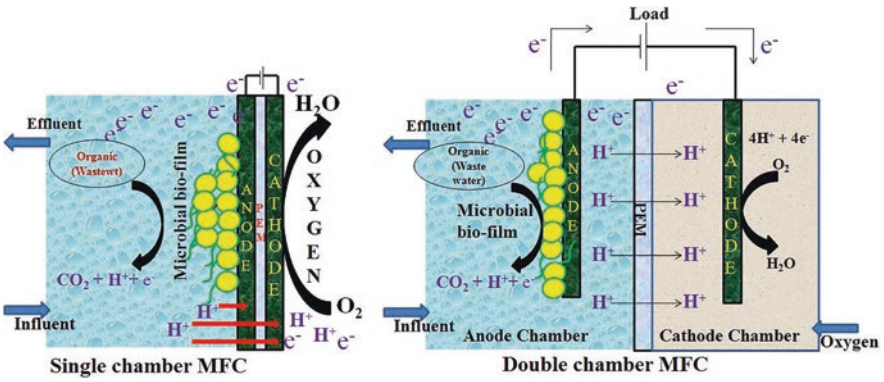


Fig. 23.1 A schematic illustration of different types of MFCs

$$\text{Overall reaction}: \; C_6H_{12}O_6 + 6O_2 \rightarrow 6CO_2 + 6H_2O \quad \left(E_{\text{cell}} = 1.233\text{V}\right) \tag{23.3}$$

Where NHE stands for normal hydrogen electrode and a cathode, at which oxygen (usually air) is reduced to form water to complete the circuit. In effect, MFC performance is dependent on the different types of parameters, such as microbial strains involved in the process, anodic feed, type of electrodes, separating barrier/membrane, cathode catalyst and reaction kinetics of the cathodic oxygen reduction reaction (ORR). The overall system efficiency can be expressed in different ways, where it is generally obtained as systemic power density. Power (P) in watt (W) is calculated as:

$$P = I \times E_{\text{cell}}$$

Where I (A) and E_{cell} represent the respective current and cell potential (V) of the system. This is calculated from the polarization graph (I–V curve) of the system. Power is calculated and normalized by the anode surface area, where microbial action for substrate degradation occurs. Moreover, in several cases, cathodic ORR is also taken as the controlling factor in systemic power generation, where power density is normalized by the given cathodic area. In addition to these, volumetric power density also contributes in describing the obtained power density of the system, by normalizing it with the specific volume of the reactor, as:

$$P = \left(E \times I\right) / U$$

Where P depicts volumetric power density (W/m^3), E denotes cell potential (V), I represents current (A) and U is given as the total reactor volume (m^3).

The major setback in MFC is the lagged oxygen reduction reaction (ORR) that plays a crucial role in limiting the overall performance of the system. Platinum (Pt) has been widely used as a cathode catalyst for ORR, although it lags with severe

drawbacks of fouling, lowered performance over time, expensiveness and limited availability (Pattanayak et al. 2020a; Papiya et al. 2019). Thus, in order to minimize the overall systemic cost in MFCs, novel attempts have been made with low-cost alternatives for higher stability and electro-catalytical activities.

23.3 Cathode Catalysis

Reduction occurs at the cathode, where cathode catalysis influences the overall performance of the system. In a catalyst devoid MFC, a slower oxygen reduction reaction (ORR) becomes the prime concern in the system. The high activation energy barrier limits the basic reductive process at the cathode, which eventually gets aided with the lower accessibility of H^+ and hydroxyl/hydroxide ions (OH^-). This, in turn, augments the higher over potential in the system. To lower that, one needs to look closer at the mechanism involved in the cathodic reduction reaction (Ou and Chen 2013).

23.3.1 Mechanism of Oxygen Reduction Reaction (ORR)

Oxygen reduction reaction (ORR) is a multi-electron transfer reaction that is proposed with two diverse mechanisms, namely, four-electron ($4e^-$) and two-electron pathway ($2e^-$). In $4e^-$ pathway, O_2 is directly converted into H_2O molecules, whereas in $2e^-$ route, O_2 goes through a two-electron reduction process and H_2O_2 is produced as an intermediate (Table 23.1).

23.3.2 Catalyst Materials Used in MFCs

In order to avoid the slower reaction kinetics of oxygen reduction at the cathode, catalysts are generally employed to lower the required activation energy of the reaction. This, in turn, increases the overall ORR kinetics, where the role of catalysts

Table 23.1 Oxygen reduction reaction (ORR) in alkaline and acidic electrolyte (Pattanayak et al. 2020a, b; Noori et al. 2018)

Aqueous medium	Process	Oxygen reduction reaction (ORR)
Alkaline electrolyte	$4e^-$	$O_2 + H_2O + 4e^- \longrightarrow 4OH^-$
	$2e^-$	$O_2 + H_2O + 2e^- \longrightarrow HO_2^- + OH^-$ $HO_2^- + H_2O + 2e^- \longrightarrow 3OH^-$
Acidic electrolyte	$4e^-$	$O_2 + 4H^+ + 4e^- \longrightarrow 4OH^-$
	$2e^-$	$O_2 + 2H^+ + 2e^- \longrightarrow H_2O_2$ $H_2O_2 + 2H^+ + 2e^- \longrightarrow 2H_2O$

becomes quintessential for enhanced systemic performance (Sonawane et al. 2018). The most widely used ORR catalyst is platinum (Pt), which has been majorly addressed in different system designs (Mishra and Jain 2016; Lu et al. 2013). Being a cost-effective approach, the economic viability of Pt hinders its commercial usage in the long run (Yuan et al. 2010). To avoid that, numerous efforts have been put forth to find an alternative low-cost cathode catalyst for MFC usage. This includes the role of different carbonaceous materials such as activated carbon, modified carbon blacks, carbon nanofibers, CNTs and graphene as cathode catalyst (Fig. 23.2). These graphitized nanostructures possess several cutting-edge advantages such as increased surface area, higher stability and conductivity over other conventional materials (Lu et al. 2013; Papiya et al. 2018; Cui et al. 2015). As shown by Ghasemi et al. (2016), nanostructured activated carbons were employed in MFCs, owing to their enhanced surface area that qualifies as a potent cathode catalyst with low cost and high electrical conductivity. Further, their electrical conductivity has been augmented by mixing activated carbon with additional carbon blacks during fabrication (Yuan et al. 2011; Ansari et al. 2016). In effect, numerous metals like [cobalt (Co), iron (Fe), nickel (Ni), manganese (Mn), vanadium (V)], metal oxide (M_xO_x) e.g., [cuprous oxide (Cu_2O), vanadium oxide (V_2O_5), MnO_2, etc.], metal oxide- carbon hybrids such as [Cu_2O-activated carbon, MnO_2-activated carbon, etc.], metal-CNTs such as [Ni-CNT, Mn-CNT, etc.), and metal nitrogen carbon (M-N-C) complexes such as [Fe-N-carbon, Ni/N-CNTs, etc.] have also been demonstrated as possible catalysts for cathodic reactions (Lu et al. 2013; Yuan et al. 2010; Ansari et al. 2016;

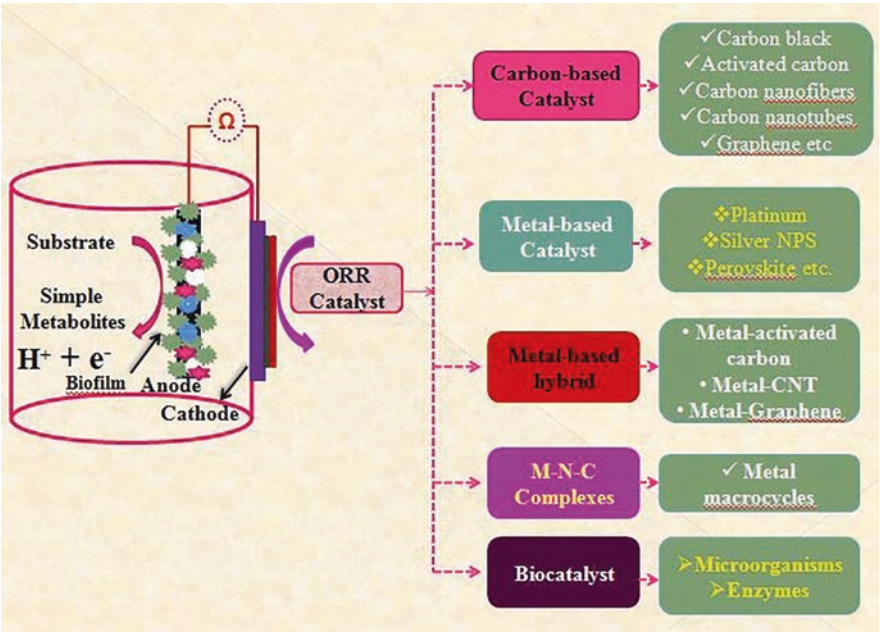


Fig. 23.2 Schematic representation of distinct ORR catalysts employed in MFCs

Khilari et al. 2014; Esmaeili et al. 2014; Kirubaharan et al. 2016). These will be dealt in detail in the next segments.

23.4 Emerging Nanomaterials in Cathode Catalysis

Several novel nanomaterials have been tried and tested in MFCs as the catalyst for augmenting the overall reaction kinetics. These can be distinguished based on incorporated nanosized fillers into the nanocomposite matrix, which plays a vital role in improving systemic performance. Here, the prime concern becomes the incorporation of specific novel properties within the designed nanocomposite structure (such as durability, electrical conductivity and chemical reactivity) that consists of single or several nanoparticle materials with one or more constituents of dimension less than 100 nm. These are grouped as follows.

23.4.1 Transition Metal/Metal Oxide and Alloy-Based Cathode Catalysts

Platinum (Pt), being the widely studied oxygen-reducing catalyst, has severe limitations in terms of high cost, limited availability and fouling tendencies (Pattanayak et al. 2019, 2020a). This brings upon other cheap substrates such as transition metals (Fe, Co, Ni, Mn) and metal-free heteroatom doped (N, P, S, F) catalysts that can also lower the activation energy required for an efficient ORR (Peera et al. 2021; Li et al. 2019). As a consequence, binary metal catalysts (like Pt-Fe, Pt-Cu, Pt-Mn) (Coleman et al. 2015; Ammam and Easton 2013) and multicomponent Pt-based catalysts have also been studied as efficient catalysts to bring economic feasibility in the system utility (Santoro et al. 2015; Liu et al. 2017). Although this brings the cost down, the durability of these catalysts is still a prime concern in its widespread usage. As an instance, Liu et al. (2017) used glycerol for stabilizing the prepared Pt-Fe alloy catalyst. This resulted in an approximate 18% higher power density over the used Pt/C catalyst. The results showed Fe leaching after some time from the alloy composition, even though its maximum power density was relatively more stable than that of Pt/C under neutral environments.

Similarly, different metal oxide (MO_x) nanoparticles such as CuO_x, NiO, VO_x and MnO_x have also been introduced as effective, affordable materials for enhancing the conductivity of the designed catalysts (Noori et al. 2016; Liu et al. 2015a; Yuan et al. 2016a). For several years, these MO_x have been known in the areas of energy conversion and fuel cell designs. However, at present, more emphasis is given on their nanocomposite usage with different base substrates. As an example, a nanocomposite cathode catalyst matrix of Ni–NiO/PPy–rGO revealed an enhanced power density of 678.79 ± 34 mW/m^2 with ~81.52% chemical oxygen demand

(COD) removal from single-chambered MFC. The results indicated this relatively inexpensive nanocomposite better over the used Pt/C catalyst (Pattanayak et al. 2019). Similarly, manganese and vanadium oxide nanocomposites in combination with carbon material have been tested as cathode catalysts in MFCs (Ghoreishi et al. 2014). In distinct attempts, investigations with V_2O_5 catalyst in lithium-ion batteries have been tested; however, quite limited studies are there in its catalytical usage in MFCs. As an example, Noori et al. (2016) have shown MnO_2 nanotubes and V_2O_5 microflowers as cathode catalysts in MFCs. The results indicated ~31% higher efficiency of V_2O_5 microflowers over employed MnO_2 nanotubes. In another instance, the group compared the performance of V_2O_5/Vulcan XC with V_2O_5 nanorods based on reduced graphene oxide in MFCs as cathode catalyst (Noori et al. 2017). Here too, V_2O_5 nanorods revealed a higher power density of 533 mW/m^2 over V_2O_5/Vulcan XC (384 mW/m^2). In comparison, the calculated overall systemic cost of V_2O_5/reduced graphene was way more economical than the commercially used Pt/C catalyst (Noori et al. 2017). Similarly, several other MO_x nanocomposites, e.g. calcium titanium oxide, CoO_x, PbO_2 and ZrO_2, have been used in MFCs as potent catalysts for ORR.

23.4.2 Metal-Carbon Hybrid Catalysts

The segment here will enumerate different metal-carbon oxygen-reducing hybrids (e.g. activated carbon-metal, CNTs-metal, graphene-metal hybrids, etc.) as cathode catalysts for enhanced ORR activity in MFCs.

23.4.3 Metal-Activated Carbon Hybrids

The excellent electrical conductivity of activated carbon has put it on top of carbon black, as an efficient alternative base support material for other metal catalysts. For instance, Ge et al. (2015) prepared nano-cobalt (II, III) oxide (nano-Co_3O_4) via a hydrothermal process, where mixing it with activated carbon as support yielded an enhanced power density from the system. The effects were apparently visible in the system, where lower internal resistances were particularly observed, especially with the coated electrodes (Ge et al. 2015). Similarly, a nano urchin-like nickel cobaltite ($NiCo_2O_4$) was constructed via a hydrothermal process, where again its mixing with activated carbon depicted increased power density from the system (Ge et al. 2016). Initial experimentations on activated carbon were done on silk fibroins, which were used to fabricate activated carbon from it (Zhang et al. 2009a). Later, it was thought to augment the catalytical activity of this activated carbon. This was primarily achieved by incorporating heteroatom (e.g. N) into the structural backbone of carbon materials. In an instance, Huang et al. (2017) showed cobalt (II) oxide (CoO) nanosheets layered with N-incorporated activated carbon, as an efficient MFC

cathode catalyst for oxygen reduction reactions. This in situ formulated composite indicated an enhanced performance of ~1650 mW/m^2, with ~122.5% more efficiency over the control system. The effect of nanocomposite depicted higher ORR activity from the employed MFC cathode catalyst (Huang et al. 2017).

23.4.4 Metal-Carbon Nanofibers (CNFs) and Nanotubes (CNTs)

Numerous investigations on CNTs and CNFs have been focused as cathode-based catalysts, for analysing their performance in MFCs (Teng et al. 2019; Karra et al. 2013; Liu et al. 2010a). Primarily, CNTs and CNFs exhibit high surface area, anti-corrosive property and superior electro-activity because of its increased graphitic nature of composed sp^2 carbons. KOH activation is commonly done to attain a high surface area and porosity in CNTs and CNFs. Similarly, activated carbon, carbon black and graphite also undergo acid and alkaline treatment for activation and surface area increment of the material. Another route of transformation is heteroatom incorporation, which eventually enhances the ORR activity in CNTs and CNFs. Besides, incorporating various transition metals, e.g. Co, Fe, Mn on CNTs and CNFs, has also shown superior oxygen reductive property in MFC setups (Yaping et al. 2011; Liu et al. 2010b; Yong et al. 2011; Jung-Chen et al. 2019). CNTs are mainly categorized as single-walled CNTs (SWCNTs) and multiwalled CNTs (MWCNTs). Both have been evaluated as cathode catalysts in MFC operation. As mentioned earlier, MnO_2 is an efficient low-cost metal catalyst, whose combined effect with CNTs has been equally studied in MFC application. For instance, in an in situ hydrothermal process, MnO_2 was deposited over CNTs that showed marked increments in ORR electron transfer and thereby resulted in enhanced performance in MFC setups (Zhang et al. 2011). In another study, novel manganese-polypyrrole-carbon nanotube (Mn-PPY-CNT) composites were formulated by a solvothermal method that exhibited higher ORR activity with a catalyst loading of 2 mg/cm^2 in the system (Lu et al. 2013). This, in effect, showed an increased power output and durability in MFCs in comparison to the conventionally used Pt/C catalyst.

23.4.5 Metal-Graphene-Based Nanocomposites

In general, pristine graphene is considered inert, as it lacks the defects that are used as electroactive centres for catalytical activity and higher conduction. To avert that, one atom thick graphene is projected as an electroactive substrate that allows easier physiochemical modifications in its graphitic structure. This, in turn, improves the overall nature of the material with a larger surface area and enhanced electro-conductivity (Kannan and Gnanakumar 2016). In effect, both graphene and graphite

Table 23.2 Graphene/graphite-based nanocomposites as cathode catalysts in MFCs

Catalyst	Cathode material	Type of MFC	Maximum power density (mW/m^2)	References
NG/Co-N	Carbon cloth	Single chambered	713.6 (571.3) Pt/C catalyst (JM 40%)	Cao et al. (2016)
GO/MgO	Carbon cloth	Single chambered	755.63 (870.75)	Li et al. (2017)
Ni-NiO/PPy-rGO	Carbon cloth	Single chambered	678.79 ± 34 (481.02)	Pattanayak et al. (2019)
V_2O_5/rGO	SS wire mesh	Single chambered	533 ± 37 (512 ± 51)	Noori et al. (2017)
Ni-Co/MGO	Carbon cloth	Single chambered	1003.2 (483.48)	Papiya et al. (2019)
Ni-Co (1:1)/ SPAni	Carbon cloth	Single chambered	659.79 ± 20 (483.48)	Papiya et al. (2018)
K-(PPy-Co-PANI)-rGO	Carbon cloth	Single chambered	~763 ± 38 (483.48)	Pattanayak et al. (2020b)

have actively been studied as catalyst support, with other substrates such as metal catalysts (Table 23.2) (Yuan et al. 2016a; Quan et al. 2015). In a study, Wen et al. (2012) revealed a hybrid low-cost cathode catalyst for MFC, fabricating MnO_2-graphene nanosheets via microwave irradiation method. This resulted in enhanced cathode catalysis over simple MnO_2 with an improved power output of 2.08 W/m^2. Similarly, Khilari et al. (2013) prepared nanotubular MO_2/graphene oxide nanocomposite as an oxygen-reducing catalyst by a hydrothermal technique that again provided an overall increased performance of 3.35 W/m^2 in MFC usage. In comparison, the study revealed the better durability and shorter lag period of nanocomposites in activating the oxygen reduction reaction over other used catalysts.

23.4.6 Metal-Conducting Polymer-Based Nanocomposites

Another promising material for higher electron conduction is conducting polymers (CP) that endows specific properties like metal-like conductivity and reversible doping/de-doping characteristics that can efficiently serve in various catalytical processes (Fig. 23.3) (Wang et al. 2017). Apart from that, it plays a crucial role in augmenting the surface area for other substrates, to attach and form an active nucleation site for substrates like electron and air, for cathodic oxygen reduction.

The majority of these conducting polymers have aromatic sites, consisting of conjugated double bonds, such as polyacetylene (PA), polypyrrole (PPy), polythiophene (PTh), poly(p-phenylene vinylene) (PPV), polyaniline (PANI) and poly(3,4-ethylene dioxythiophene) (PEDOT). Some of the most widely studied CPs are polypyrrole (PPy), polyaniline (PAni), polythiophene (PTh) and poly(aniline-co-pyrrole) (Pattanayak et al. 2018). With such variations, these CPs exhibit brilliant

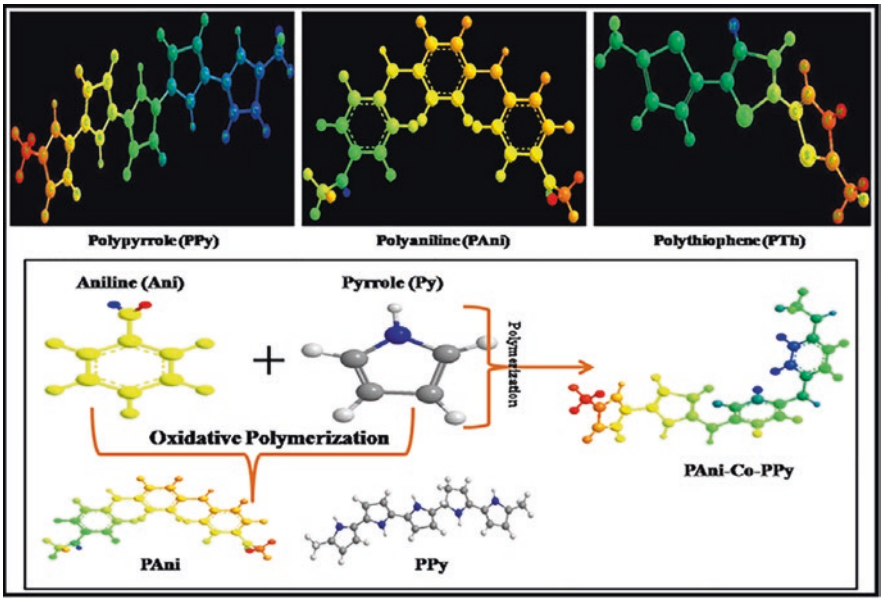


Fig. 23.3 Chemical structure and synthesis of three common CPs and copolymers such as polypyrrole (PPy), polyaniline (PAni), polythiophene (PTh) and poly(aniline-co-pyrrole)

electrochemical properties, with their conductivity ranging between 10^{-6} and 10^{3} Scm^{-1}. These can further be optimized depending on the doping level that can increase the conductivity level in a numeric span of 10^{-10} to 10^{4} Scm^{-1} (Wang et al. 2017; Pattanayak et al. 2018; Rudra et al. 2019). The chemical structures and stability characteristics of some common conducting polymers (CPs) are shown in Table 23.3.

CPs and their corresponding composites serve as the best supporting candidates for nanoparticle deposition, which, in turn, alters the electro-activity of the formed composite. With superior electrical conductivity, tunable specific capacitance and low fabrication cost, these CPs serve as a brilliant platform for different electrochemical reactions, including cathodic-ORR and anodic-microbial oxidation (Table 23.4). In effect, these also aid in increasing thermal stability within catalytical supports, which is done by infusing oxidative chemical or electrochemical sensitive nanomaterials.

23.5 Potentiodynamic Effects of Nanomaterials

The high catalytic activity and cost-effective nature are the two most desired criteria in cathode catalysis in MFCs. A broad range of nanomaterials has been investigated and tested for their efficacy and durability in the long run. Combined studies of Pt

Table 23.3 Chemical structures and characteristics of some common conducting polymers (CPs)

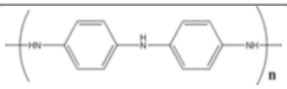
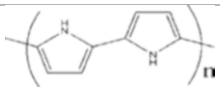
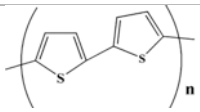
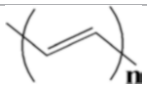
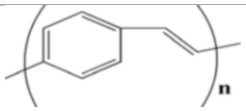
CPs	Chemical structure	Maximum conductivity (Scm^{-1})	Stability
Polyaniline (PAni)		9–10	Stable
Polypyrrole (PPy)		1000–2000	Reasonably stable
Polythiophene (PTh)		90–100	Stable
Polyacetylene		1.5×10^5	Reacts with air
Poly(p-phenylene vinylene)		1000	Stable un-doped form

Table 23.4 MFC performance with different nanomaterial-conducting polymer-based cathode catalysts

S. no.	Catalysts	Electrode type	MFC type	Maximum power density (mW/m^2)	References
1	PANI/C/FePc	Wet-proofed carbon cloth	Air-cathode	630.5	Yuan et al. (2011)
2	75% wt PANI/MWNT	Graphite felt	Single chambered	488	Cui et al. (2015)
3	PPy/C	Non-wet proofing carbon cloth	Single chambered	402	Yuan et al. (2010)
4	Mn–PPY–CNT	Glass carbon electrode (GCE)	Single chambered	213	Lu et al. (2013)
5	CNT/PPy nanocomposite	Carbon cloth	Dual chambered	113.5	Ghasemi et al. (2016)
6	$MnCo_2O_4$ NRs/PPy	Carbon paper	Air-cathode	6.11 W/m^3	Khilari et al. (2014)
7	Ni–NiO/PPy–rGO	Carbon cloth	Single chambered	678.79	Pattanayak et al. (2019)
8	Pani–MnO_2	Carbon paper	Dual chambered	0.0588 W/m^2	Ansari et al. (2016)
9	Polypyrrole (PPy)/ kappa-carrageenan(KC)	Carbon paper	Dual chambered	72.1	Esmaeili et al. (2015)
10	MnO_2/PPy/MnO_2 nanotubes	Carbon cloth	Single chambered	721	Yuan et al. (2015)
11	(PANI/C/FePc)	Carbon cloth	Single chambered	630.5	Yuan et al. (2011)

alloyed with other transition metals (e.g. Pt-M, where M = Mn, Co, Ni, Fe, V, Cu, Ti) have been used to minimize the amount of Pt and assay its overall catalytic activity in the system (Gupta et al. 2009). Being low cost, transition metal oxides nanocomposites, like manganese (IV) dioxide (MnO_2), have been widely analysed as ORR catalysts in MFCs. It is regarded as a promising cathode catalyst in MFC, because of its eco-friendly nature, low price and high chemical stability. In a study, Zhang et al. (2009b) showed three manganese dioxide materials, α–MnO_2, β–MnO_2 and γ–MnO_2 as an alternative ORR catalyst over the commercially used platinum (Pt) catalyst (Zhang et al. 2009b). It was observed that all the catalysts, especially β–MnO_2, indicated much higher catalytic activity over the corresponding α–MnO_2 and γ–MnO_2. The reason was attributed to the higher surface area of nanocomposite β–MnO_2 over other variants used. In other experiments, anchoring different carbon supports along MnO_2, such as graphite, activated carbon (AC), carbon nanotube (CNT) and graphite oxide (GO), was shown to improve the overall conductivity of the catalyst in the system. The mode of recombining ingredients also plays a crucial role in the overall performance of the catalyst. For example, in situ preparation of carbon nanotubes (CNTs) coated with manganese dioxide (MnO_2/CNTs) by hydrothermal methods revealed much higher electro-activity with increased ORR than the mechanically mixed MnO_2/CNTs (Zhang et al. 2011). Similarly, the hydrothermal preparation of manganese dioxide-graphene nanosheet (MnO_2/GNS) catalyst indicated higher ORR activity in the system. The cyclic voltammetric (CV) studies revealed the oxygen reduction peak at −0.43 V, which was higher than that of normal MnO_2 (−0.71 V), and almost equivalent to Pt/C catalyst (−0.44 V) (Wen et al. 2012). The reason was attributed to the close attachment of MnO_2 nanoparticles to graphene nanosheets, which was responsible for the excellent catalytic activity of MnO_2/GNS composite.

A study conducted by Dessie et al. (2020) revealed Mn_2O_3/C nanopowder as an efficient cathode catalyst with improved ORR and better stability over commercial Pt/C catalyst in the system. Current findings revealed that MnO_x performance can be augmented by increasing the oxygen oxidation state or incorporating materials (e.g. nanomaterials) that basically modify their electronic structure and electron transfer behaviour in catalytic reactions. For example, the nest-like oxygen-deficient $Cu_{1.5}Co_{1.5}O_4$ contains higher micropores and active sites for O_2 access that ultimately enhances the electro-activity and conduction at the catalyst surface. In an instance, Roche et al. (2010) reported MnOx/C as a cathode catalyst with a systemic power density of 161 mW/m^2, which was slightly lower than the obtained power output from Pt/C (193 mW/m^2). In order to increase the catalyst surface area with MnOx substrates, an alternative bi-metallic hybrid approach has also been employed. For example, the bimetal catalyst *h*-Co_3O_4@$MnCo_2O_{4.5}$ was shown to exhibit a higher ORR activity that was attributed to its increased specific surface area (130.4 m^2/g) in the system (Liu et al. 2019). Similarly, Hu et al. (2015) showed hydrothermal in situ preparation of $MnCo_2O_4$/C catalyst with improved ORR in dual-chambered MFC. It was highlighted that the four electron pathway was more favourable for ORR via $MnCo_2O_4$/C catalyst with a maximum power density of 545

mW/m^2, which was relatively advanced over the plain cathode (Pmax = 214 mW/m^2) used in the system (Hu et al. 2015).

A study conducted by Zhang et al. (2014) showed an N-incorporated activated carbon catalyst with increased N content (5.56% pyridinic N and 8.65% total N), activated by an acid/alkaline pre-treatment using cyanamide as the nitrogen precursor. The modified activated carbon showed a 44% higher power density over the conventionally used Pt/C catalyst. Furthermore, N-doping and nitrogenous chemicals, such as ammonium bicarbonate, were found to enhance the porosity and pore size distribution in the matrix. This, in turn, reduced the charge transfer resistance in the system and subsequently improved the overall performance of ORR and MFC. Chronoamperometric results revealed around 73% decrement in the current density of Pt/C after 7 h, whereas the nitrogen-doped activated carbon cathode showed only about 30% decrement. Moreover, linear sweep voltammetric (LSV) analysis revealed an onset potential of 180 mV with nitrogen-doped activated carbon cathode with noticeable positive shifts in ORR (Zhang et al. 2014).

Other combined effects of nanomaterials with noble metals such as Au, Ag and Pd have been duly studied. A bio-electrochemical system containing Pd nanoparticle-modified with p-type Si nanowire (Pd-SiNW) photocathode was tested by Han et al. (2017) in MFC. Here, minimal internal resistance (670 Ω) was observed from Pd-SiNW photocathode under illumination, whereas it was found highly increased in dark experiments (2184 Ω). As a control, carbon paper was studied as a photocathode that indicated respective high internal resistances, e.g. 2372 and 2376 Ω, under illumination and dark experiments. The chronoamperometric results indicated an initial current density of ~0.8 A/m^2 under illumination that gradually decreased to ~0.4 A/m^2 after 36 h of operation in Pd-SiNW electrodes. This in turn was much higher than the control system, which was attributed to the catalytical effect of used nanoparticle in the framework. A few case studies of the potentiodynamic effects of used nanoparticles in MFCs as cathode catalyst is shown in Table 23.5.

23.6 Anode Modifications

Improvisations in electrode fabrications have gathered increased attention in the last few years, where carbon materials have been widely used because of their high availability, porosity and better electrical property. To further augment the efficacy of electrodes, different nanocomposites with better characteristics such as increased durability, electro-activity and thermal endurance have been aimed and designed. For example, modified stainless steel has been used to improve the performance output in the system. This showed an enhanced power density of 2880 mW/m^2 with stainless steel wool/PAni/polypyrrole nanocomposite (Nitisoravut et al. 2017; Zhou et al. 2011). Another widely used substrate is graphene, which is known for its larger surface area and superior conductivity. In combination with different conducting polymers and nanocomposites, these have also been tested in MFCs as anode. Some examples of these modified anodes are given in Table 23.6.

Table 23.5 Electrochemical performance of nanomaterials in MFC analysis

Catalyst used	Reduction voltage (V) by cyclic voltammetry	Reduction current (mA) by cyclic voltammetry	Electrolyte used for ORR	Electrochemical impedance spectroscopy (EIS) (Ω)	Maximum current density (mA/m^2)	Maximum power density (mW/m^2)	COD removal efficiency (%)	References
In situ $MnCo_2O_4$ NRs/PPy	~0.3	–	O_2-saturated 0.1 M KOH	14.86	–	420	89.8	Khilari et al. (2014)
Ni-Co (1:1)/SPAni	~0.715	0.049	PBS solution	43.46	1778.4	659.79 ± 20	91.5	Papiya et al. (2018)
β-MnO_2	−0.16	−0.27	O_2-saturated 0.2 M NaCl solution	200	2341	172 ± 7	–	Zhang et al. (2009b)
Fe-AAPyr	0.307	–	K-PB (0.1 M) solution	–	–	482 ± 5 mW/cm^2	–	Kodali et al. (2017)
N-G@CoNi/BCNT	0.06	–	1.0 M PBS	~10	11.2 A/m^2	2.0 ± 0.1 W/m^2	–	Hou et al. (2016)
CNT/PPy	−0.5	−0.17	NaCl solution	1540	226.25	~113	96	Ghasemi et al. (2016)

Table 23.6 Comparative performance of the modified nanomaterial-based anode in MFCs

Anode materials	MFC assembly	Bacteria/seed	Power density (mW/m^2)	References
Tartaric acid doped PANI/carbon cloth	Dual chambered	*S. oneidensis* MR-1	490	Liao et al. (2015)
PANI/SSFF	Dual chambered	Domestic wastewater	360	Sonawane et al. (2018)
PANI/CNT/GF	Dual chambered	*S. putrefaciens*	257	Huang et al. (2016)
$MnFe_2O_4$/PANI/CC	Single chambered	*S. putrefaciens*	11.2 W/m^3	Khilari et al. (2015)
PANI/CF	Dual chambered	*S. cerevisiae*	460	Hidalgo et al. (2016)
Poly (3,4-ethylenedioxythiophene) (PEDOT) modified carbon cloth	Dual chambered	*S. loihica* strain PV-4	140	Liu et al. (2015b)
(PANI+G+CC)	Single chambered	Lake sediment	884	Huang et al. (2016)
Conductive polypyrrole hydrogels and carbon nanotubes composite (CPHs/CNTs)	Dual chambered	Mixed bacterial culture	1898	Tang et al. (2015)
MnO_2/polypyrrole/MnO_2 nanotubes (NT-MPMs)	Single chambered	Mixed bacterial culture	934.8	Yuan et al. (2016b)
BC/PANI nano-biocomposite	Dual chambered	Anaerobic sludge	616	Mashkour et al. (2016)
PANI-LMC	Dual chambered	Mixed bacterial culture	1280	Zou et al. (2017)
PPy-ACNF/CNT	Dual chambered	*Shewanella oneidensis*	598	Jung and Roh (2017)
PU/graph/PPy	Dual chambered	Municipal wastewater	305.5 mW/m^3	Pérez-Rodríguez et al. (2016)
PPy/SS	Single chambered	Anaerobic granular sludge	1190.94	Pu et al. (2018)
Ppy/SAC/SS	Dual chambered	Mixed bacterial culture	45.2 W/m^3	Wu et al. (2018)
PANI/rGO	Single chambered	Mixed bacterial culture	862	Zhao et al. (2018)
SS-P/PANi	Single chambered	Synthetic wastewater	0.078 mW/cm^2	Sonawane et al. (2018)
MWCNT-MnO_2/PPy	Dual chambered	Sewage	1125.4	Mishra and Jain (2016)

In effect, these modifications have shown better microbial biofilm adhesion and growth at the anode, which in turn have aided in improving the Coulombic efficiency (CE) and overall performance of the system. Whether it's the larger surface area, increased conductivity or enhancing the durability of the electrodes, nanomaterials and their hybrid modifications have proven their substantial applicability in the long run. In the last few years, such endeavours have shown an approximate 10,000-fold improvement in the overall current density of the system. To further augment the system, the multidimensional role of nanomaterials would find specificity in different areas of hydrogen evolution, microbial adhesion, anodic-feed oxidation, electronic/ionic conductivity, ORR and increased stability of the system. This will not only benefit MFCs but also aid in other areas of separation and bioelectrochemical technologies such as microbial electrosynthesis (MES), desalination and microbial electrolysis systems. It can well be predicted that the nanocomposite-based ORR catalysts would play a pivotal role in determining the fate of such existing technologies in large-scale field application.

23.7 Conclusions

The chapter here covers the implications of emerging nanomaterials as improved cathode catalysts in MFCs. This involves oxygen reduction into water, known as oxygen reduction reaction (ORR) that uses the incoming electrons and protons from the anode. Cathode catalysts lower the required activation energy for the process and thereby increases the overall oxygen reduction rate at cathode. The commercially used Pt/C has major drawbacks in terms of their expensiveness and long-term stability. As a substitute, different low-cost nanomaterials/nanocomposites, comprising of transition metals oxides, and carbon materials have been fabricated and tested in MFCs that have shown improved ORR and power efficiency in the system. The chapter here enumerates a comprehensive list of these emerging nanomaterials that have been gaining viability with electrode modifications and in other areas of catalysis. In hope to deliver better efficacy, more such nanomaterial designs and alterations are desired to achieve major adaptations in bio-electrochemical and separation technologies with practical field applications.

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Chapter 24
Metal Oxide Nanostructured Materials for Photocatalytic Hydrogen Generation

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24.1 Introduction

24.1.1 Nanotechnology in Energy Systems

In this fast-moving and automated world, rise in world's demand for energy in a continuous manner made an obvious step for improvement of sustainable and efficient technology which helps in generation and storage of energy (Zang 2011). For this reason, nanoscience and technology advancement is the potential means for increasing energy efficiency across all sectors and balancing renewable energy output economically through new technologies and optimized manufacturing techniques (Steyn 2009).

Nanotechnology is used in different fields like medical and health care (Boisseau and Loubaton 2011), electronics and IT sectors, energy and many more (Wang and Wu 2012). Nanotechnology includes fabrication, designing and creation of device (Thomas et al. 2014). This vast field of attraction is due to its size (below 100 nanometres) (Roduner 2006). This feature helps in creation, storage and transfer of energy (Zhang et al. 2013). For the nanomaterials, a good advantage is the ratio in surface area to volume (Lahann 2008), which offers a reduction in weight with improved stability and mechanical characteristics. Generation of traditional energy using fossil fuels (Serrano et al. 2009) can be replaced with the renewable energy such as solar, tidal, geothermal, wind, biomass, or hydro energy, which provides important improvement in increasing environmental security (Krstić and Wells 2010). Nano-coated (Nguyen-Tri et al. 2018), wear-resistant drill samples, nanomembranes can expand the idea of carbon dioxide separation and environment neutral storage possibilities for power generation in coal power plants because the

selectivity of molecules enables (Okeke and Iloanusi 2014; Lambauer et al. 2012; Choudhary et al. n.d.) and also extends the storage life and helps protect against various corrosion agents, in order to carry out this process for generation of power in an eco-friendly manner for long term (Fulekar et al. 2014). Nanotechnologies may make a decisive contribution to the realization of this vision by, among other things, nano-sensor devices and power-electronic components capable of solving extremely complex problems (Lin et al. 2014; Zeb et al. 2019).

The usage of nanotechnology in energy conversion and energy generation in the following areas:

Batteries: When the battery is not in operation, nanomaterials can be used as a coating to isolate the electrodes from any fluids in the battery. The liquids and solids interact in the present battery technology, producing a low-level discharge. The shelf life of a battery is shortened by this (Abu-Lebdeh and Davidson 2012; Wong and Dia 2017).

Geothermal: By allowing efficient energy generation at lower temperature, nanoscience is now helping to make geothermal power more practical. It enables the lifetime and performance optimization of systems for the production of deposits of petroleum and natural gas or geothermal energy, thereby saving costs. The fluid's heat-retaining properties are also strengthened by nanoparticles (Wiesner and Bottero 2007; Serrano et al. 2009).

Nano-optimization for fuel cell and solar cell: The use of nanomaterials such as lead selenide results in the release of more electrons (and thus more electricity) when struck by a light photon. In addition, nanotechnology modifies the structural properties of PV cells (Ghasemi et al. 2013; Gong et al. 2009; Wang et al. 2011; Tsuchiya et al. 2011; Sethi et al. 2011; Wong et al. 2014; Sharma et al. 2015).

Nanomaterial in water technology: The use of nanomaterials has been considered in point-of-use water purification systems. Nanostructured materials, like greater relative surface areas, display many advantages over traditional microstructured materials for water purification. These techniques of chlorine-free water treatment are of major relevance as carcinogenic disinfection by products may arise when natural water constituents combine with chloramines or chlorine (Carpenter et al. 2015; Savage and Diallo 2005).

Nanomembrane and nano-sieve: A type of membrane which can handle high temperature and useful in petrochemical industry for the preplacement of conventional separation technique and applications which lies in the area of removing water from solvents and bio-fuels (Rogers et al. 2011; Technip n.d.; Wang et al. 2018).

Nuclear reactions: Low-energy nuclear reactions (LENRs) are produced from hydrogen (or deuterium)-loaded metal alloy nanoparticles by pressurizing the particle-containing vessel. The key finding to date is that the excess energy found in experiments to date is well above the highest estimate of what could be applied to known chemical reactions (Sanchez and Sobolev 2010; Keller 2007).

Nanotechnology in energy applications: This technology is used mostly for energy efficiency, eco-friendly in the areas of hydrogen generation, membranes and other energy areas (Hussein 2015; Serrano et al. 2009; Hu et al. 2010).

24.1.2 Present Scenario of Conventional and Potential Methods of Energy Generation

As of now, there are different methods of energy generation and conversion in the world with the help of different machineries. The methods are as follows:

Coal Power Generation: Coal-based power plants produce steam by burning coal in a boiler. This steam under high pressure helps in spinning the turbine and creating electricity. Around 41% of energy consumption in the world is based on coal. Bituminous coal is used for energy production (Mokhatab et al. 2006; Diallo and Brinker 2011; Spliethoff 2010).

Nuclear Power Generation: This also works in the concept of transformation of thermal to electrical power, while the nuclear reactor acts as a heat source. Heat is used to produce steam which can be used to run the turbine and hence produces the required electricity. 11% of the world's energy consumption is produced from nuclear energy. U-235 is basically used for nuclear energy production (Häfele 1990; Bang and Jeong 2011; Serrano et al. 2009; Lenzen 2008; Abu-Khader 2009).

Hydropower Generation: This basically converts the potential energy to kinetic energy which results in rotation of shafts in a turbine which in return produces electrical energy. Around 16% of the world's energy consumption is based on this form of energy. This is basically built across the rivers in the form of dams (Singh and Singal 2017; Chen and Chen 2013; Serrano et al. 2010; Madhavan 2020).

Natural Gas Power Generation: This also works in the mechanism of thermal power plants where the natural gas is used for steam generation which makes the shaft rotate and thus produce electricity. 11% of the world's energy depends on this (Gür 2016; Heppenstall 1998; Kumar et al. 2011; Elcock 2007; Esmaeili 2011).

Geothermal Power Generation: This is mainly based on geothermal energy which is derived from the Earth's subsurface in the form of steam or water for production of clean electricity (Bayer et al. 2013; Zarrouk and Moon 2014).

Wind Power Generation: The main source of this is wind energy which helps rotate wind turbines which then helps in conversion of mechanical to electrical energy. Basically, this is used in high altitudes as there is chances of high wind flow (Vargas et al. 2019; Li et al. 2011; Archer and Jacobson 2005; Lu et al. 2009; Foley et al. 2012; Sivaramakrishna and Reddy 2013).

Wastewater and Biogas Energy Generation: In most instances, the biogas is utilized in combustible engines which converts into mechanical energy powering the electric generators, which probably produce electricity directly by fuel cell. But this method involves relatively clean gas and costly fuel cells. This gas has carbon dioxide, methane and traces of hydrogen, nitrogen and carbon monoxide (Hahn et al. 2014; Rasi et al. 2011; Wiley et al. 2011; Arjuna et al. 2017; Shen et al. 2015).

Tidal Power Generation: The tides coming in a seabed is basically used for this, but at present scenario, the commercial use of this energy is quite less. But this can be potential energy for energy generation. At present, this is converted into different forms of power but mainly electricity (Adcock et al. 2015; Khan et al. 2017;

Westwood 2004; Khan et al. 2009; Schiermeier et al. 2008; Rourke et al. 2010; Ahmadi et al. 2018).

Solar Power Generation: In this case, the sun is the source of energy with the help of photovoltaic cells which converts the sun radiation into electric, and it is called solar thermal power generation. Using solar panels, we can directly transform solar radiation into electricity. In the recent days, there are different methods coming up which uses solar energy into different energies like hydrogen energy, etc., with the help of modified photovoltaic cells (Khan and Arsalan 2016; Qi et al. 2018; Veziroglu 2007; Singh 2013; Hosenuzzaman et al. 2015; Dincer 2011; Müller-Steinhagen and Trieb 2004; Abdin et al. 2013; Vayssieres 2010; Reddy et al. 2014).

In present scenario, the total world production of energy is produced by fossil fuels (80.6%), renewable sources (16.7%) and nuclear (2.7%) as of 2010 (Fridleifsson 2001; Boyle 2004). The major renewable sources are biomass energy (11.44%), hydro energy (3.34%), wind energy (0.51%), etc. (Fronk et al. 2010; Holm and Arch 2013; Goldemberg 2000).

The upcoming renewable energy technologies are solar power, floating wind turbines, printable organic cells, biomass gasification, tidal energy, microbial fuel cell and different starting stage technologies like graphene-based super caps, monolithic microscale heat pumps, hydrogen energy, etc. which are nanotech-based projects which have futuristic scope (Ellabban et al. 2014; Dincer 2000; Sun et al. 2011; Rabaey and Verstraete 2005; Santoro et al. 2017; Huang et al. 2012; Vivekchand et al. 2008; Iverson and Garimella 2008). The usage of these technologies is less in number because the installation cost of these projects are higher compared to present form of fossil fuel-based projects. In this past few years, the cost of production is decreasing, and efficiency is increasing day by day. Thus, the dependency of world market in this green technology is becoming greater day by day (Jhariya et al. 2018; Zerta et al. 2008).

24.2 Fundamental Photocatalytic Hydrogen Generation Process

In the growing world of the twenty-first century, finding an energy source which can fulfil all the demands to being a sustainable energy and environment friendly is still a major challenge for the world (Acar et al. 2016). Due to significant advantages of renewable energies, they are considered as a sustainable alternative over the fossil fuel (Bilgen et al. 2004). Fossil fuels are limited and release toxic gases into the atmosphere. With so many drawbacks, demand of fossil fuels is still at peak since its discovery and is used in diverse applications. The consumption of the highly in-demand fossil fuels leads to increasing rate of releasing CO_2 into the atmosphere. Due to human activities, the rate of net increase of CO_2 is 3×10^{12} kg yr^{-1}, which consequences the annual increase in CO_2 concentration by 0.4%. These kind of growth of CO_2 gases impacts on the world very negatively by increasing the

intensity and frequency of weather events like floods, hurricanes, heat waves, etc. which put a direct impact on glacier retreat and agricultural yield and decrease the rate of growth in human development. After overlooking all the consequences of using fossil fuels, hydrogen is considered as a clean source of energy to overcome all drawbacks of fossil fuel and cover the demand of energy in future. It's carbon-free impacts on environment can be an advantage for the future generation to view the nature and utilize it properly (Züttel et al. 1923).

24.2.1 Thermochemical Water Splitting

Among the various ways for splitting of water, thermochemical water splitting process is a very old and impactful process. It requires high temperature, which can be taken by concentrated solar power (Abanades et al. 2006). Another way to produce the high temperature is from the waste heat of nuclear power reactions and chemical reactions, which acts as a very feasible solution to generate hydrogen and oxygen from water through thermochemical water splitting process (Brown et al. 2002).

In the thermochemical water splitting technique, the major energy source is high temperature, which separate the hydrogen from the mixture which was earlier in equilibrium condition. Gibbs function (ΔG or free energy) needs to be zero for this process; otherwise, the hydrogen and oxygen will mix together to form water. To make sure the Gibbs function to be zero, the temperature needs to be about 4700 K. Apart from the temperature, there are also material separation at high temperature, and STP thermodynamics of water are also some difficulties in this process. However, after that project of the 1960s, many attempts were done to improve the efficiency and feasibility of the process (Funk 2001).

Attempts to increase the efficiency of the cycle (process) was taken into good result in the late 1960s. Hydrogen generation rate to the amount of heat supplied shows efficiency of this process. Some cycles were done using different elements like Cl, S, Li, Ni, Fe, Ca, I, Ba, Sb, etc. The Fe-Cl family cycles among others show some good results (Funk 2001). After all this experiments, some projects were done in international level at Ispra, Italy, through a program named Direct Production of Hydrogen with Nuclear Heat. The summary of the research performed was published by Beghi (Beghi 1986). The main outcome of this program is a process which is known as "GA process". That process was on the development of Mark 16 process, which is also known as the "three closures for sulphuric acid decomposition" shown in Fig. 24.1. The attractive thing in GA process is the determination of Bunsen reaction of iodine, sulphur dioxide and water. The overall efficiency of this process was estimated to be about 47% (O'keefe et al. 1982).

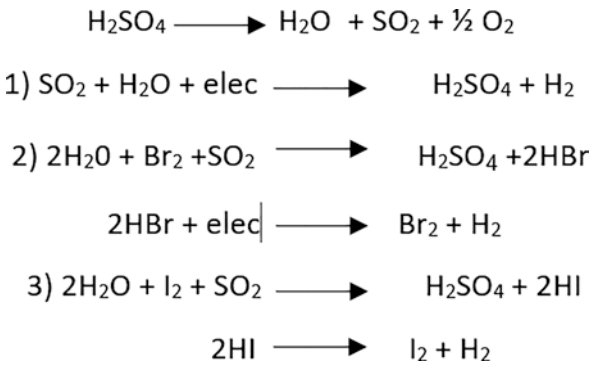

Fig. 24.1 Three closures for sulphuric acid decomposition (Abas et al. 2015)

24.2.2 Photobiological Water Splitting

In the present world, the consumption of fossil fuel only covers 86% demand of required energy. Photobiological water splitting is an effective way to generate hydrogen molecules by using photoautotrophic microorganisms from water and sunlight (Ghirardi et al. 2009). These microorganisms such as algae, dark fermentative bacteria, sulphur bacteria and cyanobacteria are used to generate biohydrogen by consuming the carbon dioxide gas (CO_2) (Benemann 1997). In this whole process, the sunlight and the microorganisms' main role is to produce biohydrogen. Basically, these microorganisms synthesized the hydrogen using CO_2 and H_2O. There are two techniques for this process: (i) direct photobiological hydrogen generation and (ii) indirect photobiological hydrogen generation. In direct process, hydrogen is directly generated by hydrogenase process with the help of molecules such as carbohydrates, whereas in indirect method, the gas is produced after storing glycogen or carbohydrates (Dasgupta et al. 2010). Hence, here is the described reaction of indirect method:

$$6H_20 + 6CO_2 + \text{light} \rightarrow C_6H_{12}O_6 + 6O_2 \tag{24.1}$$

$$C_6H_{12}O_6 + 2H_2O \rightarrow 4H_2 + 2CH_3COOH + 2CO_2 \tag{24.2}$$

$$2CH_3COOH + 4H_2O + \text{light} \rightarrow 8H_2 + 4CO_2 \tag{24.3}$$

In the process of photobiological hydrogen production, the microalgae donate e^- for which it requires sunlight. This process can produce oxygen or not depending upon the microorganisms carried out in this process. Oxygen is generated when the process was carried out by eukaryotic microalgae and cyanobacteria (Melis et al. 2000), whereas the process does not generate oxygen when purple non-sulphur bacteria takes part in this process (McKinlay 2014). There are two enzymes available, i.e. hydrogenase and nitrogenase, which activities concluded the production of biohydrogen depending upon the presence of molecular oxygen. However, the molecular oxygen produced by photosynthesis creates a burden for the microorganisms; the

production of biohydrogen is shown in Fig. 24.2 for which the researches are going to overcome this problem (Prince and Kheshgi 2005).

Earlier there are only two methods for this process, i.e. aerobic and anaerobic. However, these reactions can give a short description about the two methods (Kruse et al. 2005):

$$H_2O \rightarrow 2H^+ + 2e^- + \frac{1}{2}O_2 \quad (\text{Aerobic}) \tag{24.4}$$

$$2H^+ + 2e^- \rightarrow H_2 \quad (\text{Anaerobic}) \tag{25.5}$$

24.2.3 Photoelectrochemical Water Splitting

Direct use of light radiation for splitting water to oxygen and hydrogen, when light energy interacts with the surface of semiconductor (SC), is called photoelectrochemical (PEC) water splitting. Producing of hydrogen with this process is very acceptable for current world and future world. In this process, the first step includes choosing a suitable photoelectrochemical material or SC, which has suitable band

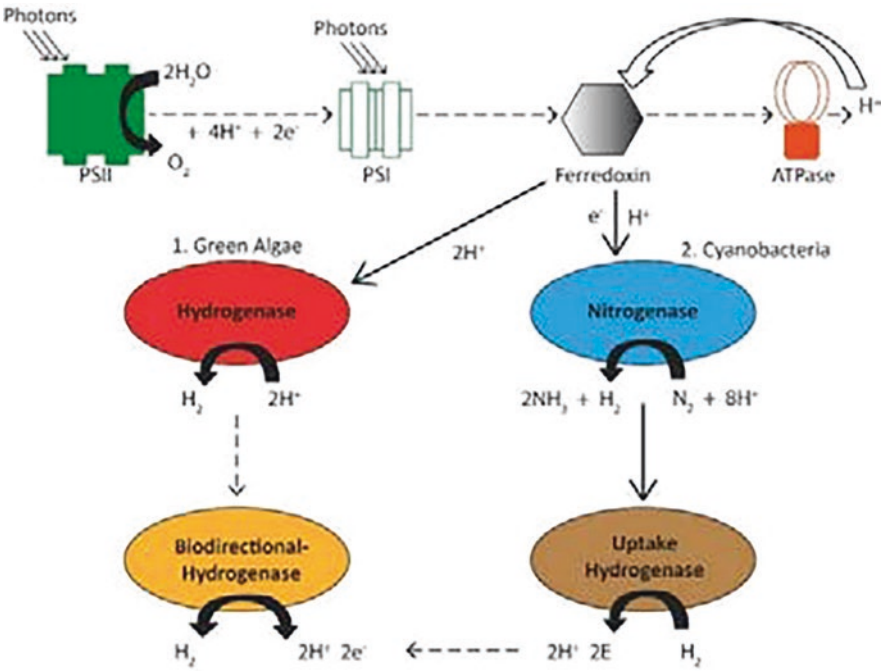

Fig. 24.2 Mechanism of photobiological hydrogen production

gap, efficient performance in visible light, photostable, resists to photo corrosion, etc. However, in a single material, it is very difficult to find all these properties as well as at affordable cost for large scale implementation. Because some material has small band gap but may not have good stability, so in this way different materials have different types of advantages and disadvantages. To overcome this burden, many ways have been founded to develop the material properties, which have put a positive factor on the efficiency of the substrate for production of hydrogen and for industrial-level purpose also.

As choosing of material is an important step of this process, Fig. 24.3 shows the band gap of different materials and the position of CB and VB according to E vs NHE bar. For water splitting action, the CB and VB need to be at least 1.23 eV band gap, so that both the reaction, i.e. photo reduction at CB and photo oxidation in VB, can be processed smoothly. We can consider TiO_2 for this process due to its number of advantages, which can clarify the reasons of each material properties required for hydrogen production BY photolysis of water. If we consider the minimum required band gap and position of CB and VB for the photoreduction and photooxidation, respectively, then we may find many materials. But some have large band gap, and there might not be any positive future modifications that can be done with the material for this disadvantage. However, in TiO_2, some modifications have been done for its large band gap issue.

Mechanism has been shown in Fig. 24.4. The light energy having adequate energy to penetrate the material can excite an electron to jump from VB to CB. Further, a hole is generated at VB which interacts with the water and generates oxygen molecule and H^+ ions, which will interact with the free electron and form hydrogen molecule.

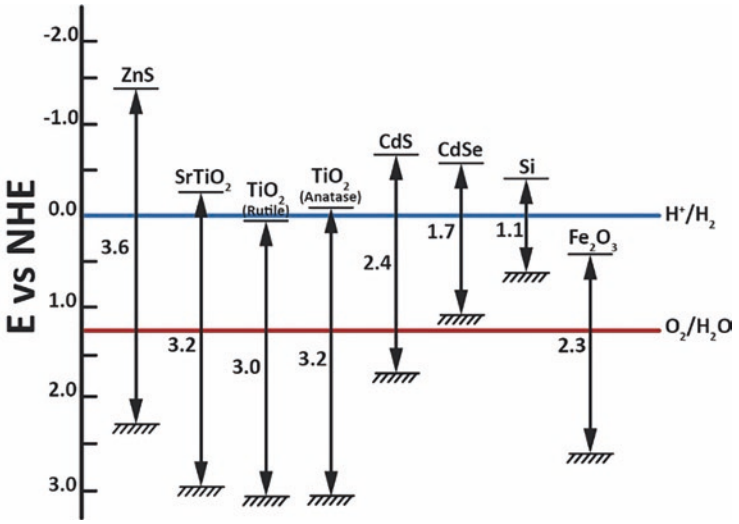

Fig. 24.3 Band gap of different semiconductors

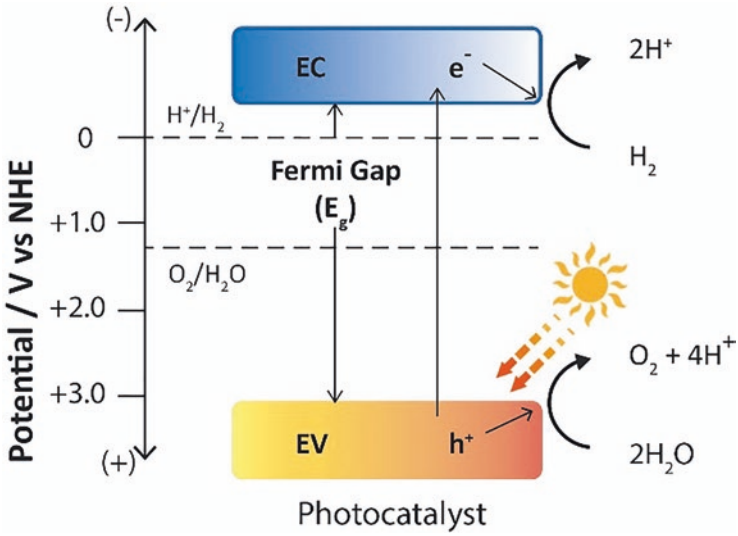

Fig. 24.4 Mechanism of photocatalytic hydrogen generation

However, apart from all these processes, there are some limitations like not able to utilize longer-wavelength photons or light energy from sun for hydrogen production. Some recent development was done to overcome these burdens up to some instant, and they are doping of metals in semiconductor to lower its band gap and make it functionable at the frequency of visible light or little bit longer wavelength. This metal doping also helps in decreasing the rate of recombination of electron and holes which are generated to interact with water, so that the efficiency can increase. Apart from all these developments, there are also heterogeneous structures formed for better efficiency.

24.2.4 Photocatalytic Water Splitting

The process in which water splits using semiconductor as a catalyst is called photocatalytic water splitting. It was believed that this process was discovered in the early 1980s, and from that moment till now, the research is going on for the development of its catalyst, as it is acting as a main role in the process of photocatalysis; however, the cocatalyst's improvement is also important (Maeda 2011). Titanium dioxide or titania (TiO_2) has acquired a major role in this field and was studied over more than quarter of a century because of its suitable material properties which are very much reliable for this application. Those reliable qualities are its robust architecture, which makes it more stable than other materials; low cost, which makes it more suitable for commercial purpose; and environment friendly, a very much required advantage to replace fossil fuel in the field of energy. However, it has one major

drawback, which lags its efficiency and purpose of application. That major drawback is its large energy band gap (~3.3 eV), which ensures its efficiency is maximum only in the UV radiation than the visible light, which makes it very much unrealistic to be implemented for practical purpose (Luo et al. 2004; Dholam et al. 2009; Selcuk et al. 2012). No doubt the researches are going on regarding its improvement, and many ways have been founded (Fujishima and Zhang 2006). Some ways to improve the material properties of TiO_2 are metal oxide doping, dye sensitization, heterogeneous structure, etc. These ways not only make TiO_2 work under visible light but also improve its efficiency by increasing some other aspects which ensure its growth in production of hydrogen from water splitting (Ni et al. 2007). Apart from TiO_2, there are also many materials that have been founded performing good performance like TiO_2; they are ZrO_2, $SrTiO_3$, $KTaO_3$ and $BiVO_4$ (Sakata et al. 1983; Serpone and Pelizzetti 1989), but there are some SCs available which are quite less compatible for this application due to their drawbacks, and those drawbacks are not environment friendly, not stable with its properties for this particular application and photo corrosion occurs while application is going on, which means anion generated from photocatalyst is oxidized by the photogenerated holes instead of water. Those semiconductors are SiC, CdS and ZnO (Kudo and Miseki 2009; Linsebigler et al. 1995; Zou et al. 2011).

24.2.4.1 Thermodynamics and Kinetics of Photocatalytic Water Splitting

Photocatalysis is an endothermic and a multi-electron process (Colón 2016). This process requires an initial energy to fulfil Gibbs free energy change which is $\Delta H^{\circ} = 238$ kJ mol^{-1} and can be used for rearranging valence electrons of water for the production of hydrogen and oxygen molecules (Maeda 2011; Acar et al. 2014). In general, water splitting process can be explained by Eqs. (24.6) and (24.7). As shown in Eq. (24.6), to generate a single hydrogen molecule, the energy necessary by H_2O to decompose and produce hydrogen molecule is 2.458 eV (Zamfirescu et al. 2012). Since complete water splitting process requires four hydrogen molecules as shown in Eq. (24.7), required input energy will be 4.915 eV, which could be done using UV radiation of smaller wavelength than 252.3 nm or by photons from visible wavelength (<504.5 nm) (Zamfirescu et al. 2011). This process involves two half reactions, oxidation of water to form O_2 molecule and reduction of protons to form H_2 molecule.

$$\text{Half reactions} \quad H_2O \xrightarrow{TiO_2/h\nu} \frac{1}{2}O_2 + 2H^+; \quad 2H^+ + 2e^- \rightarrow H_2 + \frac{1}{2}O_2 \tag{24.6}$$

$$\text{Complete water splitting reaction} \quad 2H_2O \xrightarrow{TiO_2/h\nu} O_2 + 4H^+;$$
$$4H^+ + 4e^- \rightarrow 2H_2 + O_2 \tag{24.7}$$

When the photocatalyst is subjected to radiation having larger energy than E_g, it excites the e^- to CB and leaves a hole behind at VB. These excited electrons and

holes can move freely so they have chances of being delocalized within the semiconductor. As a result, the electrons may quickly attain internal equilibrium within energy level rather than moving out beyond band gap as shown in Fig. 24.5. Electron state at equilibrium known as "quasi-equilibrium states" and potential of e^- and h^+ in these states are shown in Eqs. (24.8) and (24.9) (Liu et al. 2014; Shehzad et al. 2018). In radiation energy more than E_g, e^- and h^+ dependent reactions can be explained from Eq. (24.10). Although when photocatalyst is at thermal equilibrium $\Delta H = 0$, i.e. $\Delta G = 0$, as a result, zero net force requires to carry out the photocatalysis reaction. This shows heat is not responsible force for generating e^- and h^+ pairs. Thus, for photocatalysis:

$$F_n = E_c + k_B T \ln \frac{n}{N_c} \tag{24.8}$$

$$F_p = E_v + k_B T \ln \frac{n}{N_v} \tag{24.9}$$

$$\Delta G = -\#F_n - F_p\# = -E_g - k_B T \ln \frac{np}{N_c N_v} \tag{24.10}$$

The efficiency of hydrogen generation is affected by band gap and intensity of light. Mainly, there are two types of light being considered from the electromagnetic spectrum: UV light whose wavelength range lies in between 200 and 400 nm, while the other one is visible light whose wavelength lies in between 400 and 800 nm. Light absorption gets very less in semiconductors having wider band gap. Semiconductor having band gap higher than 3.15 eV can be activated in ultraviolet light; semiconductor having band gap lower than 3.15 eV visible light can be used to drive reaction. Thus, a semiconductor is suitable for being a photocatalyst having band gap 1.23 eV < Eg < 3.15 eV (Yan et al. 2010; Chun et al. 2003).

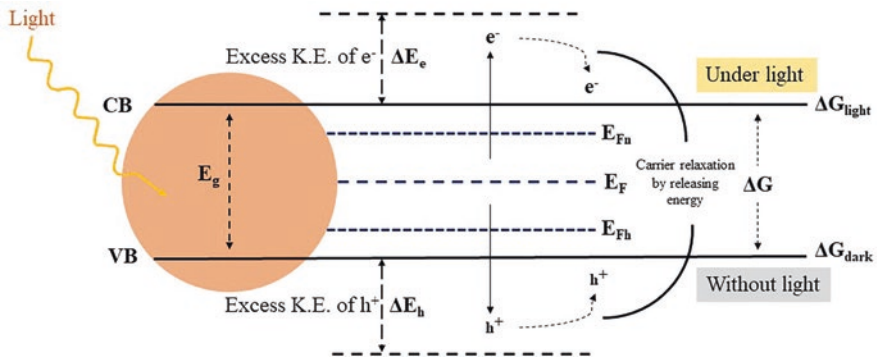

Fig. 24.5 Thermodynamics and Gibbs free energy in presence and absence of light

24.2.4.2 Hydrogen Generation Efficiency

Comparing the efficiency of photocatalysis has always been difficult to judge, as different researchers used different methods or chemical tests for their respective experiment. These chemical tests mainly include the finding of solar-to-hydrogen conversion and quantum efficiencies or apparent quantum yields of the photocatalytic activities. Basically, at particular wavelength, the quantum yield is calculated, similarly at particular spectrum of light the solar-to-hydrogen conversion calculated. However, some universal principles or standards have been taken into consideration for finding all these efficiencies. Solar-to-hydrogen conversion is the very genuine term used for finding the efficiency of hydrogen production from any process.

That term is given here by Eq. (24.11):

$$\mathrm{STH} = \left[\frac{\left| j_{\mathrm{sc}} \left(\frac{\mathrm{mA}}{\mathrm{Cm}^2} \right) \right| \times (1.23\,\mathrm{V}) \times \eta \mathrm{F}}{P_{\mathrm{total}} \left(\frac{\mathrm{mW}}{\mathrm{cm}^2} \right)} \right] \mathrm{AM1.5G} \tag{24.11}$$

where power density of incident light (AM 1.5G) is represented by P_{total} and the product of faradic efficiency (η_{F}), the thermodynamic voltage necessary for decomposition of water (1.23 V) and photocurrent density (j_{sc}) at zero potential (short-circuit photocurrent) are in the numerator. Similarly, SHE can be represented as shown in Eq. (24.12):

$$\mathrm{STH} = \left[\frac{(\mathrm{mmole\,H_2\,/\,s})(237\,\mathrm{KJ\,/\,mole})}{P_{\mathrm{total}} \left(\frac{\mathrm{mW}}{\mathrm{cm}^2} \right) \times \mathrm{Area}\left(\mathrm{cm}^2\right)} \right] \mathrm{AM1.5G} \tag{24.12}$$

where the product of area in contact with incident light and total power the incident sunlight (AM 1.5G) are represented in denominator section. In numerator, the H_2 evolution rate is multiplied by the Gibbs free energy required for the generation of one mole of hydrogen from water.

There are some conditions and methods upon which the observable quantum yields depend, i.e. the reaction conditions, measuring methods, etc. So, Eq. (24.13) shown here is the general equation for calculating apparent quantum yields. This equation is only valid for catalysts radiated at source of monochromatic wavelength:

$$\begin{aligned} \text{AQE}\% &= \frac{\text{No.of reacted electrons}}{\text{No.of incident photons}} \times 100 \\ &= \frac{2 \times \text{No.of evolved} H_2 \text{ molecules}}{\text{No.of incident photons}} \times 100 \end{aligned} \tag{24.13}$$

However, hydrogen generation performance could be evaluated by the photocatalysts radiated under sunrays. This is shown in Eq. (24.14):

$$\text{SHE}\% = \frac{\text{Output energy as H2 evolved}}{\text{Energy og incident solar light}} \times 100 \tag{24.14}$$

After all these equations, one thing can be concluded that depending upon the light source, different equations can be applied for calculating the efficiency, but for one particular system or source of light, all the conversation cannot be applied.

24.3 Heterojunction Architecture

Till today, various semiconductor photocatalyst (e.g. Fe_2O_3 (Sivula et al. 2010), WO_3 (Hodes et al. 1976; Bignozzi et al. 2013), $BiVO_4$ (Sayama et al. 2003; Li et al. 2013)) have been reported for water splitting purpose. Out of all these, very less amount of materials is able to split water in visible light conditions. This poses a major downside and decreases the efficiency of solar-to-hydrogen conversion, which eventually affects the rate of generation of hydrogen. Thus, there is an urgent need of new materials and strategies for increasing efficiency in energy conversion. Lowering the rate of recombination of the generated e^- and h^+ pairs is one of the main factors in rising the hydrogen gas generation. When light falls on the top of SC, e^- and h^+ pairs are produced, the e^- from the VB promoted to the CB leaving behind a h^+ at VB.

There are different techniques reported for lowering the recombination speed of e^- and h^+ pairs: (i) using sacrificial agents, it removes either of the holes or electrons in the system and making the other charge carriers isolated which helps to carry out one half reaction (oxidation/reduction) (Kudo et al. 1998); (ii) alternating the morphology of the photocatalyst, this significantly increases the efficiency as it increases the surface region and shortens the length of diffusion of the charge carriers to surface (Moniz et al. 2015); (iii) creating heterojunction structure, charge carriers generated are transferred to other photocatalyst thereby increasing the lifetime of electro-hole pairs (Rhee et al. 1998; Martin et al. 2014).

Different types of heterojunctions could be achieved by adding a SC with a metal forming a Schottky junction, whereas the assembling of two SC materials can give rise to a semiconductor heterojunction. These SC materials are of two types, p-type (majority holes carriers) and n-type (majority electron carriers). Based on this,

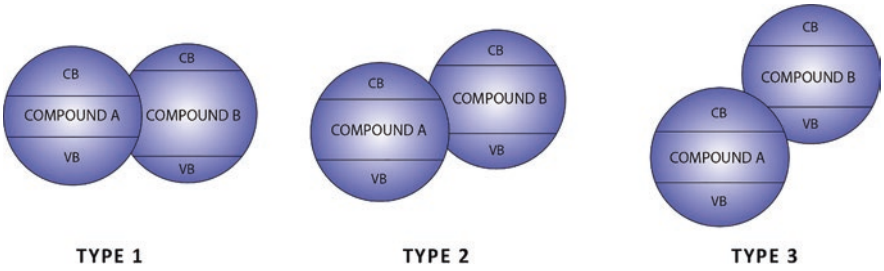

Fig. 24.6 Band alignment in type 1, type 2 and type 3 heterojunctions

heterojunction can be classified into three categories: (i) p-p type, two p-types of SCs; (ii) n-n type, two n-types SCs; and (iii) p-n type in which one p-type semiconductor and one n-type semiconductor is used. There exist three forms of heterojunctions for band alignment as shown in Fig. 24.6.

24.3.1 Type 1

In type 1 heterojunctions, first material E_{CB} is more −ve compared to that of second, and it's E_{VB} more +ve than second. It has been reported that electron and holes tend to flow to less −ve E_{CB} and less +ve E_{VB} in SC-SC heterojunction, respectively. In this alignment, electrons start accumulating at SC having lower band gap (in this case second material, SC-2); therefore, the probability of recombination of these electrons is more which may not bring any significant improvement in photocatalysis. Further, this leads to creating very weak internal electric field, which helps in better charge separation. When first material has higher E_F level compared to second, until E_F levels are synchronized, electrons will start flowing towards second material as shown in Fig. 24.7(a). This contributes to formation of the space charge at the junction. Since first material is more +vely charged, the path of the internal electric field would be from first to second material (Zhang and Yates Jr 2012). This means after incident of photon the transfer of electron is not allowed but at the same time holes can migrate from SC-1 to SC-2. When we reverse the conditions, i.e. SC-2 becomes more positive than SC-1, electrons start migrating from SC-2 to SC-1, whereas holes are prohibited from migration and get accumulated at the interface shown in Fig. 24.7(b).

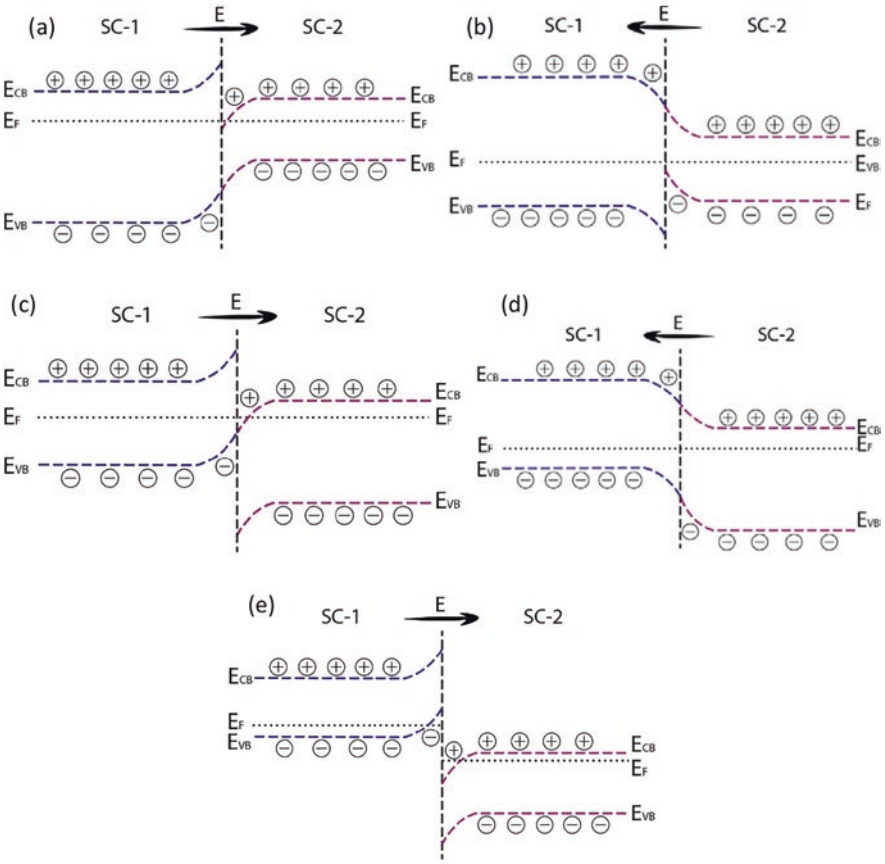

Fig. 24.7 Types of heterojunctions and their charge transfer due to existing internal electric field

24.3.2 Type 2

In type 2 heterojunction, first material E_{CB} is more −ve, while E_{VB} is less positive compared to second material. This alignment supports better charge separation. First material has a higher E_F level than second, and an internal electrical field has occurred in the direction from material 1 to material 2 shown in Fig. 24.7(c). The generated e^- in space charge area of first material will migrate towards interior, and h^+ will travel near to interface at the instant of time the charge carriers of SC-2 will oppose the flow of SC-1. Thus, recombination will occur at interface due to transfer of h^+ of material 1 and e^- from material 2 (QingáLu 2009), but material 1 e^- and material 2 h^+ are retained for catalytic reactions. All these process takes form of Z-shape therefore it is referred as Z-scheme (Liu et al. 2016; Jin et al. 2015; Zhou et al. 2014). When E_F of material 1 is lower than material 2 and material 1 is p-type SC and material 2 is n-type SC, then the internal electric field (E) will flow from

n-type to p-type shown in Fig. 24.7(d). As the E_{CB} of n-type is less −ve than p-type, e^- of p-type will start migrating towards interface and will transfer to E_{CB} of n-type, and similarly, holes will move to E_{VB} of n-type.

24.3.3 Type 3

In type 3 heterojunction, both E_{CB} and E_{VB} of material 1 are higher than that of material 2. In this type of alignment, both of the SCs across the junction can be treated as individual SCs, because e^- and h^+ transfer doesn't take place in between them shown in Fig. 24.7(e). Both h^+ of material 1 and e^- of material 2 will migrate towards junction; there they get intervened by energy levels barrier. A twisted Z-scheme can be formed by introducing an appropriate charging mediator as a bridge connecting these two semiconductors (Gholipour et al. 2015).

24.3.4 Z-Scheme

The groundbreaking idea of developing a Z-scheme photocatalysis was initiated by Bard in the year 1979. His idea was to introduce an electron mediator as a charge carrier channel between two photocatalytic systems which can be further utilized for oxidation and reduction process (Bard 1979). This proposed idea was first coming into demonstration in the year 2001, where IO_3^-/I^- shuttle redox couple was placed as an ionic mediator to monitor the charge transfer between two photosystems (Sayama et al. 2001). This became the first-generation Z-scheme photocatalytic systems, which brought a significant change in hydrogen generation process. Moreover, recently, Wang et al. proposed the idea of Z-scheme photocatalyst sheets, which confirms to be a potential candidate for STH conversion (Wang et al. 2016). Different structures of z-scheme have been studied such as powder photocatalysis, thin film form of Z-scheme which have dual layer of particulate sheet. Research on the evolutionary idea of Z-scheme photocatalysis was started since 1979, and till today extensive efforts and numerous studies have been devoted to develop a photocatalytic system which can fully utilize solar radiation.

24.3.5 Binary Semiconductor Photocatalyst

24.3.5.1 Oxide-Based Binary Photocatalyst

Teoh et al. synthesized TiO_2 nanoparticles (NPs) via the flame spray pyrolysis (FSP) process, which showed higher activity of photomineralization of sucrose shared with commercially available Degussa P-25 (Teoh et al. 2005). FSP techniques yields

NPs which have high crystallinity, regulated surface area and morphology without involving any post-treatment process. He also published a comprehensive analysis of his successful attempt for using FSP to produce different binary photocatalysts (Teoh 2013). Similarly, Zhanxia et al. developed nanoflower made up of zirconia (ZrO_2). They used zirconium oxide sulphate and sodium acetate as precursor materials and adapted hydrothermal process to furnish the required 3D nanoflower. They found that using ZrO_2 nanoflower enhances photocatalytic activity for dye degradation and hydrogen generation which could be due to superior absorbance of photons. Many researchers have explored ZnO and CeO_2 nanomaterials synthesized in hydrothermal process for hydrogen generation and found to have well-defined properties for photocatalysis (Roig et al. 2011; Slostowski et al. 2013).

24.3.5.2 Nitride-Based Binary Photocatalyst

In comparison to binary chalcogenides/oxides, binary nitrides are being recently explored for photocatalytic purpose. Gallium nitride was chosen as a parent semiconductor photocatalyst after having seen its excellent properties in the field of sensing because of its stability and mechanical power (Ye et al. 2018). Kida et al. was first to report the use of GaN for water splitting, for which he used GaN in powdered form (Hu et al. 2005). Apart from GaN, tantalum nitride is an important transition binary nitride compound used for photolysis of water, due to its narrow band gap and preferable band gap potentials (Luo et al. 2012; Jing and Guo 2006).

24.3.5.3 Chalcogenide-Based Binary Photocatalyst

Heterojunction SCs binary chalcogenides such as zinc sulphide (ZnS) and cadmium sulphide (CdS) photocatalyst were studied in vast scale in the last four decades because of its potential applications in environment purification, hydrogen production and CO_2 reduction. Out of these ZnS chalcogenides, one is most commonly studied due to its 3.2–4.4 eV band difference (Yonenaga 2001). Hu et al. reported a simple approach for ZnS nanoporous nanoparticles via solution phase thermal decomposition technique. He found that prepared samples outperformed the commercial TiO_2 in dye degradation by degrading eosin B dye (Kida et al. 2006). Further, he confirmed the enhancement due to spherical shape and high monodispersity.

Similarly, the synthesis of hollow spherical CdS was reported by Luo et al. (Tabata et al. 2010). Jing et al. developed a new technique to replace the conventional synthetic precipitation process for the generation of nanostructured CdS photocatalysts. Its thermal sulphidation process reduces the CdS phase transition and crystallization temperature. The synthesized CdS by this process enhanced their stability against air and photo corrosion. CdS-based photocatalyst displayed a significant performance due to its narrow band gap and higher conduction potential as compared to H_2O/H_2 reduction potential (Chun et al. 2003).

24.3.6 Ternary Oxide Photocatalysts

Ternary oxide SCs comprise of two different metallic cation and single anion. In recent decades, these materials are being studied more due to their stable nature.

24.3.6.1 Perovskite Photocatalysts (ABO_3 Type)

Perovskite oxide materials having general formula ABO_3 as SC photocatalyst has been used in wide scale due to phenomenal properties of converting STH. Here, A is a cation either rare earth metal or alkali, and B is cation transition metal element having smaller size than A. Its ideal structure is in cubic lattice form. Strontium titanate ($SrTiO_3$) has immense application in heterojunction photocatalysis because of its thermal stability and photo-corrosion resistance, and its chemical physical properties can be altered by changing its composition (Fujinami et al. 2010). $SrTiO_3$ have band gap of 3.2 eV which helps to absolute mineralize or degrade organic dye and enhance water splitting reaction (Ohno et al. 2005; Ahuja and Kutty 1996; Kato and Kudo 2001). Unlike titanates, tantalates also exhibit photocatalytic properties, in which they can split water without any addition of reduction and oxidation catalyst, due to their high CB and VB edge than redox potential of water. Similarly, lithium tantalate ($LiTaO_3$) is also being utilized for decomposing water in the presence of UV light without any addition of catalyst due to wide forbidden energy gap of 4.6–4.7 eV (AkilaKesavan 2014; Kato and Kudo 2001).

24.3.6.2 Delafossite Photocatalyst (ABO_2 Type)

This type of oxides has general formula of ABO_2, where A and B are metals with +1 and +3 oxidation states, respectively. They possess a layered structure with a sheet of linearly coordinated A cations and BO_6 octahedral edges sharing its boundaries. These set of oxides have Ag containing group-3 elements of $AgMO_2$ (M = Al, Ga, In) (Maruyama et al. 2006; Ouyang et al. 2006; Maruyama et al. 2006; Ouyang et al. 2008). These oxides also include α-$AgInO_2$ (1.92 eV), α-$AgGaO_2$ (2.38 eV), β-AgAlO2 (2.95 eV) and C (2.18 eV), where α refers to delafossite and β refers to cristobalite structure. Ouyang et al. performed a photocatalytic experiment using these SCs and found their efficiency was in the order of α-$AgGaO_2$ > β-$AgAlO_2$ > β-$AgAlO_2$ > α-$AgInO_2$ (Ouyang et al. 2008; Ouyang et al. 2009).

24.3.6.3 Spinel Photocatalyst (AB_2O_4 Type)

These compounds have a general formula of AB_2O_4, where A and B are metals with oxidation state of +2 and +3, respectively. They have a cubic with close-packed lattice. Compounds such as calcium indate ($CaIn_2O_4$), containing p-block element

indium with d_{10} configuration comes under this division. $CaIn_2O_4$ shows photodegradation of organic dyes under viewable light (Tang et al. 2003; Tang et al. 2004a). The process of $CaIn_2O_4$ via solid state reaction involves high temperature (>1000 °C) and long calcination time (12 h) (Tang et al. 2003; Tang et al. 2004a; Tang et al. 2004b). In order to address this, Ding et al. has implemented a combustion synthetic route method to replace the conventional SSR method for the production of high crystalline and surface area $CaIn_2O_4$ nanotubes. He found that the synthesized $CaIn_2O_4$ photocatalyst shows 66% of degradation of toluene gas, and when dispersed in water in presence of Pt, it was able to produce hydrogen 1.23 μmol h^{-1} g^{-1}, which is 24 times higher than traditional SSR method (Ding et al. 2009).

24.3.6.4 ABO_4 Type Photocatalyst

Bismuth vanadate is a viewable light-responsive SC that has acquired more popularity due to its ferroelastic, polymorphic and electronic properties. Such properties are highly dependent on crystalline structure of material. There are three polymorphic kinds of $BiVO_4$, which are scheelite-monoclinic (SM), scheelite-tetragonal (ST) and zircon tetragonal (ZT) (Tokunaga et al. 2001; Bierlein and Sleight 1975). These three SM are found to be more effective to produce O_2 from aqueous $AgNO_3$ and degradation of endocrine compounds. Compared to conventional aqueous process routes, Yu and Kudo found hydrothermal routes to synthesize SM-$BiVO_4$ with improved morphology and surface texture to boost the photocatalytic hydrogen evolution for O_2 from $AgNO_3$ by changing the pH of the medium (Yu and Kudo 2006).

24.4 Metal-Semiconductor Heterojunction Photocatalysis

Recent developments in plasma noble metals (Linic et al. 2011; Duan et al. 2014; Pradhan et al. 2001) and semiconductive nanomaterials (Trotochaud et al. 2013; Ma et al. 2012; Zandi and Hamann 2014) remain the most important inorganic material for photocatalysis. These can be utilized for removing organic pollutant, bacterial detoxifications and producing hydrogen (Trotochaud et al. 2013; Zandi and Hamann 2014). The recent studies show that the combining plasmonic metals and semiconductors give rise to a better catalyst for solar-to-energy conversion. These combination of metal-semiconductor forms a heterojunction which may generate new properties when both are placed close to each other shown in Fig. 24.8(a). This can aid in the rapid transfer of charge carriers produced from one carrier to another; it will remove the electrons from metal and semiconductor which will further hinder the process of recombination (Yu et al. 2014; Costi et al. 2010). Also, these materials give different amalgamation of facets on its surfaces, giving an opportunity to substrate molecules getting absorbed. All mentioned advantages make these kinds

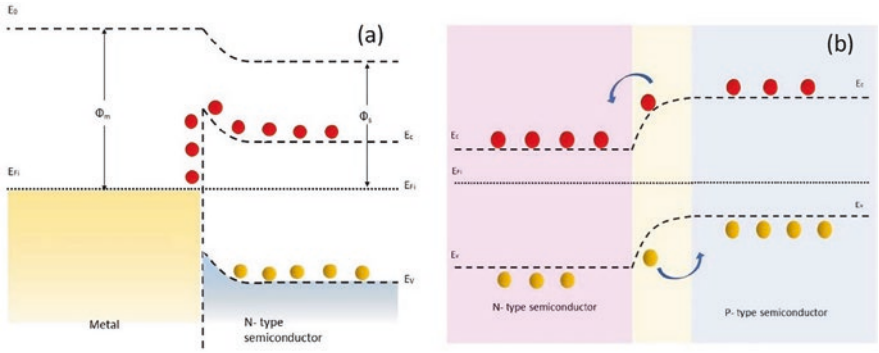

Fig. 24.8 (**a**) M-S junction and (**b**) S-S heterojunction

of structures more favourable to use. These structures can be further categorized into: (i) In first case materials are photoactive which means on excitation charges will get transfer from one to other material. For instance, plasmonic gold is combined with high band gap semiconductor materials such as TiO_2; charge will start flowing from gold to TiO_2 to initiate the catalytic reaction (Linic et al. 2011; Duan et al. 2014); (ii) the second one is metal and SC; both of them are photoresponsive and absorb solar radiation such as Au-CdS and Au-CdSe (Costi et al. 2010). However, very few reports are available till date for these materials, their promising advantages encourage the researchers to work more on it, and proper band alignment may help more facile electron transfer.

24.5 Semiconductor-Semiconductor Heterojunction Photocatalyst

Recently, heterojunctions formed by combining two SCs are most common; generally p- and n- SC are chosen for this. Figure 24.8(b) shows the junction of S-S type heterojunction. As a result, space charge region is created at the interface and electric field is produced due to diffusion of charge carriers. This type heterojunction is related to band alignment of SC. Having knowledge of band structure of semiconductor is crucial as the band alignment could be easily drawn by assigning band edge positions in energy diagram. Further, band structure tells about the redox ability of semiconductor heterojunction. The more −ve E_{CB} represents strong reducing strength, while more +ve E_{VB} means more strong oxidizing strength.

24.6 Modifications in Photocatalysts

24.6.1 Metal and Non-metal Implantation

The effectiveness of photocatalytic hydrogenation is governed by how effectively the rate of recombination is decreased and charge carriers get separated to take part in oxidation and reduction reaction (Hoffmann et al. 1995). It has been a continuous point of discussion for materials scientists to find more active materials which can improve the performance of photocatalytic process for industrial-scale applications (Ollis and Al-Ekabi 1993; Parent et al. 1996). One of the best approaches to resolve this issue by doping of different metal or non-metal ions in to the host photocatalyst. Plenty of potential dopants have been found and studied for photocatalytic dye-degradation rate. Various metals such as rhodium (Rh), silver (Ag), platinum (Pt), copper (Cu), iron (Fe), vanadium (V), chromium (Cr), nickel (Ni), aluminium (Al), gold (Au), Lithium (Li), palladium (Pd), Magnesium (Mg), etc. are some of the most common dopants that are being used (Choi et al. 2002; Serpone et al. 2010; Siemon et al. 2002; Litter 1999; Tan et al. 2003; Su et al. 2004; Vamathevan et al. 2002; Tayade et al. 2006; Tayade et al. 2011). Doping involves, the guest metals/non-metals is incorporated into the parent semiconductor material which create vacant sites and defects in atomic structure. It improves the base properties of the host material by modifying its material properties. Doping of metals in TiO_2 stops the electrons to move away from the surface which prevents it from recombining with the valance band holes (Gerischer and Heller 1992; Gerischer and Heller 1991; Wang et al. 1992). It also facilitates electron transfer at TiO_2 surface; thus, an effective e^- transfer occurs to e^- acceptors than donors in case of the undoped TiO_2. Oxygen traps the electron and produces superoxide ion, whereas hole oxidizes the hydroxyl ion to hydroxyl radicals. Various chemical and physical methods are used for the metal doping in semiconductor such as chemical vapour deposition, sol-gel, water in oil microemulsion, wet impregnation, hydrothermal, ion-assisted sputtering.

Ghasemi et al. investigated photocatalytic activity of different transitional metal ions (Fe, Cr, Co, Fe, Ni, Mn and Zn)-loaded TiO_2 film for acid blue 92 dye degradation. He claimed that with the presence of metal ions, the photocatalytic behaviour of TiO_2 was dramatically increased and the most prominent and active metal was Fe. Further, he confirmed that this was due to its and reduced band gap, high surface area and small crystallite size (Ghasemi et al. 2009). Sobana et al. explored the degrading Direct blue 53 (DB 53) and Direct red 23 (DR 23) dyes using Ag-doped TiO_2 through wet impregnated process in UV radiation. This change was due to e^--h^+ segregation by e^- trapping of Ag nanoparticles (Sobana et al. 2006). In addition, similar findings were found by Whang et al., highest degradation rate of methylene blue (MB) was at 2.0 wt% of Ag-doped TiO_2 (Whang et al. 2009). Choi et al. analysed chloroform degradation by doping various valance metal ions (Fe^{3+}, Os^{3+}, Rh^{3+}, Al^{3+}, Co^{3+}, V^{4+}, Re^{5+} and Mo^{5+}) into TiO_2 photocatalyst. In all cases, they used 0.5% of dopant concentration. He found that Fe^{3+}-doped TiO_2 showed maximum efficiency, while Al^{3+} and Co^{3+} doping caused decrease in efficiency. For the

degradation of rhodamine B in aqueous solution under visible light and UV, the photocatalytic activity of cerium-doped TiO_2 was investigated (Choi et al. 2002). Cerium doping improved performance with a maximum photocatalytic behaviour at a doping concentration of 0.2–0.4%. This facilitated formation of super oxide anion radicals and enhances the charge separation. However, overdoping of Ce causes adverse effect on photocatalytic activity (Tong et al. 2007). Similarly, using V^{5+}-doped TiO_2 synthesized by coprecipitation method showed decrease in photocatalytic activity, while using V^{4+} showed increase in photocatalytic activity (Martin et al. 1994).

Beside using metal dopants, many non-metal dopants also showed very good efficiency photocatalytic activity. Asahi et al. are considered to be the first people who reported the use of non-metal as a dopant and its significance of efficient overlap between dopant and band states of titania oxide (Asahi et al. 2001). In addition, Zheng et al. reported enhanced the photocatalytic activity by using N-doped TiO_2 nano-fibers and removing surface bonded N species via post treatment in air (Zheng et al. 2013). This makes top of nano-fibres to become efficient for absorbing organic molecule and improve activation for oxygen molecules. Boron was first documented by Zhao et al.; in this he prepared B-doped TiO_2 via sol-gel method with boric acid (Zhao et al. 2004). Band gap was shifted 2.93 eV through boron doping and lowered by the use of Ni-B-doping to 2.85 eV. Both B-doped and Ni-B-doped TiO_2 showed a large increase in activity relative to uncoupled TiO_2. Tailoring of TiO_2 with several other halogen elements are also referred in some articles. Iodine doped of TiO_2 was first reported by Hong et al. through tetrabutyl titanate hydrolysis in the presence of HIO_3 (Wu et al. 2018). Prepared samples are being used for photocatalytic phenol degradation, exhibiting photocatalytic activity under visible irradiation, 59% degradation after 2 h.

24.6.2 Effect of Co-catalyst Loading

Nobel metals and transition metals are most commonly used co-catalyst for photocatalytic hydrogen generation. When loading of metal co-catalyst is done in to photocatalyst, generated e^- start moving towards the surface of photocatalyst which get interrupted by the co-catalyst due to low E_F level of noble metal than parent photocatalyst (shown in Fig. 24.9). Meanwhile the generated h^+ remains in the parent photocatalyst and moves towards the surface. Subsequently, this process creates two separate half reactions oxidation and reduction. Loading of co-catalyst on semiconductor is necessary as it reduces the overvoltage for oxygen and hydrogen evolution systems. Different transition metals are being employed to enhance the photoreduction of the proton (Matsumura et al. 1983). These co-catalysts lower down the activation energy for the hydrogen generation and capture the generated electron to suppress the charge carrier's recombination rate (Maeda et al. 2007a; Jang et al. 2008). Till date most used co-catalyst are transition metal oxides (Lu and Hwang 2011; Husin et al. 2011), Pt (Zou and Arakawa 2003), Ru (Hara et al. 2003), NiO

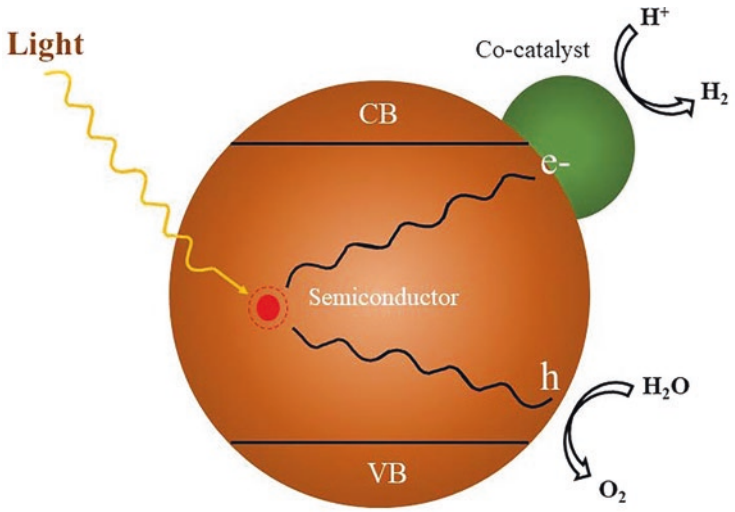

Fig. 24.9 Charge transfer between co-catalyst and photocatalyst

(Hu and Teng 2010), Co_3O_4 (Long et al. 2006), Rh (Long et al. 2006), Pd (Sayama et al. 1998) and Au (Jin et al. 2006). It has been seen that without co-catalyst many of the photocatalyst doesn't shows hydrogen generation. Compared to the photocatalyst/solution interface, the barrier height of the photocatalyst/noble metal interface is thin, enclosing effective charge separation of photogenerated electrons and holes (Daskalaki et al. 2010; Prousek 1996). Nozik designed a system as Schottky-type photochemical diode (Nozik 1977). Later, Sathish et al. stated that there exists a dependency in transition metal properties and the rate of development of hydrogen (Sathish et al. 2006). The most promising candidates to drive the reaction are the co-catalyst metal having more redox potential and work function and weak metal-H bond strength. Jang et al. developed platinized CdS/TiO_2 photocatalyst using different methods such as photo deposition, wet impregnation and chemical reduction. He found that Pt fabricated by PD showed very less photocatalytic activity because part of Pt resides inside CdS, whereas all other Pt located at surface of TiO_2 nanoparticles particles in case of WI and CR. Domen et al. were first to perform water splitting using NiO-loaded $SrTiO_3$ powder (Domen et al. 1982; Domen et al. 1986). NiO for hydrogen evolution is activated by reducing hydrogen and oxidizing oxygen to make NiO/Ni dual layer which supports e^- movement from parent photocatalyst to co-catalyst (Maeda et al. 2006a). They also introduced a new co-catalyst, Rh-Cr metal oxide ($Rh_{2-y}Cr_yO_3$) nanoparticles, that improves the decomposition of water (Maeda et al. 2006b; Maeda et al. 2007b). Dispersion of $Rh_{2-y}Cr_yO_3$ nanoparticles on $(Ga_{1-x}Zn_x)(N_{1-x}O_x)$ (x = 0.12; GaN:ZnO) produced an effective catalyst for H_2 production (Maeda et al. 2006a; Maeda et al. 2007b).

24.6.3 Dye Sensitization

The dye-based sensitization is utilized variably because of its visible light utilization which would be helpful for conversion. Some unique property-based dye which has redox and viewable light responsivity property could be utilized widely in solar cells and photo splitting activity. Whenever light is illuminated, the dye gets excited and sends the e^- to E_{CB} of the semiconductor as illustrated in Fig. 24.10 which in return helps in starting the catalytic reaction (Ni et al. 2007). In this process, the dyes potential energy level should be higher than that of semiconductor so as to inject electron to that particular semiconductor (Nahak et al. 2021; Mondal et al. 2011; Mahata et al. 2015). The significance of dye is that it utilizes the visible light of sun which has more effect compared to that of UV light (Mahata and Kundu 2009).

There is low production in hydrogen if the semiconductor is absent as this acts as charge separators. The excited electrons can transfer to noble metals whose prime target is to start the water reduction reaction. To continue the reaction cycle electron-rich components like iodine pair, EDTA can be used in the solution (Mahshid et al. 2007). It follows a following reaction which is expressed:

$$dye \xrightarrow{hv} dye^*$$

$$dye^* \xrightarrow{TiO_2} dye^+ + e^-$$

$$dye^+ + e^- \rightarrow dye$$

For increasing the efficiency of converting into electrical energy or hydrogen energy, flow of electron injection should be high, and backward reaction should be low, which perfectly combines the electron and hole ratio (O'regan and Grätzel 1991; Dhanalakshmi et al. 2001). The fast injection and slow backward reaction make the dye-sensitization method suitable for the generation of hydrogen. The dye

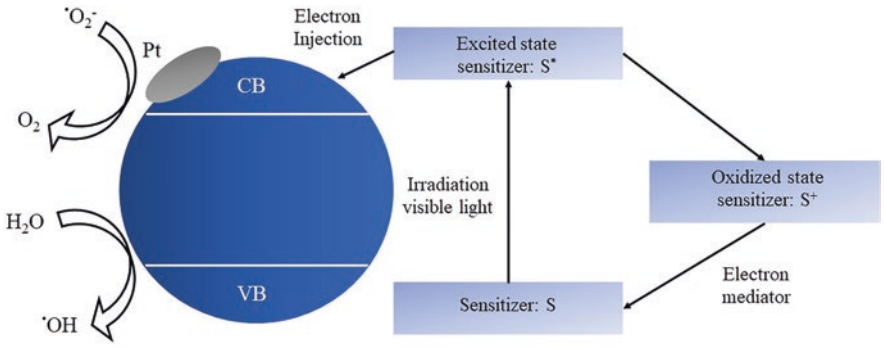

Fig. 24.10 Photo splitting activity of dye sensitized hydrogen generation process

molecules which are absorbed by the semiconductor could effectively inject electrons to the semiconductor for photocatalytic activity. By the help of maxima wavelength, it is not possible to say which dye will be helpful for energy generation which may be due to electron injection into the semiconductor (Gurunathan et al. 1997). Further research is required to understand charge injection dynamics of different dyes for better understandings.

24.7 Operating Conditions Affecting the Photocatalytic Hydrogen Generation

24.7.1 Particle Size

Morphology of photocatalyst such as agglomerate and particle dimension is one of the key factors affecting the process of photocatalysis. In photocatalytic dye-degradation, there exists a relation between photocatalyst morphology and the organic compound; thus, particle size of the synthesized photocatalyst plays a vital role in it. Particles having smaller size possess many active sites at their surface. These active sites absorb molecules of water, that is further reduced by photogenerated electrons. Smaller particles minimize diffusion length from their core to the bulk of surface photocatalyst for photogenerated electron and hole pairs (Liu et al. 2008; Kumar and Pandey 2017).

24.7.2 Surface Area

Many studies show that anatase TiO_2 having higher crystallinity and large surface area is more suitable for hydrogen generation (Jitputti et al. 2007). It becomes important to control thermal treatment of the photoelectrode to maintain the proper crystalline of anatase phase. It is preferable to use anatase phase of TiO_2 with high surface area and crystallinity (Sreethawong et al. 2005; Sreethawong and Yoshikawa 2005; Jitputti et al. 2008; Leung et al. 2010).

24.7.3 Reaction Temperature

The reactor temperature is considered as important factor while studying on photocatalytic hydrogen generation. It is expected that temperature inside the reactor gradually increases due to continuous radiation of lamp. Rodriguez et al. reported that as they increased the reaction temperature, hydrogen production also increased. Photocatalytic efficiency improves with an increase in reaction temperature, but if

we increase temperature more than 80 °C, it starts promoting recombination of electron and hole pairs (Hashimoto et al. 2005).

24.7.4 Catalyst

Co-catalyst addition increases the overall hydrogen processing performance and accelerates the chemical reaction of the surface. The most widely used metals are Pd, Ru, Pt and Rh and meal oxides such as NiO and RuO_2. Amount of catalyst loaded at a certain solution volume will influence and improve the efficiency of hydrogeneration, and for different photocatalysis, the amount of loading varies. For instance, some catalyst shows optimum activity at 100 mg of catalyst, while others may show at 50 mg of catalyst Transition metals, especially noble metals, are considered as effective co-catalyst for photocatalytic reactions. When these metals are doped onto the surface of photocatalyst, the electrons (generated due to photon incident) starts migrating towards the surface of the parent photocatalyst. The noble metal is impeded here, as the noble metals' fermi level is often lower than the parent photocatalyst (Kumar et al. 2013). Meanwhile the h^+ stay at parent semiconductor photocatalyst, and then it starts migrating towards surface. Thus, a separation of charge carriers takes place, and separated e^- and h^+ will get involved in reduction and oxidation, respectively.

24.7.5 Effect of pH

pH plays a vital role in hydrogen generation in photocatalytic solutions. By adding NaOH, KOH, HCl, CH_3COOH, H_2SO_4 and HNO_3 to the solution, the solution's pH can be adjusted to a specific concentration. In order to explore more how pH affects the photocatalytic action, several experiments have been performed at different concentration of pH. It has been reported that hydrogen production gets increased at pH = 6–8 but decreases for pH = 9–10. This occurs due to the presence of sacrificial ions like HS^- to S^{2-} ions, etc. (Preethi and Kanmani 2014).

24.8 Photocatalytic Reactors

Apart from all other factors discussed in previous sections of the chapter, photocatalytic reactors also influence the rate of hydrogen production. An ideal photoreactor must distribute the light uniformly throughout the chamber so that each particle gets sufficient light radiation which results higher hydrogen generation efficiency. For water splitting applications and photocatalytic degradation by light irradiation,

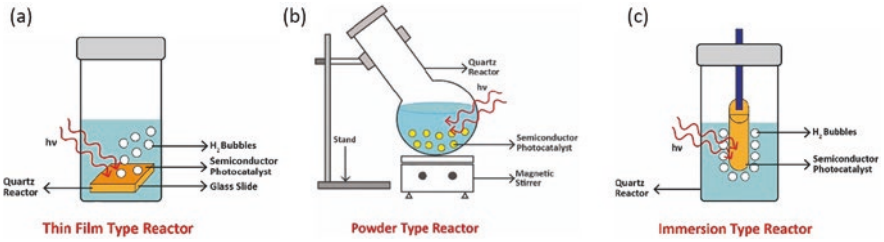

Fig. 24.11 Different types of reactors: (**a**) thin-film-type photocatalytic chambers, (**b**) immersion-type photocatalytic chambers, (**c**) powder-type photocatalytic chambers

various types of reactors may be used. These are usually categorized into two types: (1) thin-film-type photoreactors and (2) slurry-type photoreactors shown in Fig. 24.11 (Reddy et al. 2018).

24.8.1 Thin-Film-Type Photocatalytic Reactors

In reactors of these types, thin layer of the photocatalyst material is to be coated on the glass/metal slide and light is being irradiated on it. These reactors are not much effective and commercially used as compared to powder-type reactors, as only side of the glass slide interact with the light, while the other side gets very less amount of light on its surface. Hence, these reactor systems are so popularly used.

24.8.2 Slurry-Type Photocatalytic Reactors

Reactors of these types are much advantageous and also mostly used than thin film photocatalytic reactors. Further, slurry-type reactors are divided as (1) dispersion-type and (2) immersion-type reactors. Out of these two, dispersion types are very famous, since it contains the photocatalysts in powder form due to which each particle will come in contact with light and can actively take part in photocatalytic reaction, whereas in immersion-type reactors, photocatalyst is coated on a road-like shape and light is being irradiated from all the side, so that each surface will come in contact with light and can give maximum efficiency. These kinds of photoreactors are commonly used when both gas and liquid phase reactants come in, while the catalyst is solid phase.

24.9 Challenges and Future Perspective

In this chapter, we have discussed hydrogen as a good alternative for existing conventional energy source in near future. However, apart from these advantages, it also has some demerits; the nature of hydrogen is highly destructive, low density and highly reactive. Efficient generation and storage of clean hydrogen are commonly adopted as two key technical problems in extending the use of hydrogen. Today, renewable power-generating techniques such as biomass, tidal, hydro, solar and wind account for a very less percent of the world's overall power consumption (Guo et al. 2008). Further, there are some problem arises for refilling, evaporation loss occurs when hydrogen is transported from the reservoir to the tank through a transfer line which is cooled up to −253 °C. Due to difference of temperature gradient across the valves, there is evaporation loss which cannot be supressed fully (Schüth 2009). However, there are some solutions that can minimize the loss during filling by using coaxial cryogenic connectors (Topsøe et al. 2004). Transportation of hydrogen is very expensive because the weight and cost of hydrogen storage container is very high and the containers are vacuum isolated and are coated with radiation shield up to 40 layers, which is quite difficult to assemble (Guo et al. 2008).

Hydrogen needs to be stored safely and effectively to use as an energy carrier, particularly for vehicle applications. Hydrogen storage on board a vehicle can be seen as a key to the fuel cell's commercial success. The key challenge is the storage of adequate hydrogen on board and also provide equivalent driving range of 300 miles without sacrificing passenger or cargo space with regard to vehicle safety, weight, length, performance and cost constraints (Chalk and Miller 2006). It can be stored as gaseous or liquid or an atomic form as of a hydride. Another key challenge for hydrogen generation is the separation of hydrogen processes like hydrolysis and reforming. The cost of generation of hydrogen is too high.

Semiconductor-based photocatalysts has been considered as a potential material for renewable hydrogen generation (Topsøe et al. 2004). The studies upon this sector had taken many decades, in which the development of the photocatalysts and the efficiency has been focused. Those studies concluded regarding the metal doping, efficiency study in visible light, changes of band gap taken through some methods, capping and many more (Liao et al. 2012; Dvoranova et al. 2002; Ohno et al. 2003; Yanagida et al. 1995). Apart from all these, some conclusions were found, which can help this sector to implement future purpose at a large scale. Some assumptions are also taken which attracted interests to keep on the development on this.

One of them is large-scale implementation of photocatalytic water splitting over an area of 5 Km × 5 Km which can produce 570 tons of hydrogen a day, which can cover up to one-third of the energy requirements of future generations (Soltani et al. 2013). Some studies are going on for more development in heterogeneous photocatalysts which efficiently increases the production of hydrogen; some are trying to develop an inexpensive water splitting reactor in which a thin film with solutions and photocatalysts will generate hydrogen (Maeda and Domen 2010; Wang et al. 2019). The consequences of all these studies had come one by one, and this impacts

on the future studies upon this sector, which may ensure an industrial-level acceptable way to hydrogen generation for various of applications (James et al. 2009; Takata and Domen 2019; Chowdhury et al. 2017).

24.10 Applications of Hydrogen Generation

In these chapter, we discuss about the hydrogen generation; here a question arises in everyone's mind, why only hydrogen? As we have studied from our childhood that our earth's atmosphere consists of direct hydrogen of 0.000055% and indirectly consist of 99.96% in the form of water, compounds, etc. Due to its abundant availability, we choose hydrogen for various applications. The "G20 Karuizawa Innovation Action Plan on Energy Transitions" and "the Global Environment for Sustainable Growth" was launched on 16 June 2019 by the International Renewable Energy Agency (IRENA) to build future sustainable pathways to hydrogen-enabled clean energy (Du and Eisenberg 2012). Hydrogen is a rising star. Hydrogen enables the greater integration of renewable energy. The environment-friendly nature of hydrogen is taken into consideration; when it combusts, no CO_2 is exhausted as it releases heat and water as byproduct (Chalk and Miller 2006). It is used in vehicles, industry, electricity and transports for its decarbonizing nature. As a clean energy vector, hydrogen can easily transport and stored.

Hydrogen is versatile in nature and can be utilized in different ways. On the basis of their use, it is classified into two categories: one is feedstock and another as an energy vector (Deng et al. 2008).

24.10.1 Hydrogen as a Feedstock

In the current era of development, the attention is towards the renewable energy; that's why different industries used hydrogen in different industrial processes. The basic building block of manufacturing NH_3 is hydrogen; thus, around 55% of hydrogen produced in the world is used for the synthesis of ammonia (Balat and Balat 2009), 25% is used in refineries where it is used to process intermediate oil product, 10% is used for the methanol production, and rest of it is used for different worldwide application (Cheekatamarla and Finnerty 2006).

24.10.2 Hydrogen in Fertilizers Industries

Above we have studied that the majority of hydrogen produced is used in the production of ammonia or also known as azane, which is obtained by artificial nitrogen fixation process called Haber-Bosch process (Bogdanović and Schwickardi 1997).

This process employs high pressure to force chemical reactions; it fixes atmospheric nitrogen with natural gas hydrogen to create ammonia. The method uses large amount of pressure, since the N_2 are bound together by triple bonds (Weber et al. 2006). Haber-Bosch method uses a catalyst made of ruthenium or iron with an internal temperature of more than 800° F (426° C) and 200 atm pressure to unite nitrogen with hydrogen.

Hence, the outcome of these process is ammonia, which is used as a refrigerant in plants. The below image is the experimentation setup of ammonia by Haber-Bosch process (Asadullah et al. 2002).

24.10.3 Fuel Industry

The demand of crude oil is increasing drastically; to maintain the demand, more crude oil is extracted. The more the crude oil, the more the hydrogen for the refining of crude oil (Soria et al. 2006). Hydrogen is used as a catalyst to transfer crude oil to refined fuel like gasoline and diesel (Kalamaras and Efstathiou 2013). Hydrogen is used to remove contaminated element like sulphur. There are two processes of using hydrogen:

- Hydrocracking
- Hydroprocessing

Hydrocracking is the process of breaking and the hydrogenation of hydrocarbons to produce refined fuel with higher H/C ratio, whereas in hydroprocessing, the sulphur and the nitrogen compounds are hydrogenated and produce H_2S and NH_3 as a waste (Weber et al. 2006).

24.10.4 Methanol Production

Methanol is the widely used chemical, it is widely used in different field like production of acetic acid and formaldehyde, and it is also used as an antifreeze element (Ni et al. 2006); it is also used in the production of hydrocarbons (Suelves et al. 2005). In the presence of high pressure and temperature, hydrogen reacts with carbon dioxide to form m ethanol (Asadullah et al. 2002):

$$CO_2 + 3H_2 \rightarrow CH_3OH + H_2O$$

24.10.5 Hydrogen in Electronics Industry

Hydrogen is used as a scavenger to reduce residual oxygen and to protect the device from the deposition of oxygen in the top layer so no damage occurs (Hohn and Schmidt 2001). It is also used in the epitaxial growth of polysilicon to reduce the silicon tetrachloride to silicon to obtain a pure silicon water (Ogden et al. 1999).

24.10.6 Hydrogen as a Fuel

Fuel is a basic demand in our day-to-day lives, without fuel we can't imagine the world. Fuel plays a vital role in the development of the country. It is used in different fields like logistic, transportation, electricity, etc., but there is a problem of using crude oil products (Ogden et al. 1999). The petroleum products release polluted gas when combusted (Zaluski et al. 2003). So, in order to overcome these circumstances, people are looking towards the alternative renewable energy (Asadullah et al. 2002). For this, hydrogen is considered as a fuel due to its abundant availability and ease of transportation and storage (Farrauto et al. 2003). Hydrogen can be utilized directly and indirectly as fuel. Directly means without further converting the hydrogen into different form, and it is utilized in combustion engine and fuel cell (Kordesch 1967). Indirectly means the molecular hydrogen is converted to gas, liquid or energy, and it is used like liquid hydrogen is used in the rockets and aircrafts.

24.11 Conclusion

This chapter addresses the main aspects of generation of hydrogen for the future society for increasing sustainability in the development of energy system. These approaches are discussed in the preceding sections; there are many other options which are explored for hydrogen generation, such as thermochemical water splitting, photochemical water splitting, photobiological water splitting, etc. While the key photocatalytic activity monitoring factors in semiconductor photocatalyst have been established, several aspects of the role of inorganic photocatalysts remain unknown. For the photocatalytic water splitting, compounds having electrons in d_0 cell (Ti, Zr, Nb and Ta) and d_{10} cell (Ga, In, Ge, Sn and Sb) both showed significant enhancement in performance. Oxides are dominant, but the response has also been shown to be catalysed by nitrides and chalcogenides. Most notably, the underlying mechanism for decomposing water into reduction and oxidation on the surface of the semiconductor has not been fully elucidated yet. There has been no complete analysis of the impact of variable material preparations and surface impurities on the catalytic activity of semiconductors. The growth of better photocatalysts will also benefit from recent developments in nanoscience. Quantum size effects can

now be used to refine both the electronic structure and nanostructure reactivity, while synthetic techniques can be used to monitor catalyst morphology down to the nanoscale in order to further improve the efficiency of photochemical water splitting systems. Further efforts to develop novel co-catalysts could provide additional breakthroughs in the acquisition of highly effective photocatalysts. Such scientific progress is currently underway alongside new technological directions for the preparation of photocatalysts and innovative processes for system development.

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Chapter 25
Recent Advances in the Synthesis of Heterocycles Over Heterogeneous Cerium-Based Nanocatalysts

Cong Chien Truong, Dinesh Kumar Mishra, and Hoang Long Ngo

Contents

Abbreviations

$(NH_4)_2Ce(NO_3)_6$	Ceric ammonium nitrate
$(NH_4)_2CO_3$	Ammonium carbonate
Brij35	Polyoxyethylene (23) lauryl ether
$Ce(NO_3)_3.\ 6H_2O$	Cerium (III) nitrate hexahydrate
$CeCl_3$	Cerium (III) chloride
CeO_2/ceria	Cerium (IV) oxide

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CH_3CN	Acetonitrile
CH_4	Methane
CO	Carbon monoxide
CO_2	Carbon dioxide
CTAB	Cetyltrimethylammonium bromide
$Cu(NO_3)_2$	Copper (II) nitrate
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethyl sulfoxide
$Eu(NO_3)_2$	Europium (III) nitrate
Luperox 101	2,5-Bis(*tert*-butylperoxy)-2,5-dimethylhexane
Lupersol TAEC	2-Ethylhexyl 2-methylbutan-2-yloxy carbonate
$Mg\ (NO_3)_2$	Magnesium (II) nitrate
MIL-101	Chromium terephthalate metal organic framework
NH_3	Ammonia solution
NO	Nitrogen (II) oxide
NPs	Nanoparticles
PEG 400	Polyethylene glycol 400
Pluronic 17R4	Poly(propylene glycol)-*block*-poly(ethylene glycol)-*block*-poly(propylene glycol)
Pluronic P123	Poly(ethylene glycol)-*block*-poly(propylene glycol)-*block*-poly(ethylene glycol)
PVA	Polyvinyl alcohol
PVP	Polyvinylpyrrolidone
$Zr(NO_3)_2$	Zirconium (II) nitrate

25.1 Introduction

Heterocycle is an important class of compounds in organic chemistry, which can be found in wide applications from natural to man-made products. In nature, numerous heterocyclic skeletons can be found in plant/marine metabolites, chlorophyll, genetic building blocks, vitamins, essential oils, enzymes and so on (Walsh 2015). Alternatively, novel synthetic compounds containing various heteroatoms and/or fused ring systems have been successfully constructed over the years (Taylor et al. 2016). For the assembly of complex molecules, these privileged structures turned out to be versatile and valuable building blocks in the synthesis of natural products (Carson and Kerr 2009; Majumdar and Chattopadhyay 2011), organic semiconductors (Zhao et al. 2017), high-density energy materials (Yin and Shreeve 2017), agrochemicals (Lamberth 2013), polymers (Lu 1998), etc. Due to the diverseness in architectural complexity, molecular functionality and bioactivity, the exploration of heterocycles is considered of great significance in medicinal chemistry (Fig. 25.1) (Gomtsyan 2012). For instance, the US FDA databases show that 59% of small-molecule drugs are composed of *N*-heterocyclic fragments (Vitaku et al. 2014). In addition, other top-selling heterocyclic pharmaceuticals are currently exploited as

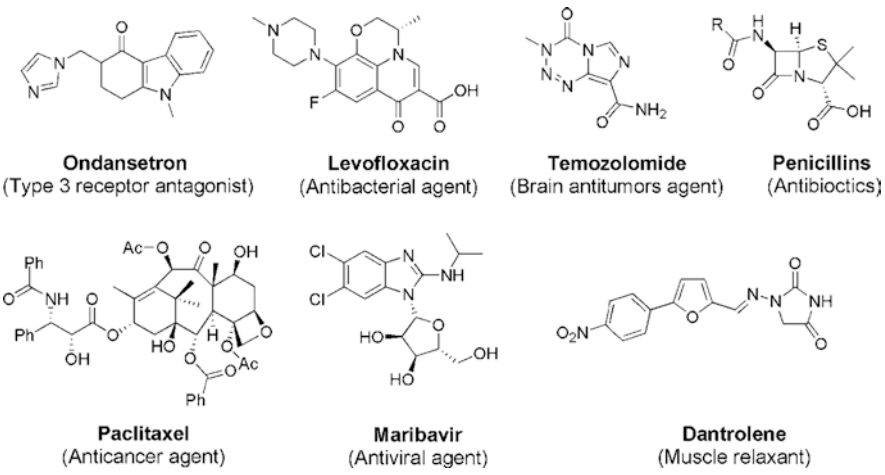


Fig. 25.1 Heterocyclic pharmaceuticals

anticancer, antibiotic, antiviral, antibacterial, diuretic and antineoplastic agents (Baumann et al. 2011; Baumann and Baxendale 2013; Ali et al. 2015; Feng et al. 2016; Delost et al. 2018). From these reasons, seeking simple but effective processes for the eco-friendly production of heterocycles has been considered as formidable challenges in both academia and industry throughout the years.

Recently, nanocatalysts have been widely acknowledged as powerful tools in the domain of heterogeneous catalysis, where nanostructured metal oxides and their hybrid materials attracted significant attention due to their superb catalytic efficiency in many chemical transformations (Wang et al. 2009; Guo et al. 2014; Gadipelly and Mannepalli 2019). In this manner, simple preparation, excellent thermal/chemical stability, high surface area, tunable control of acidity/basicity, low cost and recyclability are conducive to their versatility. Among the rare earth metal-based nanoparticles, most of the researches focused on the application of cerium-based materials as both catalyst and support due to the abundant, unique and tunable features of cerium (Sun et al. 2012; Zhang et al. 2012; Paier et al. 2013; Huang and Gao 2014). For example, the oxygen vacancies and reversible valence change (Ce^{4+} and Ce^{3+}) in CeO_2 allowed this nanostructure to participate in copious reactions such as oxidation, hydrogenation, methane reforming, water-gas shift, CO_2 conversion and others (Chang et al. 2019; Rodriguez et al. 2017). Moreover, the outstanding catalytic performance of ceria-supported transitional metals (e.g., Pd, Pt, Rh and Au), cerium mixed oxides, or cerium-doped solid materials in CH_4/CO/NO oxidation (Cargnello et al. 2012; Colussi et al. 2009; Spezzati et al. 2017; Qi and Li 2015), ozonation (Orge et al. 2012; Xu et al. 2016), hydrogenation (Akbayrak 2018; Hu et al. 2018) and photochemical reactions (Channei et al. 2014; Fiorenza et al. 2016; Shi et al. 2011) was also realized. Prompted by aforementioned reasons, several research groups have recently turned their keen eyes on the utility of cerium-based solids in organic chemistry (Vivier and Duprez 2010; Naaz et al. 2019), where

the acid/base, redox or dual (acid/base-redox) sites on these heterogeneous catalysts served the crucial roles in determining the activity. To the best of our knowledge, a holistic overview on the practicality of cerium-based nanocatalysts in the construction and functionalization of heterocycles has not been reported. In this book chapter, numerous examples on the green and sustainable assembly of heterocyclic frameworks over well-defined cerium oxide/mixed oxides, cerium composites, cerium-doped solids and ceria-supported metals are introduced. In particular, the deployment of nanoceria in the chemical fixation of CO_2 towards valuable cyclic products is also explored. Furthermore, mechanistic description on each transformation is discussed in detail to give further insight on the activity of cerium-based nanocatalyst.

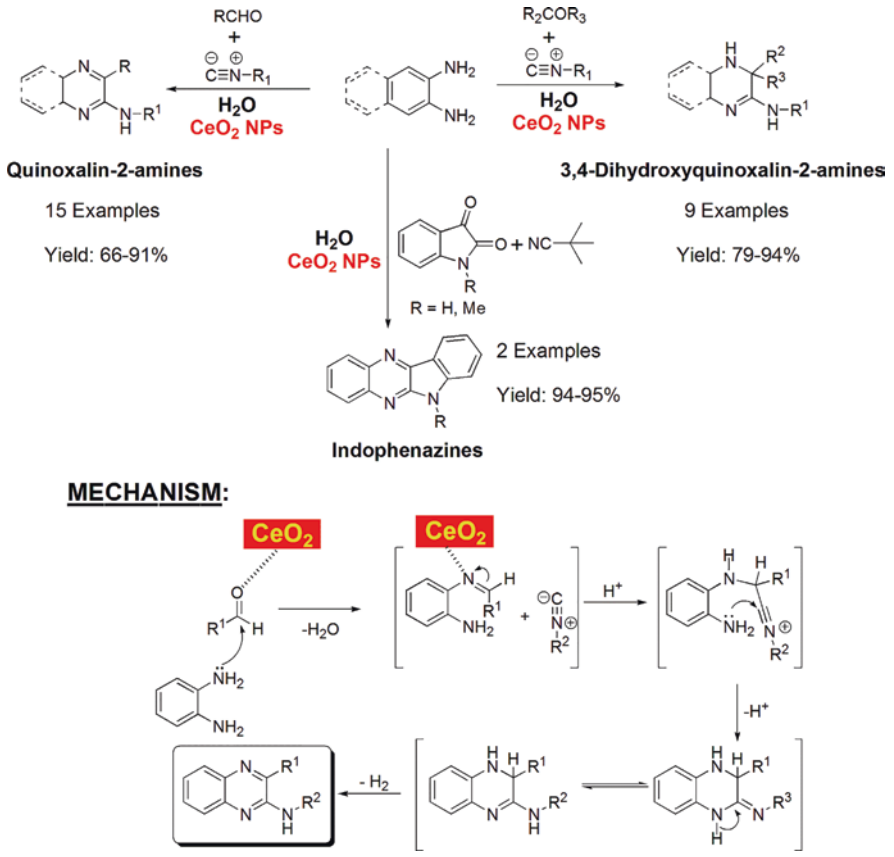
25.2 Applications of Cerium-Based Catalysts in the Synthesis and Functionalization of Heterocycles

25.2.1 Commercial CeO_2

In 2014, Edayadulla and Lee (2014) explored the catalysis of commercial CeO_2 NPs in the divergent synthesis of quinoxalin-2-amines and 3,4-dihydroquinoxalin-2-amines. By using 5 mol% of CeO_2, the one-pot condensation of 1,2-diamines, isocyanides with aldehydes or ketones could undergo smoothly in water to render a multiple of quinoxalin-2-amine and 3,4-dihydroquinoxalin-2-amine derivatives, respectively. Furthermore, the utility of CeO_2 NPs was also successfully attempted in the construction of indophenazine derivatives from the coupling of 1,2-phenylenediamine, isatins with *tert*-butyl isocyanide. The model mechanistic concourse towards quinoxalin-2-amine starting from 1,2-phenylenediamine, aldehyde and isocyanide is described to follow a cascade of imine formation/addition of isocyanide/annulation/isomerization/oxidation (Scheme 25.1), where CeO_2 NPs are demonstrated to facilitate the generation of imine and the insertion of isocyanide into imine.

Later, Shrestha et al. (2016) expanded the utility of CeO_2 NPs for the eco-friendly assembly of spiro[indoline-3,4-pyrano[2,3-*c*]pyrazole] derivatives. Under assistance of 30 mol% of CeO_2, a plenty of fused spirooxindoles could be afforded in the range yields of 75–93% from the aqueous-phase condensation of β-ketoesters with phenylhydrazines, malononitrile and isatins (Scheme 25.2). Particularly, a number of designed spirooxindole derivatives showed promising results on the potent antioxidant and antibacterial activities.

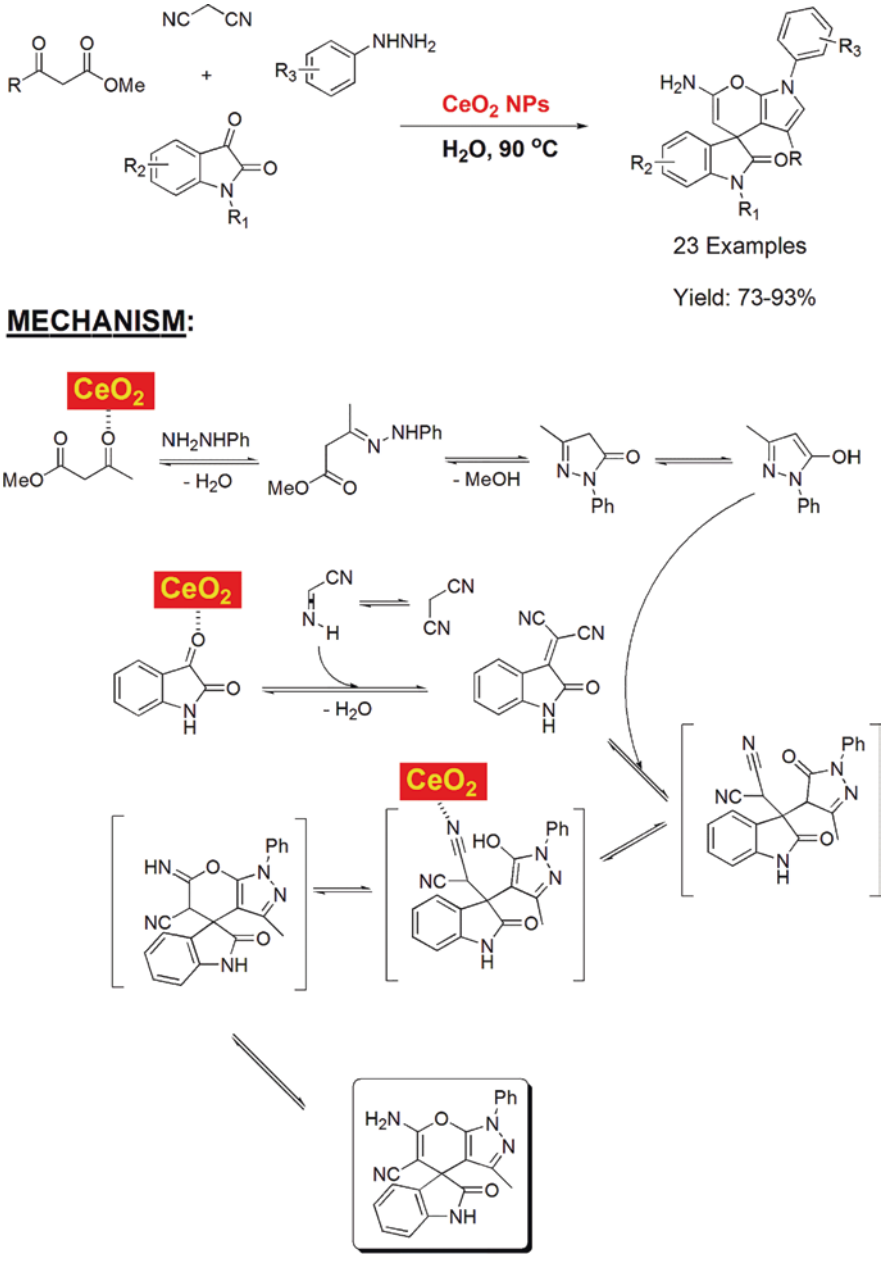
In another case, Sharma et al. (2018) established a novel synthetic strategy for fused tetrahydroisoquinolines and pyrrolo[3,4-c]quinoline-1,3-diones by coupling *N*,*N*-dimethylanilines **1** with *N*-substituted maleimides **2** over CeO_2 NPs. As shown in Scheme 25.3, tetrahydroisoquinoline derivatives with a high tolerance of functionality were obtainable upon performing the oxidative annulation of **1** and **2** with



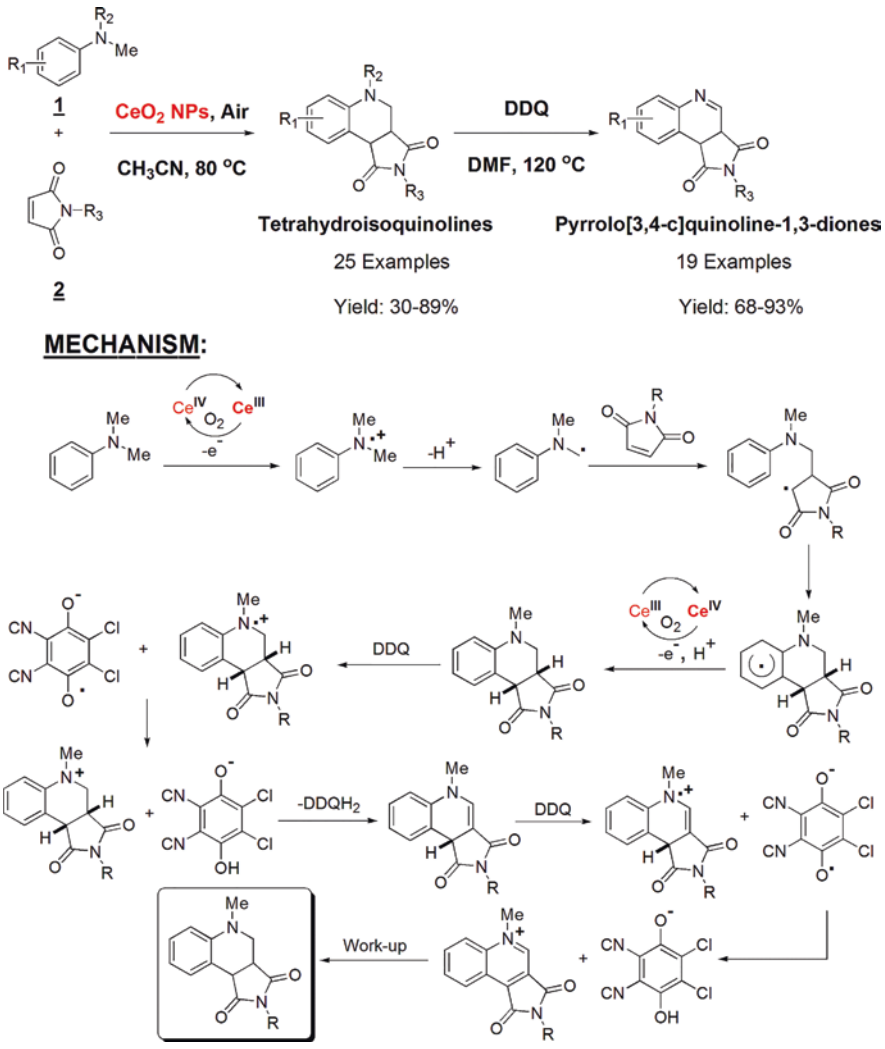
Scheme 25.1 Divergent synthesis of quinoxalin-2-amines, 3,4-dihydroquinoxalin-2-amines and indophenazines over CeO_2 NPs

20% mol of CeO_2 in air under optimal conditions. Afterwards, these resulting tetrahydroisoquinolines were efficiently transformed into quinoline-1,3-diones through the dehydrogenative/*N*-demethylative cascade in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). Unluckily, the activity of recovered CeO_2 NPs was found to gradually drop after four recycles. In the mechanistic proposal, the model assembly of pyrrolo[3,4-c]quinoline-1,3-diones is proposed to follow the sequential stage of oxidative annulation/dehydrogenation/*N*-demethylation.

Besides, CeO_2 was also exploited as a robust catalyst in functionalizing the heterocyclic skeletons. For example, CeO_2 NPs was effective in promoting the aerobic cross-dehydrogenative coupling (CDC) of *N*-aryl tetrahydroisoquinolines with either nitroalkanes or acetone, which delivered a collection of corresponding 1-sub stituted-2-aryl-1,2,3,4-tetrahydroisoquinoline derivatives (Sharma et al. 2016a). Through a set of control experiments, the model mechanism for the oxidative CDC of *N*-phenyl tetrahydroisoquinoline and nitromethane via radical pathway is



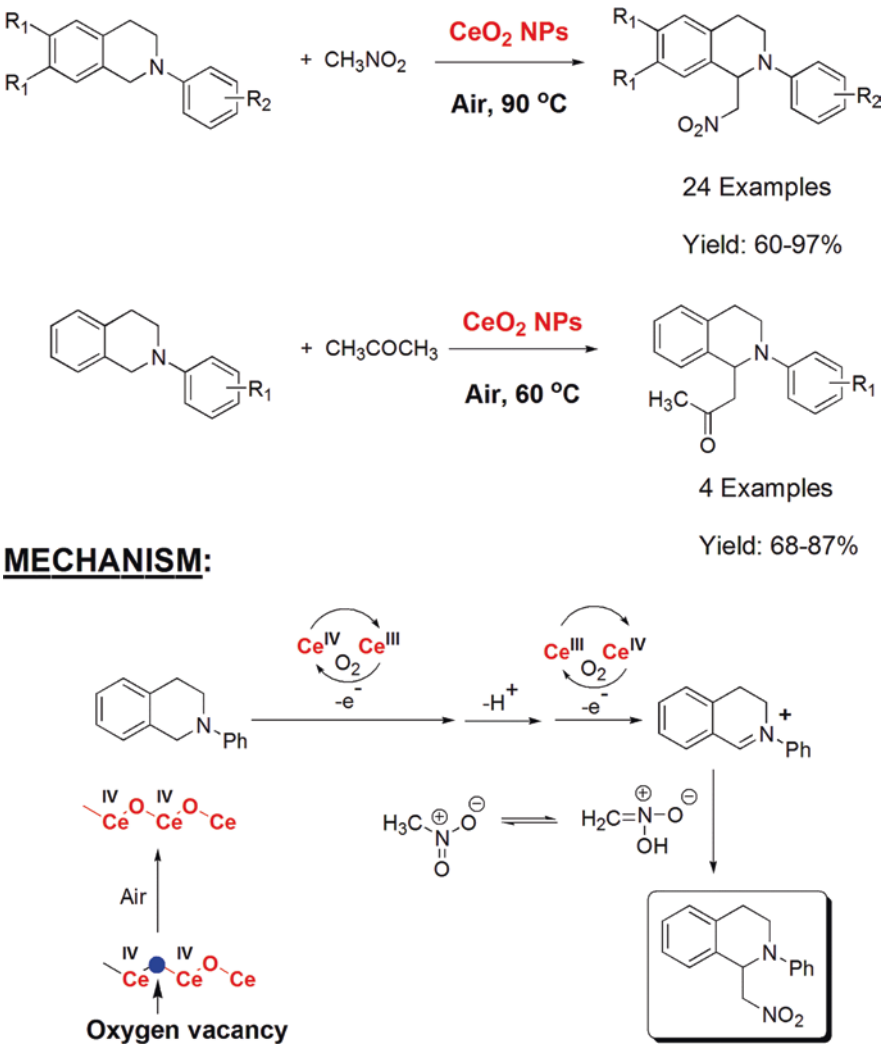
Scheme 25.2 CeO_2-mediated assembly of spiro[indoline-3,4-pyrano[2,3-*c*]pyrazole] derivatives in water



Scheme 25.3 Synthesis of tetrahydroisoquinolines and pyrrolo[3,4-c]quinoline-1,3-diones from the CeO_2/DDQ-mediated coupling of *N*,*N*-dimethylanilines and *N*-substituted maleimides

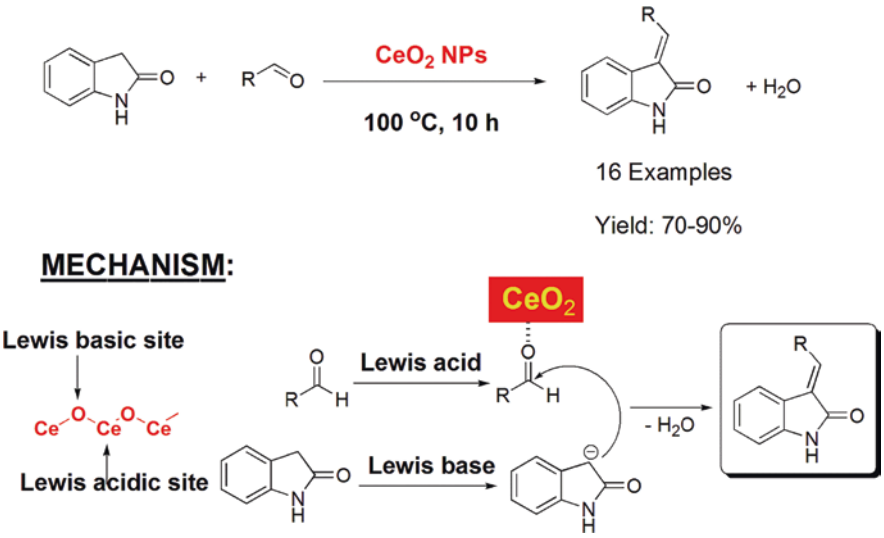
established in Scheme 25.4. In this context, Ce^{4+} would be transformed into Ce^{3+} and vice versa in the presence of O_2 during the single-electron transfer (SET) to facilitate the formation of iminium intermediate. Significantly, only a minor diminution in the yields of *N*-aryl tetrahydroisoquinoline was observed after four circulations of spent CeO_2.

In addition, Rashed et al. (2020) demonstrated that the commercial CeO_2 (JRC-CEO-1, 185.3 m^2/g) could stimulate the solvent-free alkenylation of oxindole with aldehydes (Scheme 25.5). Specifically, this synthetic protocol was applicable to



Scheme 25.4 Functionalization of *N*-aryltetrahydroisoquinolines with nitroalkanes and acetone over nanostructured CeO_2

both aliphatic and aromatic aldehydes, furnishing 87–99% yields of C_3-alkenylated oxindole products with high selectivity in *E* isomers. In this study, a close relationship between catalytic activity and morphology of CeO_2 calcined at different temperatures (i.e. 300, 500, 600, 800 and 1000 °C) was described. Surprisingly, the ceria with increasing calcination temperature would display higher catalytic activity despite their lower specific area, which might be attributed to the presence of non-defect (111) surface as active sites for the alkenylation reaction. Another reason came from the assumption that elevating the calcination temperature in the



Scheme 25.5 C_3-alkenylation of oxindole with aldehydes towards 3-alkyledene oxindoles over CeO_2 NPs

pretreatment stage led to a higher density of Lewis active sites. Indeed, the outstanding catalytic activity of nanostructured CeO_2 in this alkenylation was accredited to the bifunctional Lewis acid-base property, in which the basic sites (oxygen atom) would deprotonate the C_α-H bond of oxindole to trigger the corresponding enolate ion. Meanwhile, the acidic sites (cerium atom) would activate the carbonyl group of aldehyde, thereby enhancing the reactivity of C=O bond towards the nucleophilic attack of enolate.

25.2.2 Synthetic Nano-CeO_2

In nanotechnology, a plethora of techniques have been developed to fabricate the metal oxide nanoparticles (Table 25.1) (Rane et al. 2018). With each type of synthetic mode, the nanostructured oxides with different physical-chemical properties (e.g. particle size, porosity, defect, crystal structure, polarity and acidity/basicity) can be selectively controlled. In this regard, the reaction conditions such as starting precursors, capping agents, pH, ageing time/temperature and calcination temperature are key factors governing the outcome of final nanostructures. For instance, copious exemplars showing the impact of synthetic procedures on the specific morphology of CeO_2 NPs are illustrated in Table 25.2.

In this chapter, all of the reported nanostructured CeO_2 could be prepared from four main synthetic categories of co-precipitation, template, biological and sol-gel pattern.

Table 25.1 Synthetic techniques of nanoparticles

Synthetic modes of nanoparticles			
Co-precipitation synthesis	Sol-gel synthesis	Ultrasound synthesis	Laser ablation synthesis
Hydrothermal synthesis	Template synthesis	Microwave-assisted synthesis	Sputtering synthesis
Inert gas condensation synthesis	Microemulsion synthesis	Spark discharge synthesis	Biological synthesis

Table 25.2 Impact of synthetic methods on the morphology of CeO_2

Method	Cerium precursor	Capping agent	Particle size (nm)	Morphology	References
Precipitation	Cerium (III) nitrate	–	9–18	Cubic hexagonal	Chen and Chen (1993)
		PVP	27	Spherical	
Microemulsion	Cerium (III) nitrate	Hexamethylenetetramine	7–10	Spherical	Arya et al. (2014)
	Cerium (III) nitrate-Cerium (III) chloride	Brij35	6–13	Cubic	Bumajdad et al. (2004)
Hydrothermal	Cerium (III) nitrate	–	8–16	Cubes, rods	Arya et al. (2014)
	Cerium (III) chloride	Citric acid	<5	Spherical	López et al. (2015)
Biological	Cerium (III) nitrate	*Hibiscus sabdariffa*	3.9	Amorphous	Thovhogi et al. (2015)
	Cerium (IV) ammonium nitrate	Fructose/glucose/lactose	2–6	Spherical/ agglomerate	Kargar et al. (2015)
Sol-gel	Cerium (III) nitrate	Oleylamine	1.2–35	Spherical, tadpole, wire	Yu et al. (2005)

Co-precipitation (Guo et al. 2015) This is the most facile and convenient strategy to fabricate metal oxide nanoparticles by adding a precipitating agent (organic or inorganic bases) into the aqueous solution of metal salts at room or elevated temperature. As soon as the concentration of species present in the solution reaches the critical point, a cascade of nucleation/growth/agglomeration reaction will take place. In some cases, employing the surfactants and capping agents is necessary to selectively manipulate the physiochemical and catalytic features of the final metal oxides. Undoubtedly, multiple factors such as precursors, nature of bases, pH of the reaction medium, temperature, and stirring rates strongly influence the property of designed metal nanoparticles. For instance, Chen and Chang (2005) disclosed that increasing the temperature in the co-precipitation of $Ce(NO_3)_3.6H_2O$ with NH_3 led to a morphological change of CeO_2 particles from cubic to hexagonal, whilst lower-

ing the temperature induced the smaller size of ceria particles. On the other hand, the elevation of pH towards 12 in the reaction medium helped to decrease the crystallite size of CeO_2 (Ramachandran et al. 2019). Other influential factors in the co-precipitation for CeO_2 such as cerium precursors and precipitating agents are illustrated in the Table 25.3 as well. In fact, rapid, safe, low-cost, facile and organic solvent-free aspects are acknowledged as remarkable merits of this synthetic strategy.

Sol-gel synthesis (Parashar et al. 2020; Laberty-Robert et al. 2006) This model is associated with the rapid hydrolysis of metal-organic precursors in water and/or organic solvents to generate the corresponding metal oxo-hydroxides, which subsequently undergo the condensation to form an extended matrix of metal hydroxides. Next, the polymerization of these hydroxides will lead to the establishment of a dense network porous gel. Afterwards, the ultrafine porous metal oxides can be obtained upon drying and heating the gel at high temperatures. In this situation, the nature of both metal precursors and solvents considerably determines the morphology and particle size of final metal oxides. As an example, Yu et al. (2005) revealed that spherical CeO_2 could be triggered from the sol-gel treatment of $Ce(NO_3)_3.6H_2O$, diphenyl ether with oleylamine. On the other hand, the addition of oleic acid in this mixture resulted in wired or tadpole-like CeO_2 regarding to the amount of oleic acid. More examples on the sol-gel approach towards different CeO_2 NPs are depicted in Table 25.4.

Template-assisted synthesis (Yu et al. 2013) This technique mainly concerns with the deployment of hard/soft materials (e.g. carbon nanotube, alumina, zeolites, silica and polymers) as a host, where the nanoparticles will be fabricated and confined within the pores or channels of the template after calcination. By applying a proper choice of starting precursors, loading amounts and type of templates, it is able to render controlled-sized nanostructures with various morphologies (Table 25.5).

Table 25.3 Different types of nano-CeO_2 obtained from the co-precipitation

Cerium precursor	Precipitating agents	Particle size (nm)	Morphology	References
Cerium (III) nitrate	Ammoniac-ammonium bicarbonate	120–460	Spherical	Zhang et al. (2009)
	Sodium hydroxide	5	Rod	Du et al. (2007)
	Ammonia-hydrogen peroxide-hexamethylenetetramine	6	Cubic	Kamruddin et al. (2004)
Cerium (IV) ammonium nitrate	Urea	~8	Cubic	Tsai (2004)

Table 25.4 Different types of nano-CeO_2 obtained from the sol-gel strategy

Cerium Precursor	Medium	Particle size (nm)	Morphology	References
Cerium (IV) nitrate	Oleylamine-trioctylamine-diphenyl ether	1.2–3.5	Spherical, tadpole, wire	Yu et al. (2005)
Cerium (III) salts	PVA-sucrose	6–9	Cubic	Soni and Biswas (2013)
Cerium (IV) ammonium nitrate	CTAB-methanol-aniline	3.4–10.4	Sponge-like	Tillirou and Theocharis (2008)

Table 25.5 Different types of nano-CeO_2 from the template-directed synthetic pattern

Cerium precursor	Template	Particle size (nm)	Morphology	References
Cerium (III) nitrate	Carbon spheres	300	Hollow spherical	Xu et al. (2014)
Ammonium cerium (IV) nitrate	Polymethyl methacrylate	5	Tubular	Schneider et al. (2011)
Cerium (III) nitrate	Chitosan	~4	Cubic	Sifontes et al. (2011)

Biological synthesis (Malik et al. 2017) This synthetic mode involves the application of biological materials such as microorganisms (e.g. bacteria, fungi, yeast and algae), plant parts (e.g. leaves, fruit, flower, bark and seed) or sugars as natural reducing agents to assist the fabrication of nanoparticles. In the presence of these biochemical reductants, the metal ions from precursor salts are initially reduced to atoms which subsequently nucleate into small clusters. Originating from these metal clusters, the nanoparticles will grow in different manners depending on the concentration of metal ions, pH, reaction time, temperatures, and types of reducing agents. For example, the plate-like CeO_2 could be fabricated by employing fresh egg white (Kargar et al. 2015; Maensiri et al. 2007), in which ovalbumin/lysozyme (egg proteins) were demonstrated to serve the function of bio-capping/stabilizing agent. Alternatively, several investigations on the plant-mediated synthesis of CeO_2 NPs using the extract of *Hibiscus sabdariffa* flower, *Petroselinum crispum* leaf and *Olea europaea* leaf as phyto-chelating/capping agents were also reported (Thovhogi et al. 2015; Korotkova et al. 2019; Maqbool 2017). Additionally, Thakur et al. (2019) were able to produce spherical CeO_2 (5–20 nm) by using the culture filtrate of *Curvularia lunata*. As depicted in Table 25.6, various exemplars on the bio-directed fabrication of CeO_2 NPs are also introduced.

Table 25.6 Different types of CeO_2 NPs obtained from the biological synthetic pattern

Capping agent	Cerium precursor	Particle size (nm)	Morphology of NPs	References
Egg white	Cerium(III) acetate	6–30	Plate-like	Maensiri et al. (2007)
Gloriosa superba	Cerium(III) chloride	5	Spherical	Arumugam et al. (2015)
Ricinus communis leaf extract	Cerium(III) chloride	34	Irregular	Suvetha Rani (2020)
Honey	Cerium(III) nitrate	23	Cubic	Darroudi et al. (2014)
Aspergillus niger culture filtrate	Cerium (III) chloride	5–20	Cubic-spherical	Gopinath et al. (2015)

25.2.2.1 Nanostructured CeO_2 from the Co-precipitation Method

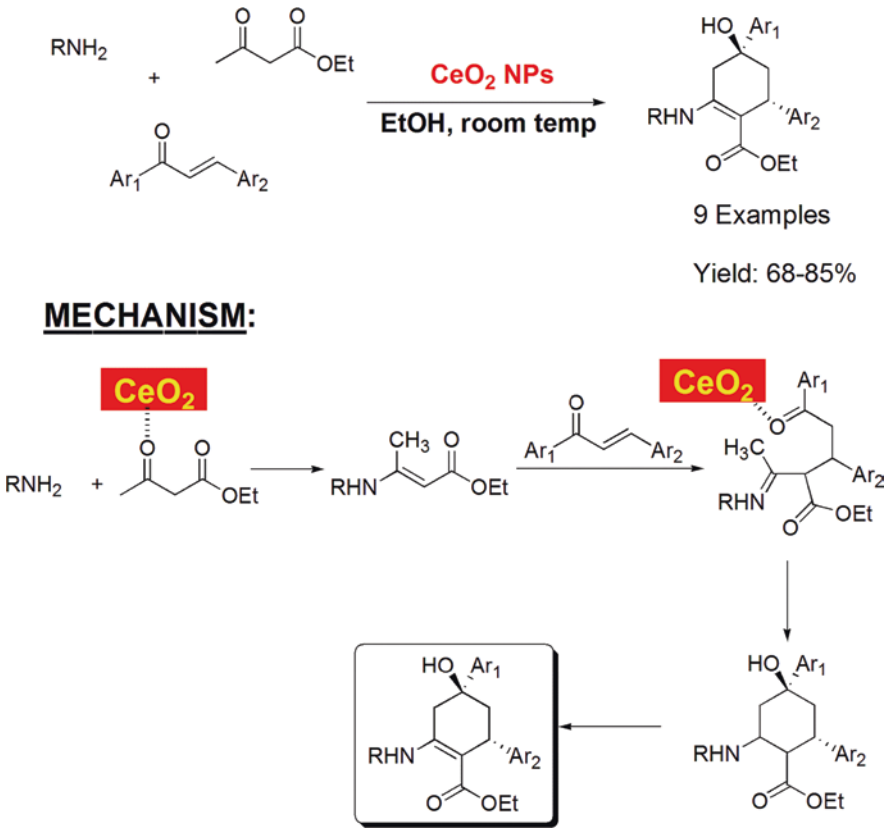
In 2015, Safaei-Ghomi et al. (2015a) reported the application of CeO_2 derived from the co-precipitation of $Ce(NO_3)_3.6H_2O$ with NH_3 as an effective nanocatalyst for the assembly of 2-aminocyclohex-1-ene-1-carboxylic esters (Scheme 25.6).

Later, the co-precipitated CeO_2 NPs was also deployed to facilitate the room-temperature synthesis of polysubstituted dihydropyridines from the four-component coupling of aromatic aldehydes, ethyl cyanoacetate, arylamines and dimethyl acetylenedicarboxylate (Safaei-Ghomi et al. 2015b). In this study, the CeO_2 with particles size of 11 nm showed the superior activity over other nanosized catalysts such as CaO (35 nm), ZnO (24 nm), CuO (40 nm), MgO (18 nm) and SnO (28 nm), therefore enabling for high yields of polysubstituted dihydropyridines. As shown in the Scheme 25.7, the CeO_2-mediated coupling followed a set of sequential reactions of Knoevenagel condensation/Michael addition/annulation/tautomerization.

Subsequently, a high-yielding process of C-tethered bispyrazol-5-ols from the CeO_2-mediated multicomponent condensation of dimethyl acetylenedicarboxylate, phenylhydrazine and aromatic aldehydes in water was described by Safaei-Ghomi et al. (2015c). In this setting, the excellent activity of lab-prepared CeO_2 NPs was attributed to the high surface area (33.2 m^2/g) with respect to that of bulk CeO_2 (5.2 m^2/g), CaO (1.2 m^2/g) and ZrO_2 (4.9 m^2/g). Another reason came from the high distribution of oxygen vacancies as Lewis acidic sites on the surface of lab-designed CeO_2 NPs. On account of these factors, the CeO_2 NPs was able to produce derivatives of C-tethered bispyrazol-5-ol in high isolated yields (Scheme 25.8).

Likewise, Safaei-Ghomi et al. (2016) also introduced CeO_2 as a recyclable nanocatalyst for the *mechanochemical* synthesis of 2-amino-4,6-diarylbenzene-1,3-dicarbonitriles. As depicted in Scheme 25.9, the CeO_2-mediated reaction is suggested to undergo a mechanistic sequence of Knoevenagel condensation/Michael addition/annulation/aromatization at room temperature.

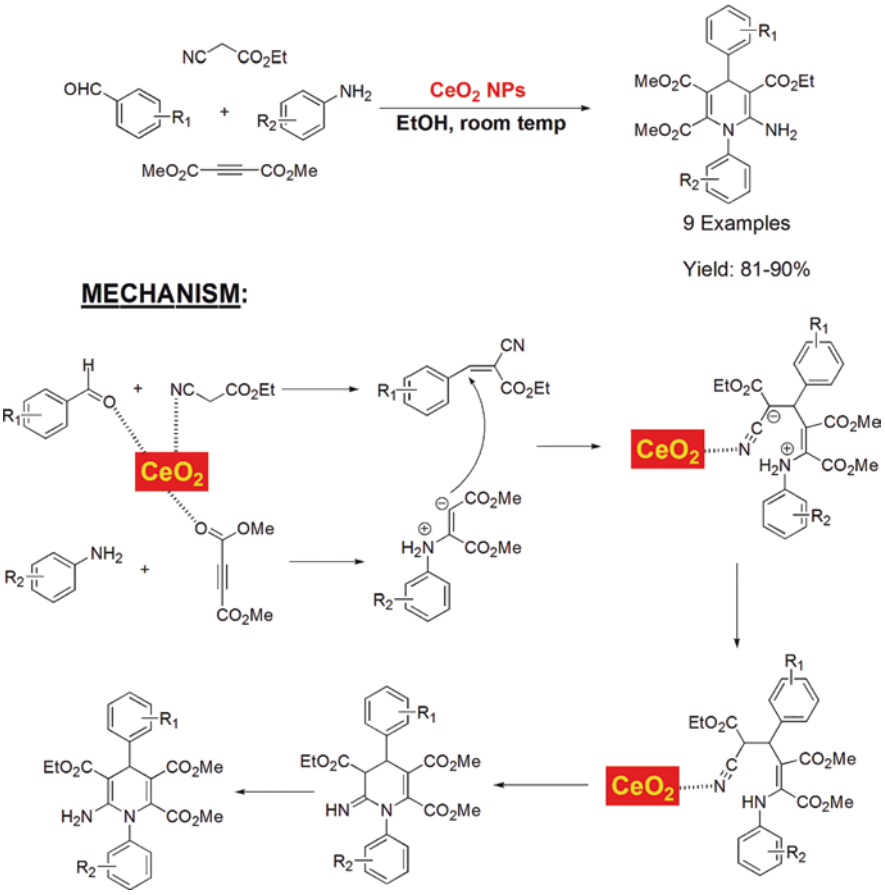
Later, D'Alessandro et al. (2015) described the usefulness of CeO_2 in triggering the solvent-free multicomponent Hantzsch reaction. Remarkably, it is revealed that a switchable construction of 1,4-dihydropyridine and 2-phenylpyridine could be



Scheme 25.6 Room-temperature synthesis of 2-aminocyclohex-1-ene-1-carboxylic esters over CeO_2 NPs

accomplished from the coupling of benzaldehyde, methyl acetoacetate and ammonium acetate under different temperatures. Remarkably, it is found that 97% yield of phenylpyridine was generated at 25 °C, while elevating the reaction temperature to 80 °C offered 75% yield of 1,4-dihydropyridine. In both cases, the recovered CeO_2 NPs could maintain the original activity after four consecutive trials. Similarly, Suresh et al. (2016) disclosed that a novel scaffold of fused triazolo/tetrazolo[1,5-*a*]pyrimidine could be assembled under the catalysis of CeO_2 NPs. In this manner, the CeO_2-mediated condensation of substituted aromatic aldehydes, benzoylacetonitrile with 5-aminotriazole/5-aminotetrazole, took place smoothly in water to generate two types of fused pyrimidine products. The catalytic role of CeO_2 NPs in this tandem Knoevenagel/Michael addition/intermolecular cyclization/intermolecular dehydrogenation reaction is clearly clarified in Scheme 25.10.

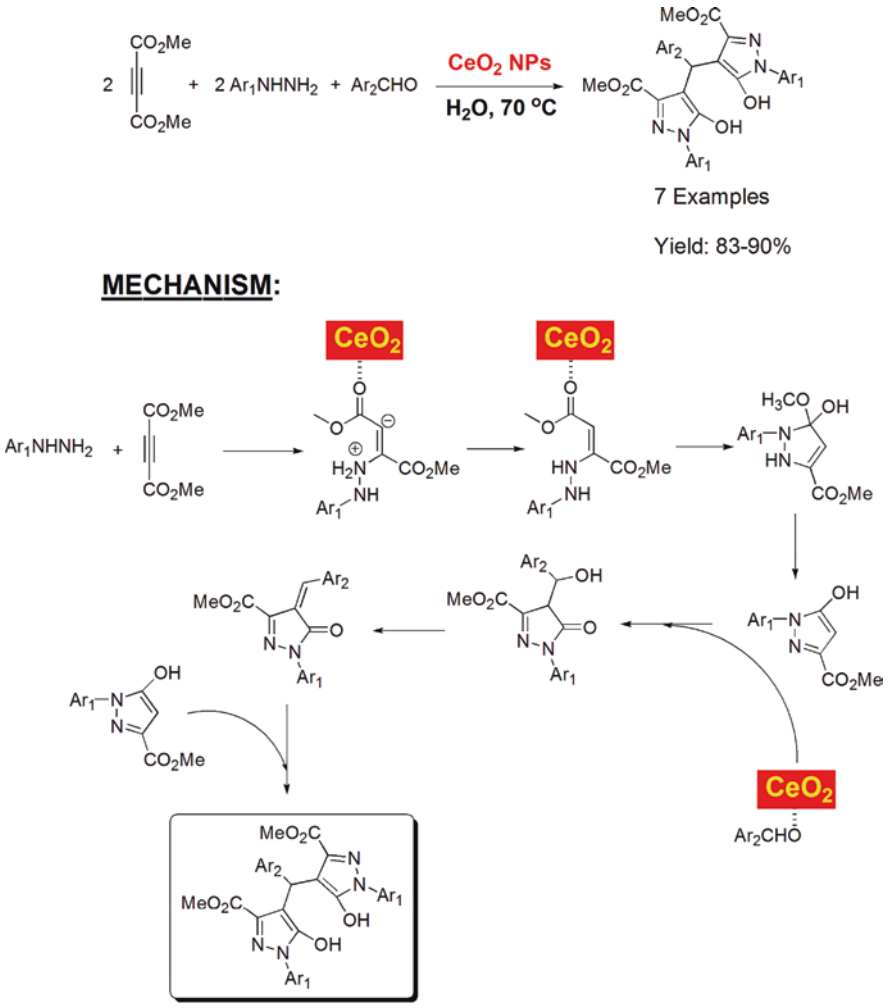
In another example, Gharib et al. (2013) fabricated the nanostructured CeO_2 by precipitating the aqueous solution of $(NH_4)_2Ce(NO_3)_6$ with NH_3. Thanks to the high surface area, the lab-designed CeO_2 was capable of promoting the *aqueous-phase*



Scheme 25.7 Construction of polysubstituted dihydropyridines over CeO_2 NPs

coupling of Lawsone reagent with 3-methyl-1-phenyl-1*H*-pyrazol-5-amine and substituted benzaldehydes under reflux condition. Accordingly, seven derivatives of 3-methyl-1-phenyl-1*H*-benzo[*g*]pyrazolo[3,4-*b*]quinoline-5,10-diones could be furnished in good to excellent yields (66–94.5%).

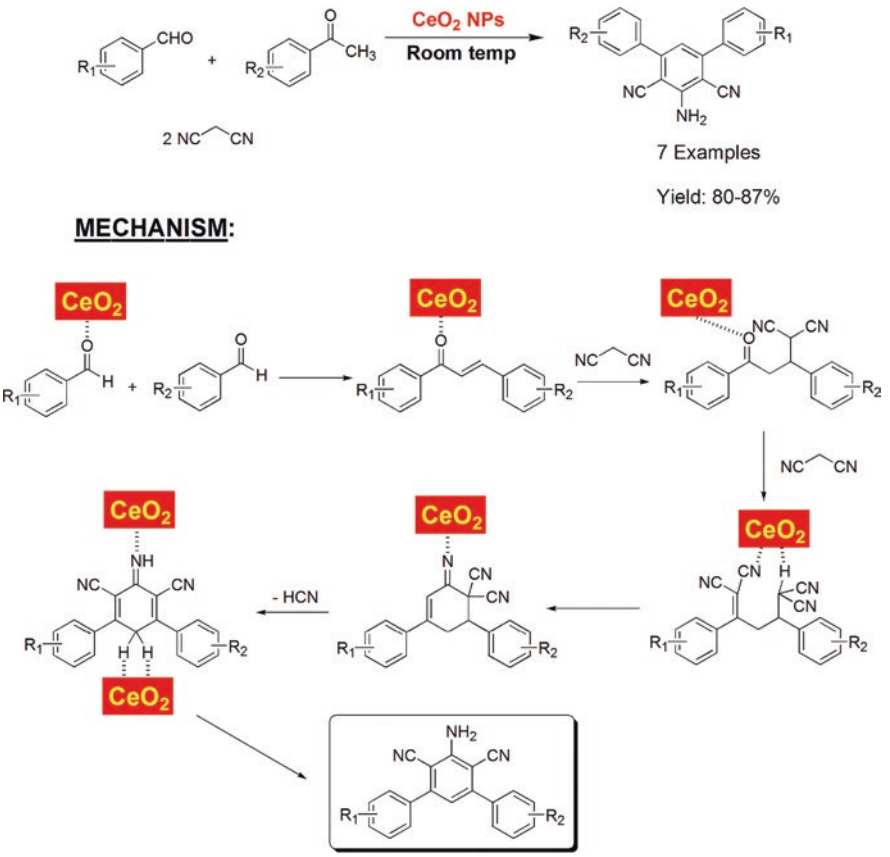
To construct the multiple heterocyclic scaffold of imino-pyrrolidine-thione, Wang et al. (2016) applied the porous CeO_2 nanorods obtained from the hydrothermal treatment of $Ce(NO_3)_3.6H_2O$ with $(NH_4)_2CO_3$ to mediate the coupling of 2-mercaptobenzoxazole/2-mercaptobenzothiazole with a mixture of substituted benzaldehydes, malononitrile and isocyanide. As illustrated in Scheme 25.11, the Ugi four-component condensation could run smoothly in a binary mixture of CH_3CN-H_2O (3:1, *v/v*) with 5 mol% of nanoporous CeO_2 to deliver a broad library of imino-pyrrolidine-thiones. Under identical condition, commercial and other synthetic CeO_2 NPs with different morphologies (i.e. linear, granular and fusiform) were found to give lower yield of coupling product with respect to the titled



Scheme 25.8 Construction of C-tethered bispyrazol-5-ols over CeO_2 NPs

nanoporous CeO_2. Unfortunately, the loss of oxygen storage in the spent CeO_2 was assumed to take place, thereby leading to a significant drop in the catalytic performance after the third recycle.

To address intrinsic drawbacks in the current manufacture of azole compounds (benzimidazoles, benzothiazoles and benzoxazoles), Shelkar et al. (2013) established a facile and eco-friendly strategy to construct these privileged skeletons upon employing CeO_2 nanocatalyst prepared from the surfactant-assisted co-precipitation under ultrasonic irradiation (Terribile et al. 1998). In comparison with other tested metal oxides (i.e. ZnO, TiO_2, MnO_2, SiO_2, Al_2O_3, La_2O_3 and Cu_2O NPs), the robust CeO_2 NPs displayed the preeminence in fostering high yields of benzimidazoles,

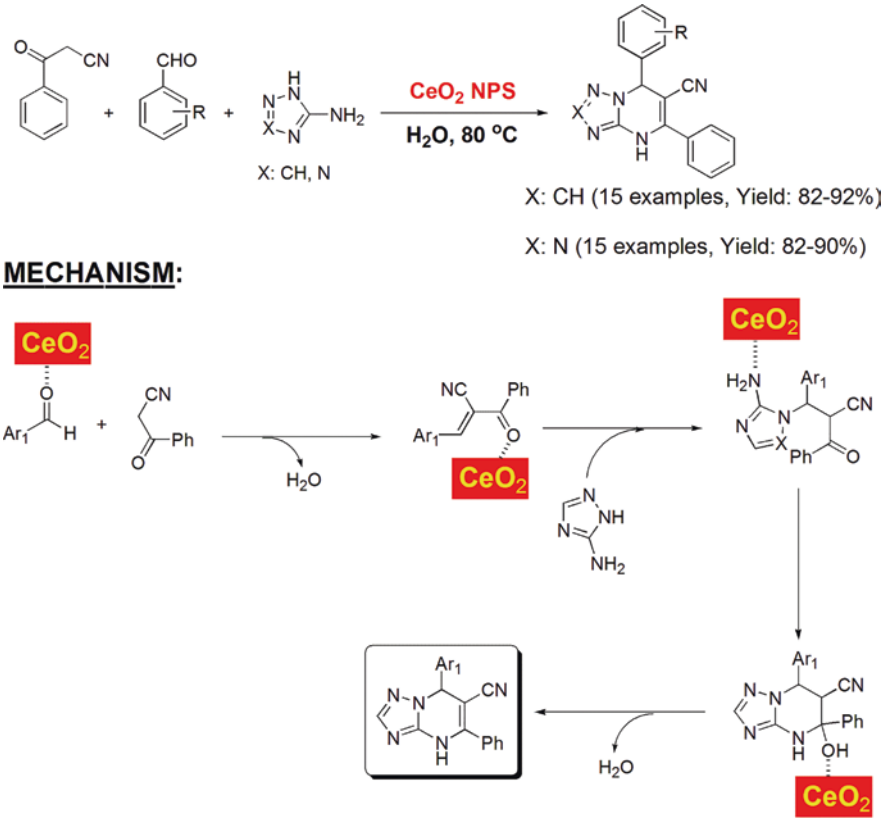


Scheme 25.9 Solvent-free access of 2-amino-4,6-diarylbenzene-1,3-dicarbonitriles over CeO_2 NPs

benzothiazoles and benzoxazoles from the aqueous-phase coupling of 1,2-phenylenediamine/2-aminothiophenol/2-aminophenol with aldehydes, respectively (Scheme 25.12).

25.2.2.2 Nanostructured CeO_2 from the Polymer-Directed Method

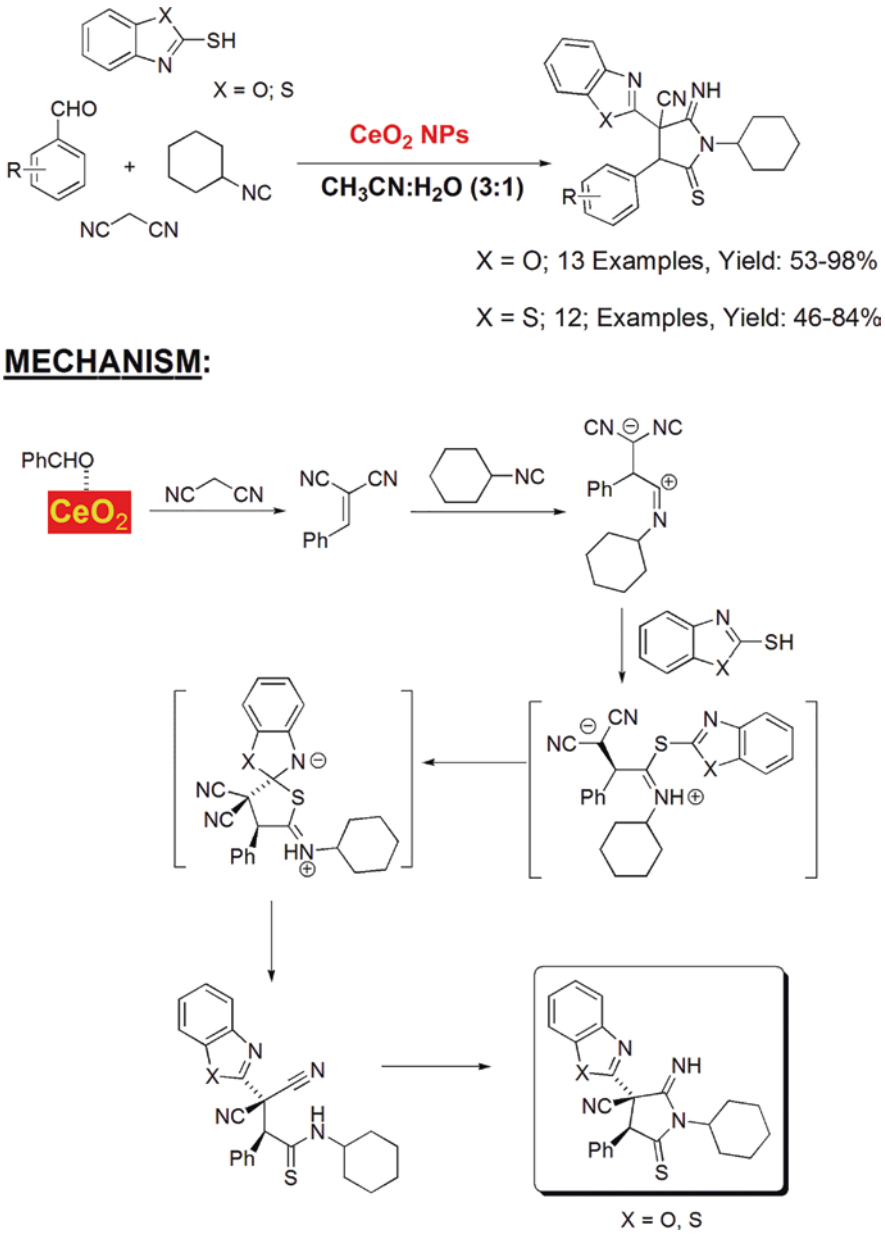
In 2011, Girija et al. (2011) fabricated the polymer-directed CeO_2 nanoparticles by treating the mixture of $(NH_4)_2Ce(NO_3)_6$, hexylamine and polyethylene glycol 6000 (PEG-6000) under microwave irradiation, which was then examined for the catalytic assembly of polyhydroquinolines. In this context, the solvent-free multicomponent condensation of aldehydes, ethyl acetoacetate, dimedone and ammonium acetate was carried out under the assistance of both microwave radiation and CeO_2 NPs, finally providing 88–97% yields of target polyhydroquinolines. However, a



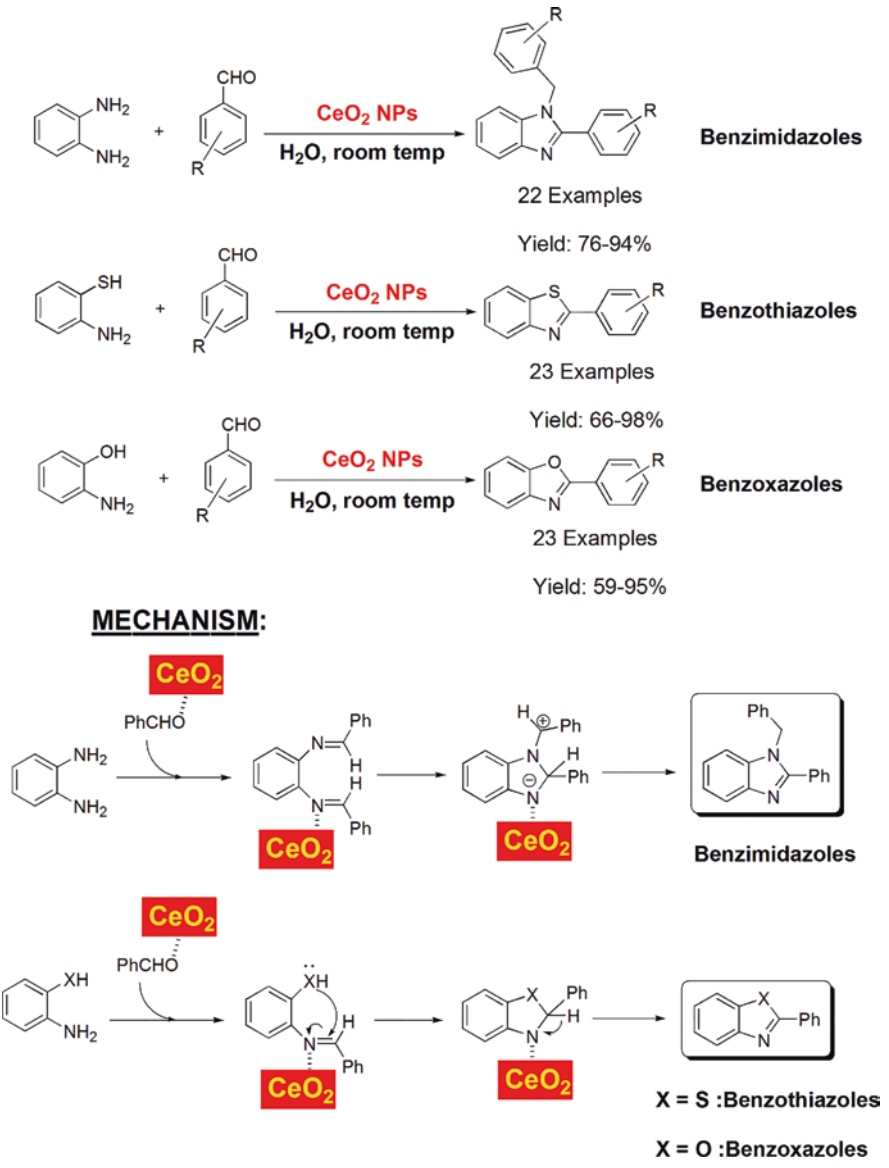
Scheme 25.10 Construction of fused triazolo/tetrazolo[1,5-*a*]pyrimidines over CeO_2 nanocatalyst

gradual loss in the catalytic activity of recovered CeO_2 was observed due to the slow oxidation of Ce NPs during the recycling trials.

By combining the reverse microemulsion system of bis(2-ethylhexyl) sulfosuccinate-lecithin-isooctane-water with different polymers of polyvinylpyrrolidone (PVP), block copolymer P123 or reverse block copolymer 17R4 as structural controller during the preparative procedure, Samai et al. (2016) were able to prepare a set of CeO_2 (i.e. CeO_2-PVP; CeO_2-P123; and CeO_2-17R4) with controlled nanoparticle sizes. Noticeably, it is uncovered that the relationship between the morphology and the catalytic performance of these titled nano-CeO_2 was intimately correlated with the directing polymeric agents. In this aspect, CeO_2-PVP with the largest surface area (58.0 m^2/g) displayed superior results in comparison with CeO_2-P123 (45 m^2/g) and CeO_2-17R4 (40.96 m^2/g) upon coupling nitrostyrene, 1,3-dicarbonyl compounds and aromatic primary amines. Accordingly, a collection of *N*-aryl pyrroles in the range yields of 59–77% was successfully produced over recyclable CeO_2-PVP nanocatalyst.



Scheme 25.11 Multicomponent synthesis of imino-pyrrolidine-thiones over CeO_2 nanoparticles



Scheme 25.12 Nano-CeO_2-mediated synthesis of benzimidazoles, benzothiazoles and benzoxazoles

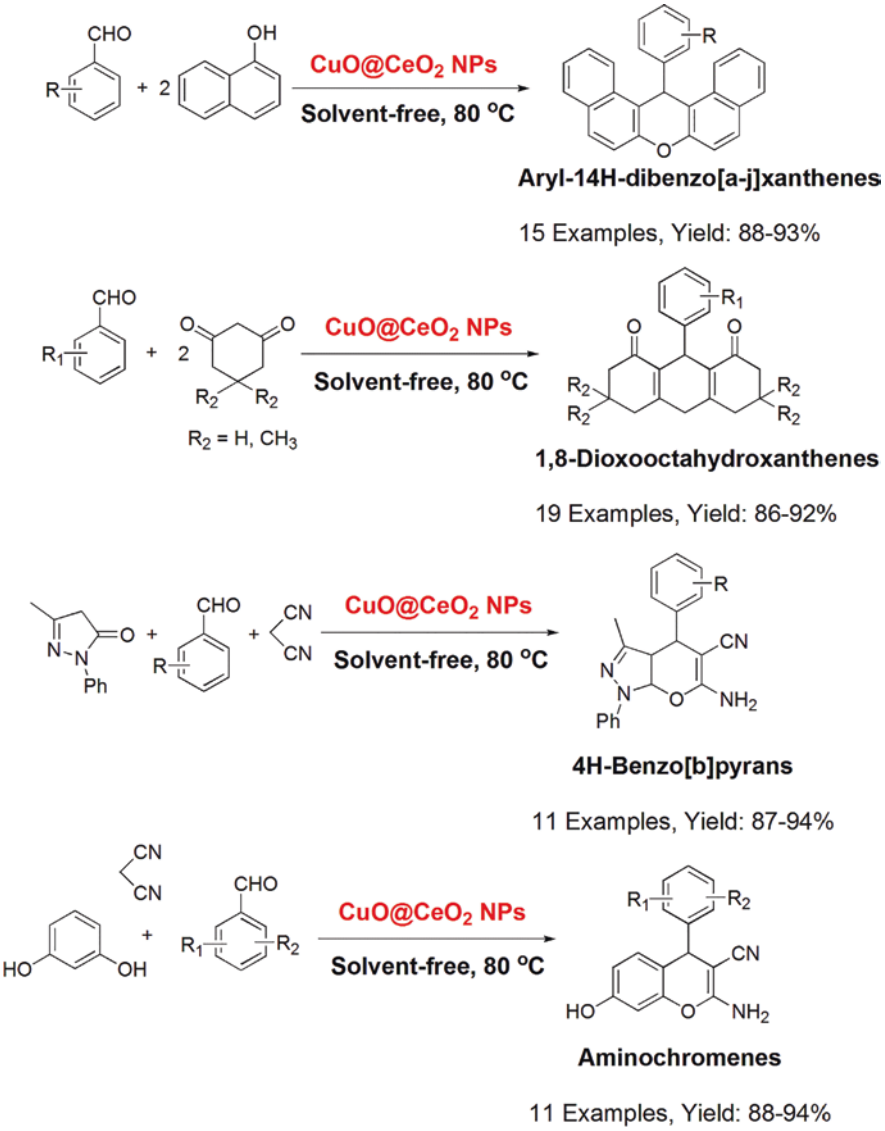
25.2.2.3 Nanostructured CeO_2 from the Biology-Directed Method

Recently, plant extracts or bio-based materials have been deployed as greener alternatives to chemical reductants/oxidants/precipitating agents (e.g. cetyltrimethylammonium bromide, polyethylene glycols, monoethanolamine, ammonium hydroxide

and polyvinylpyrrolidone) in the fabrication of ceria nanoparticles (Arumugam et al. 2015; Ferreira et al. 2016). With these nature-derived compounds, the preparative procedure can circumvent a complicated and tedious purification process (washing, calcination, Soxhlet extraction, etc.) to deliver organic-free CeO_2 NPs. Prompted by these examples, Zamani et al. (2018) explored the walnut shell powder to assist the fabrication of nano-CeO_2 in the absence of any surfactants or precipitating agents, in which the particle size could be tuned by controlling the ratio of Ce source/biomass. In this case, it is found that the presence of walnut shell as a cheap and green template is necessary to trigger smaller size of ceria, where the optimal ratio of Ce source/biomass was established at the ratio of 6.9:10. Hence, the resulting CeO_2 with a particle size of 9 nm was able to stimulate the aqueous-phase coupling of *o*-phenylenediamine and acetone with *tert*-butyl isocyanide at 80 °C to give 93% yield of 3,4-dihydroquinoxalin-2-amine.

25.2.3 Cerium Mixed Oxides

There are several documented methods for fabricating mixed metal oxides such as co-precipitation, wet impregnation, sol-gel, hydrothermal treatment, etc. (Courty and Marcilly 1976; Cousin and Ross 1990). In such cases, various true mixed oxides or solid solutions with the deposition of different metals can be readily composed to render a set of binary, ternary, quaternary or multiple-component mixed metal oxides, respectively. Undoubtedly, the mixed metal oxides display distinctive properties of acidity-basicity, oxidation-reduction, morphology (e.g. particle size, pore volume, surface area and defect) and thermal/chemical stability in comparison to pure metal oxides (Grzybowska-Swierkosz 1987; Wang et al. 2017). In addition, the bonding network between metals in mixed oxides allows the reagents to approach the active sites in an effective and selective manner, therefore increasing the yield and selectivity of the target products (Gawande et al. 2012; Burange and Gawande 2016). Thanks to these prominent features, the cerium-based mixed oxides have been widely deployed in the production of chemicals, organic synthesis, combustion of pollutants and energy applications (Orge et al. 2012; Shen et al. 2009; Zhang et al. 2018; Liu et al. 2019; Melchionna and Fornasiero 2014). For example, the nanocomposite of CeO_2-ZrO_2 obtained by the co-precipitation gave 90% yield of acetophenone from the deprotection of acetophenone oxime, whilst the pure CeO_2 only delivered 60% yield under identical condition (Deshpande et al. 2008). In another case, the catalytic activity of $Mn_3Gd_{7-x}Ce_x(SiO_4)_6O_{1.5}$ in the degradation of tetracycline was improved by the introduction of cerium in the structure, ascribable to the generation of active sites, the redox potential and an increase in the oxygen storage capacity (Fu et al. 2019). Likewise, Albadi et al. reported the practicality of CuO@CeO_2 nanocomposite for the construction of various heterocyclic structures through the multicomponent patterns (Scheme 25.13). Towards this end, the CuO@CeO_2 catalyst was composed from the co-precipitation of KOH with an aqueous mixture of $Ce(NO_3)_3$ and $Cu(NO_3)_2$. In the presence of CuO@CeO_2 nanocatalyst,



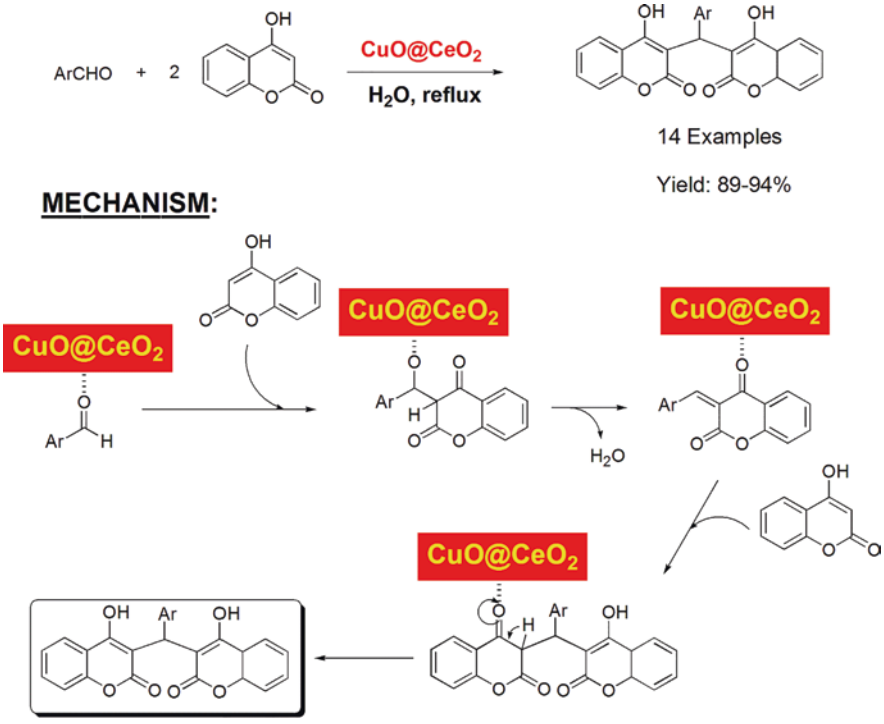
Scheme 25.13 Solvent-free synthesis of various heterocycles over $CuO@CeO_2$ nanocomposite

the solvent-free assembly of aryl-14*H*-dibenzo[a-j]xanthenes (Albadi et al. 2013a), 1,8-dioxooctahydroxanthenes (Albadi et al. 2013b), 4*H*-benzo[b]pyrans (Albadi et al. 2013c) and aminochromenes (Albadi et al. 2013d) was achievable with no difficulty.

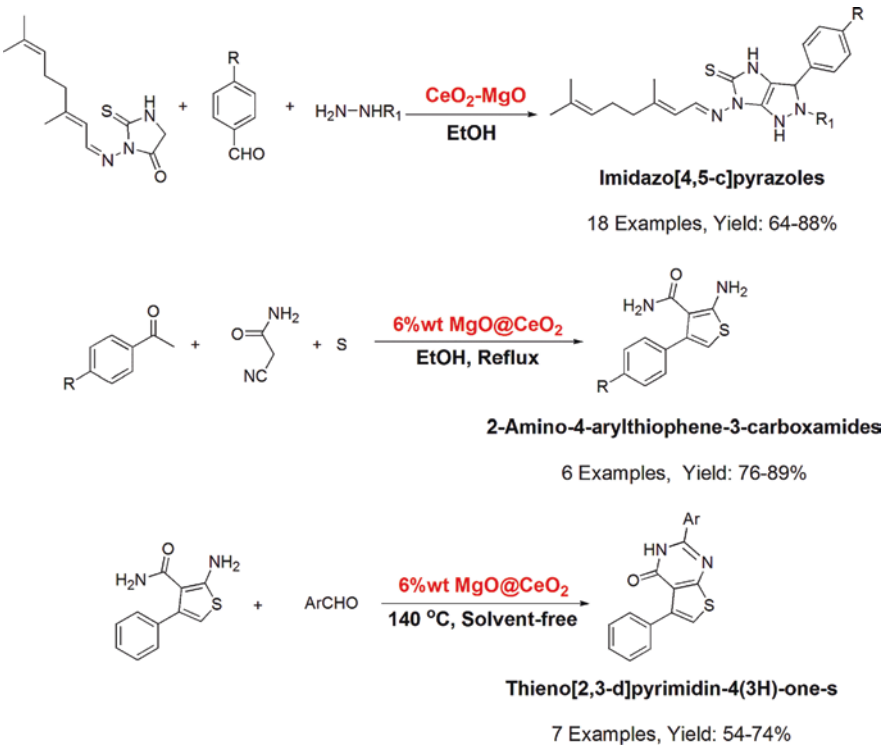
Besides, Albadi et al. (2014a) also applied the nanostructured CuO@CeO_2 as a heterogeneous Lewis acid to induce the assembly of biscoumarins from benzaldehydes and 4-hydroxycoumarin in water (Scheme 25.14).

To develop a benign protocol for 1,4-disubstituted-1,2,3-triazoles, Albadi et al. (2014b) deployed the amberlite-supported azide as an alternative source of azide ion and CuO@CeO_2 as a heterogeneous copper catalyst. In this regard, the CuO@CeO_2-mediated click synthesis of functionalized triazoles by refluxing a mixture of aryl terminal alkynes and α-bromo ketones/ benzyl bromides with amberlite-supported azide in ethanol could provide excellent isolated yields of various triazoles in an eco-friendly manner (13 examples, 88–92%). In such examples, it is verified that the robust CuO@CeO_2 with no leeching of Cu could retain the outstanding catalytic activity after several recycling trials.

Furthermore, the practicality of nanostructured MgO@CeO_2 as an active solid catalyst in the construction of heterocyclic skeletons was also recognized (Scheme 25.15). In this setting, a collection of imidazo[4,5-c]pyrazoles (Moydeen et al. 2017), 2-amino-4-arylthiophene-3-carboxamides and thieno[2,3-*d*]pyrimidin-4(3*H*)-one-s (Shafighi et al. 2018) could be furnished in a high efficacy. After several recycles, no significant loss in the performance of recovered MgO@CeO_2 was observed, indicating the robustness of this titled nanocatalyst during the transformation.



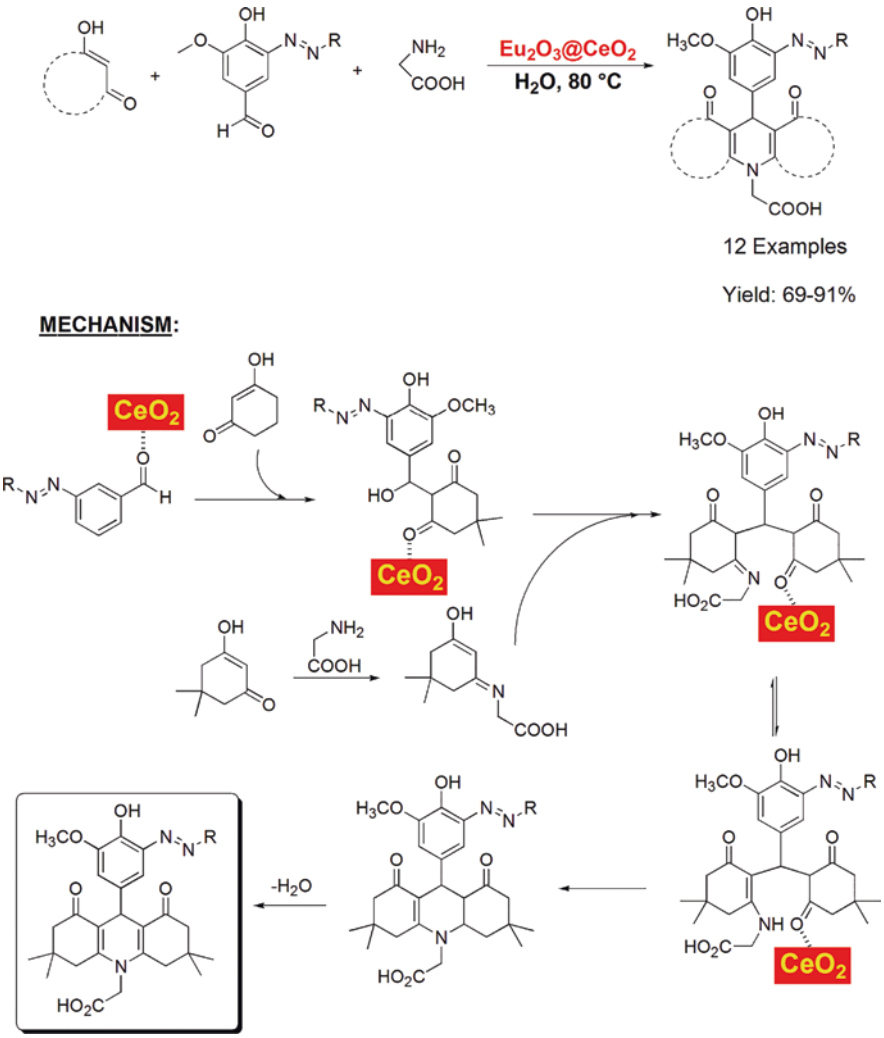
Scheme 25.14 Synthesis of biscoumarin derivatives over CuO@CeO_2 nanocatalyst



Scheme 25.15 Preparation of diversified heterocycles *over* $MgO@CeO_2$ nanocatalyst

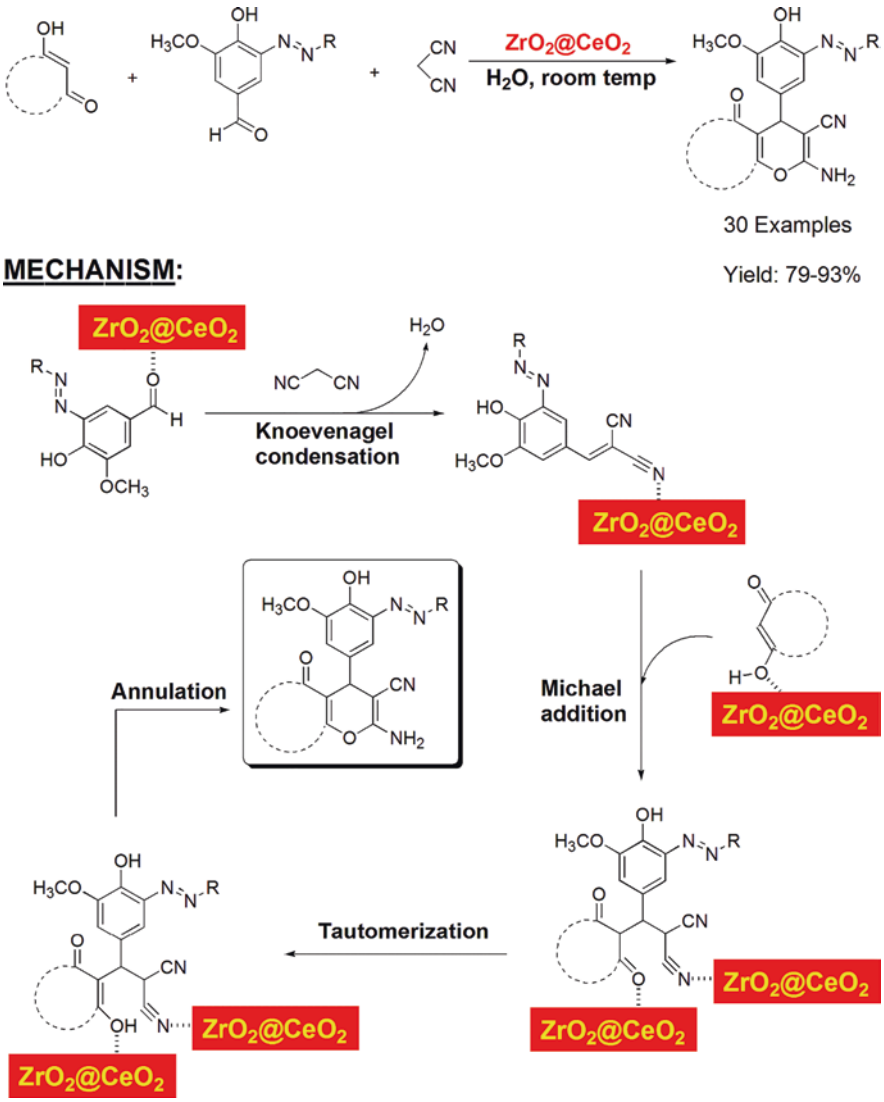
In 2016, Vijay Kumar et al. (2016) designed the $Eu_2O_3@CeO_2$ nanocomposite for the multicomponent synthesis of phenyldiazenylacridinedione-carboxylic acids. For that objective, the binary oxide was prepared from the co-precipitation of $Ce(NO_3)_3$ and $Eu(NO_3)_3$ with NH_3 solution upon setting the optimal molar of Ce/Eu at a value of 8:2. The structural analysis indicated that the introduction of Eu on CeO_2 helped to induce the oxygen defects and to increase the surface area, leading to the superior catalytic activity of $Eu_2O_3@CeO_2$ over pure CeO_2. Hence, the catalysis of $Eu_2O_3@CeO_2$ in the aqueous-phase coupling of 1,3-dicarbonyl compounds, 4-hydroxy-3-methoxy-5-(substituted-phenyl-diazenyl)-benzaldehydes with glycine, enabled high yielding of (4-hydroxy-3-methoxy-5-(substituted-phenyldiazenyl)-dihydropyridineacetic acids. As described in the Scheme 25.16, $Eu_2O_3@CeO_2$ served as a heterogeneous Lewis acid in activating the C=O bonds during the multicomponent synthesis.

In another study, Ghayour et al. (2018) introduced $ZnO@CeO_2$ with 30.1 wt% of ZnO for the solvent-free coupling of aldehydes with 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide, where 62–92% yields of the thieno[2,3-*d*]pyrimidin-4(3*H*)-ones were achievable. To stimulate the construction of novel chromene derivatives bearing azo segment, Sagar Vijay Kumar et al. (2016)



Scheme 25.16 Preparation of phenyldiazenyl-acridinedione-carboxylic acid derivatives from the Eu_2O_3@CeO_2-mediated multicomponent reaction

devised the co-precipitated nanocomposite of ZrO_2@CeO_2 (ratio Zr/Ce = 1:1) as a potential candidate for the room-temperature condensation of malononitrile, 4-hydroxy-3-methoxy-5-(substituted-phenyl-diazenyl) benzaldehydes with different compounds of 1,3-dicarbonyls. The mechanistic pathway leading to the formation of 2-amino-4-(4-hydroxy-3-methoxy-5-(substituted-phenyl-diazenyl)-chromene-3-carbonitriles is assumed to follow a set of Knoevenagel condensation/Michael addition/tautomerization/annulation reaction, in which ZrO_2@CeO_2 helped to activate the C=O and C ≡ N bond (Scheme 25.17).



Scheme 25.17 Synthesis of novel azo chromenes over ZrO_2@CeO_2

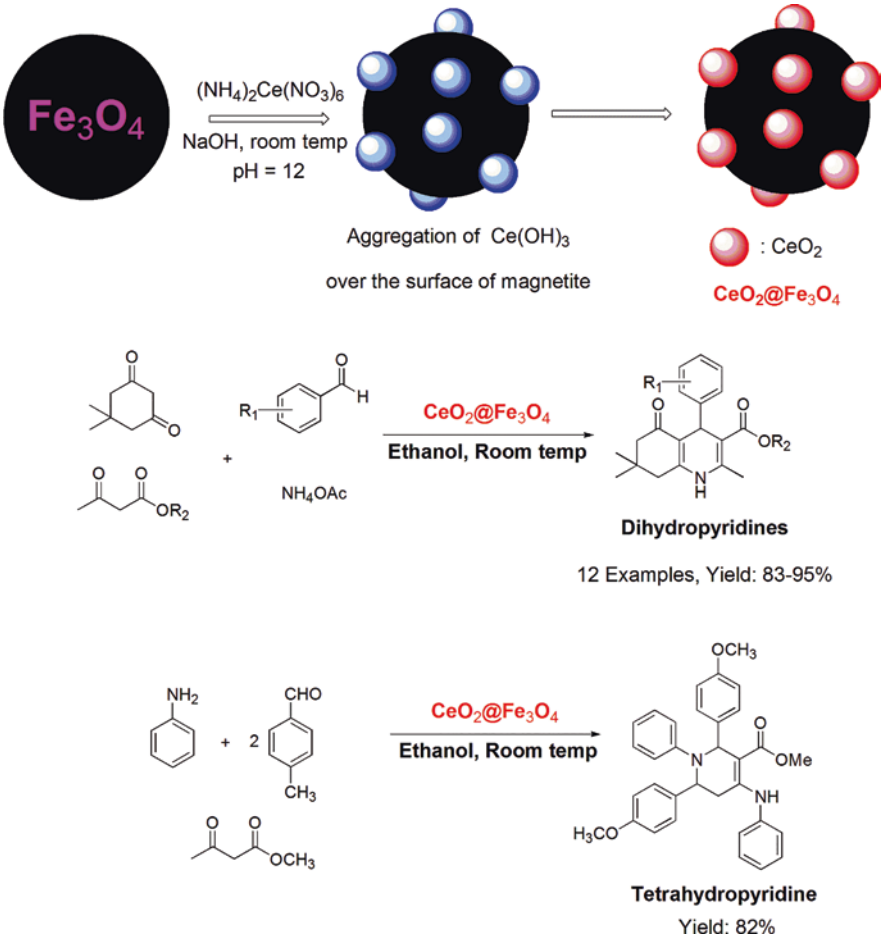
Another exemplar of cerium-based mixed metal oxides comes from the preparation of $Ce_1Mg_{0.6}Zr_{0.4}O_2$ composite as reported by Rathod et al. (2010). In this scenario, the aqueous mixture of $(NH_4)_2Ce(NO_3)_6$, Mg $(NO_3)_2$ and $Zr(NO_3)_2$ was co-precipitated with NH_3 and PEG-400, followed by calcination at 500 °C to render the titled nanocomposite. Through the structural characterization, the authors claimed that all three metals (Ce, Mg and Zr) in $Ce_1Mg_{0.6}Zr_{0.4}O_2$ had a strong mutual interaction and were highly dispersed on the surface. Besides, the insertion of

magnesium into the lattice of cerium-zirconium led to a decrease in the size of particles along with an enhancement in the acidic-basic active sites, thereby enhancing the efficiency of $Ce_1Mg_{0.6}Zr_{0.4}O_2$ NPs in promoting the construction of tetrahydrobenzo[*b*]pyrans. By refluxing the mixture of substituted benzaldehydes, malononitrile and dimedone with $Ce_1Mg_{0.6}Zr_{0.4}O_2$ in ethanol, the authors were able to obtain excellent yields of corresponding pyran derivatives (10 examples, yield: 90–94%).

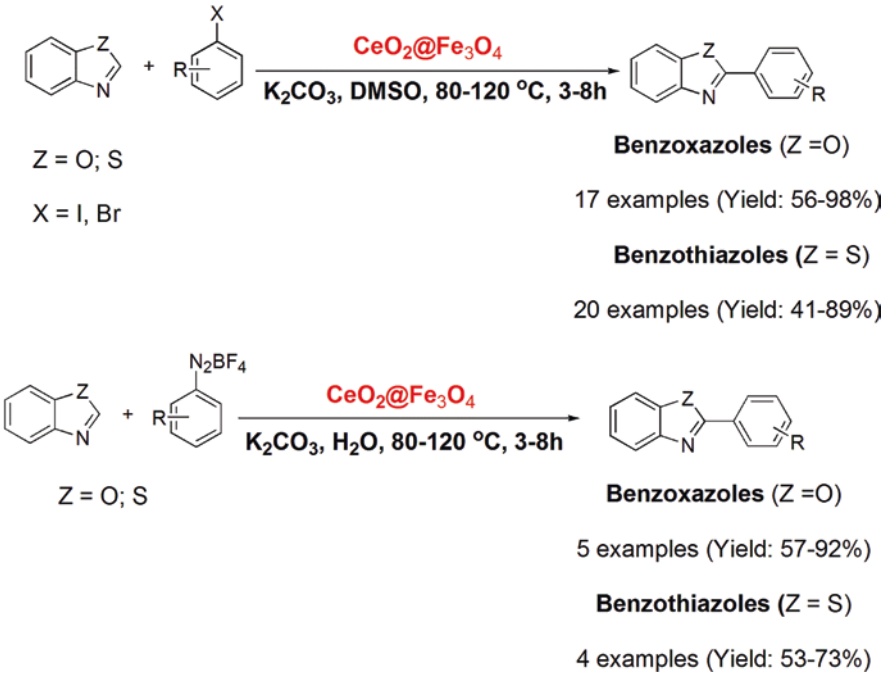
Besides, cerium is also treated as a metal dopant in some metal oxides to improve the catalytic performance of these materials in various transformations (Fu et al. 2019; Fayaz et al. 2016; Do et al. 2018). For instance, 5 wt% CeO_2 doped on NiMnO (calcined at 400 °C) could induce 100% conversion of benzyl alcohol to benzaldehyde (Sultana et al. 2015). Doping 2.5 wt% of ceria on $CuMnO_x$ helped to improve the efficacy of the catalyst in the low temperature oxidation of CO (Dey and Dhal 2020). Likewise, Samantaray et al. (2012) prepared a set of CeO_2@CaO nanocomposites by the citrate method and introduced them as main catalysts for the access of aminochromenes. It is revealed that the amorphous citrate template enabled the generation of macropores on the surface of resulting porous materials, in which the phase of binary oxide with the particle size of 5–25 nm was well dispersed in the phase of calcia. Furthermore, the incorporation of Ce^{4+} into the lattice of CaO might also increase the active basic sites on the surface of CeO_2@CaO composites, thereby improving their catalytic capability with respect to that of pure CaO. In this study, the authors stated that the CeO_2@CaO with 20 mol% of CeO_2 displayed the supreme performance in providing a structural diversity of 2-amino-2-chromenes (10 examples, yield: 76–85%) upon treating a mixture of substituted benzaldehydes and malononitrile with α-napthol in water at 80 °C. Meanwhile, Maddila et al. (2016) explored the recyclable cerium-vanadium-loaded alumina catalyst (Ce-V@Al_2O_3) for the solvent-free synthesis of multisubstituted pyridines. Herein, setting the total loading of Ce-V on the Al_2O_3 support at 2.5 wt% was verified to offer the best result thanks to the optimal distribution of acidic-basic sites on the surface of hybrid catalyst. Accordingly, the room-temperature manufacture of functional pyridines from aromatic aldehydes, malononitrile and ethanol was accomplished in a facile and selective manner (11 examples, yield: 86–94%). Subsequently, CeO_2@ZrO_2 was developed as an effective catalyst to induce the four-component annulation of substituted benzaldehydes, malononitrile and hydrazine hydrate with ethyl acetoacetate at room temperature, where a broad library of pyrano[2,3-c]pyrazole was rendered in the range yields of 89–98% (Maddila et al. 2017a). Alternatively, Khan et al. (2019) reported the high-yielding formation of quinolines from the CeO_2@TiO_2-mediated coupling of anilines, aldehydes with acetophenone in solvent-free condition.

In most cases, a proper choice of solvent to dissolve the product, suction filtration or centrifugation must be employed to separate the heterogeneous catalyst from the reaction mixture, causing great annoyances during the catalyst recovery. To overcome these barriers, magnetically recoverable nanocatalysts would become more ideal in terms of “green chemistry” viewpoint (Polshettiwar et al. 2011). In this aspect, superparamagnetic Fe_3O_4 (magnetite) which is considered as a cheap,

stable and easy-to-prepare support has been widely implemented to immobilize active catalysts in many reactions (Gawande et al. 2013a; Sharma et al. 2016b), since the active catalyst@Fe_3O_4 composite would be easy to recover from the reaction medium by an external magnet. Motivated by these works, Gawande et al. (2013b) designed a magnetic nanocatalyst of magnetite-ceria (CeO_2@Fe_3O_4) for the room-temperature construction of dihydropyridines and tetrahydropyridine (Scheme 25.18). Similarly, Shelkar et al. (2015) designed CeO_2@Fe_3O_4 with 7.44 wt% of Ce as a cheap and active nanocatalyst for the C-H functionalization of heteroarenes (Scheme 25.19). In this approach, the arylation was implemented by heating the mixture of benzoxazole/benzothiazole (1 equiv.) and aryl halides (1 equiv.) with K_2CO_3 (2 equiv.) in DMSO under the assistance of 5 mol% of CeO_2@Fe_3O_4, which led to a myriad of 2-aryl-substituted derivatives of benzoxazole and benzothiazole.



Scheme 25.18 Fabrication and utility of CeO_2@Fe_3O_4 in the manufacture of dihydropyridines and tetrahydropyridine



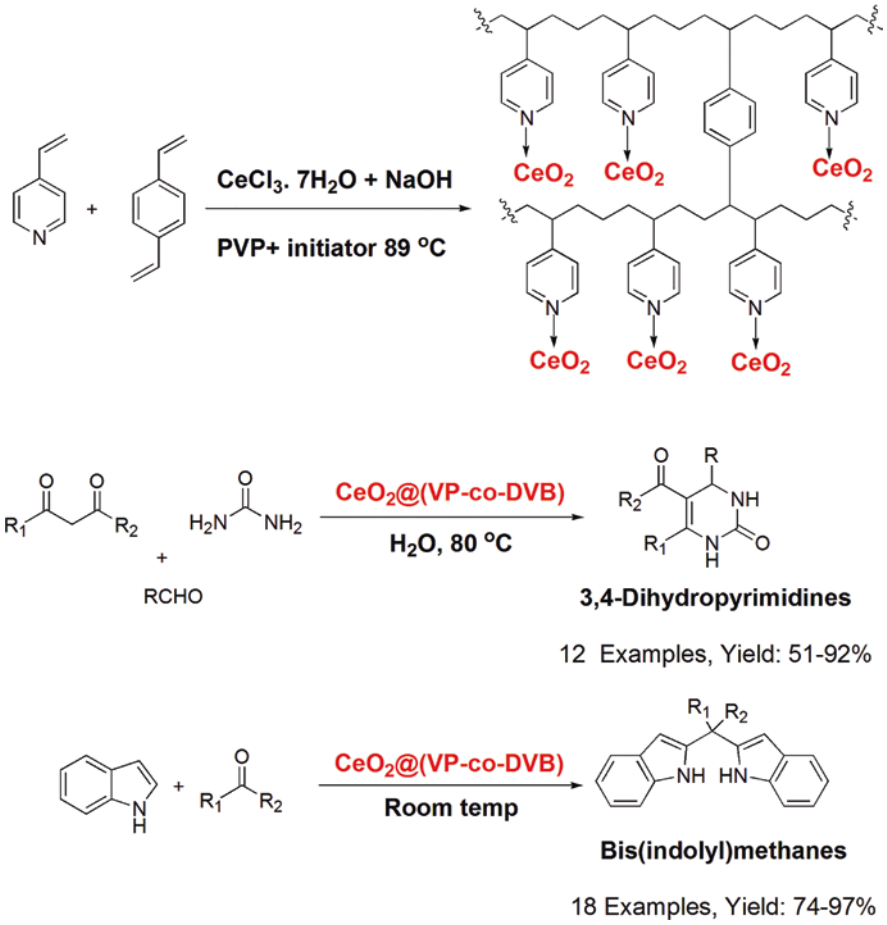
Scheme 25.19 C-H functionalization of benzoxazoles and benzothiazoles over magnetic CeO_2@Fe_3O_4 nanocatalyst

Strikingly, the CeO_2@Fe_3O_4-mediated *N*-arylation could be accomplished in greener condition by replacing the mixture of aryl halides-DMSO with a cheap combination of arenediazonium salts and water. In those examples, the magnetic CeO_2@Fe_3O_4 nanocatalyst could be readily recovered and recyclable for several batches with a negligible deactivation.

25.2.4 Cerium-Solid Material Composite

25.2.4.1 CeO_2-Polymer

In 2005, Sabitha and Shailaja (2005, 2008) designed a hybrid catalyst composed of CeO_2 NPs and polymer to promote the assembly of heterocycles. For this target, the titled composite, CeO_2@(VP-co-DVB), was readily prepared from the suspension copolymerization of 4-vinylpyridine (VP), 1,4-divinylbenzene (DVB) and $CeCl_3$ in basic condition upon using polyvinylpyrrolidone K30 as a removable template and an initiator mixture of Lupersol TAEC/Luperox 101 (Scheme 25.20). Strikingly, it is indicated that the robust CeO_2@(VP-co-DVB) catalyst could induce the synthesis



Scheme 25.20 Preparation and practicality of CeO_2@(VP-co-DVB) nanocatalyst in the synthesis of 3,4-dihydropyrimidines and bis(indolyl)methanes

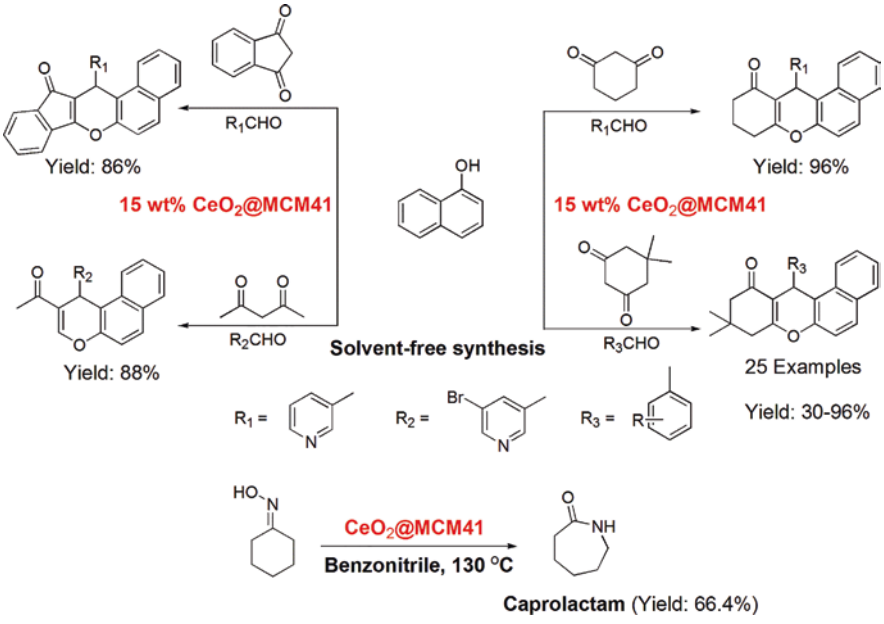
of both 3,4-dihydropyrimidines (12 examples, yield: 51–92%) and bis(indolyl) methanes (18 examples, yield: 74–97%) in high efficacy after multiple recycles.

25.2.4.2 CeO_2-Silica

Generally, silica is acknowledged as a versatile solid material owing to its own specific properties of high surface area, high thermal stability and a great flexibility in pore sizes and acidic-basic sites (Agotegaray and Lassalle 2017). Accordingly, silica has been widely employed as an exceptional template to immobilize active species in a well-dispersed manner, therefore providing a great volume of powerful silica-supported catalysts in the domain of heterogeneous catalysis (Akelah 1981).

In this context, MCM41 and SBA15 are two exemplary mesoporous silica which have widespread applications as either heterogeneous catalysts or solid supports in various transformations (Bhattacharyya et al. 2006; Rahmat 2010). Owing to a large specific surface area along with a well-defined pore structure of the mesoporous template, active species (metals or metal complexes) can be incorporated and uniformly dispersed on the wall of mesopores of MCM41/SBA15 to deliver a plenty of active heterogeneous catalysts (Liang et al. 2017). For example, Akondi et al. (2012) successfully fabricated CeO_2@MCM-41 with 15 wt% of Ce (CeO_2@MCM-41) by the wet impregnation to facilitate the oxidative coupling of 2-naphthol with substituted anilines. Similarly, the excellent catalytic activity of CeO_2@MCM-41 in the manufacture of mono- and bis-dihydropyrimidin-2(1*H*)-ones (Vadivel et al. 2013), benzoxanthenones/benzochromenones (Akondi et al. 2014) and caprolactam (Babu et al. 2016) was also recorded (Scheme 25.21). In these cases, the immobilization of cerium on the inner surface of mesopores of parent MCM41 is accountable for the improvement in the stability and catalytic performance with respect to CeO_2. Besides, Saadati-Moshtaghin and Zonoz (2019) developed a novel three-component composite of Fe_3O_4-MCM41-CeO_2 as a new hybrid solid catalyst for the solvent-free manufacture of tetrahydobenzo[b]pyrans from the condensation of aromatic aldehydes, malononitrile and dimedone (15 examples, yield: 69–96%).

Apart from MCM41, silica (SiO_2) is also regarded as a versatile solid support in heterogeneous catalysis (Ramazani et al. 2017). From the perspective of economical metrics, no template-directed SiO_2 is considered cheaper and more



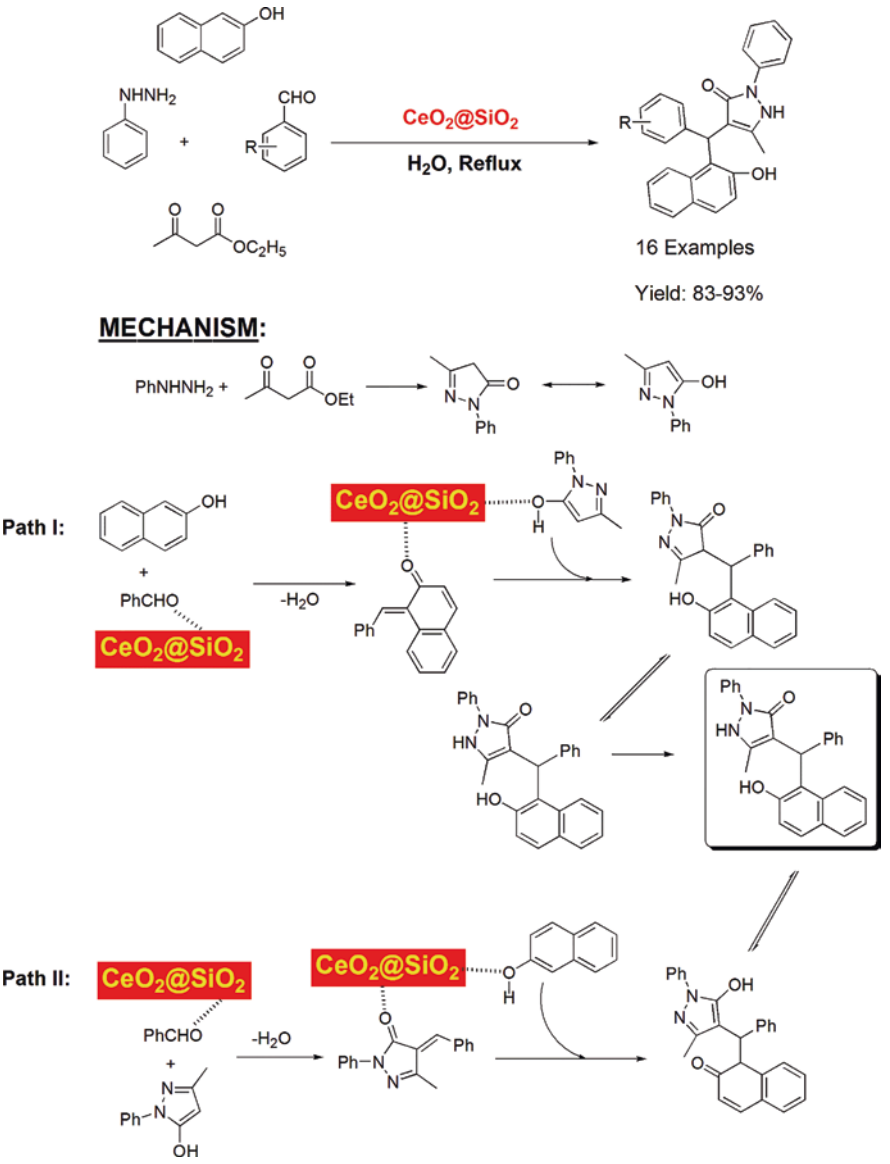
Scheme 25.21 Utility of CeO_2@MCM41 in the assembly of benzoxanthenones, benzochromenones and caprolactam

easy-to-prepare than MCM41. Moreover, the "sol-gel chemistry" is also acknowledged as a powerful tool in preparing metal oxides and oxide-supported metal catalysts (Esposito 2019). Prompted by these reasons, Akondi et al. (2016) later deployed sol-gel-derived SiO_2 in place of MCM41 to immobilize CeO_2 for the fabrication of nanostructured CeO_2@SiO_2. The textural analysis indicated that Ce^{4+} species from the oxidation of Ce^{3+} were successfully incorporated and tightly bound inside the mesoporous silica framework during the preparative procedure, thereby hampering the possible leaching of cerium to the reaction media. With only 0.9 mol% of mesoporous CeO_2@SiO_2 as main catalyst, the multicomponent condensation of aliphatic/aromatic aldehydes, 2-napthol and phenyl hydrazine with ethyl acetoacetate in water was induced to trigger a library of substituted pyrazolones in high yield and selectivity. The mechanism leading to the formation of substituted pyrazolones over CeO_2@SiO_2 is suggested to follow a sequential reaction of Knoevenagel condensation/Michael addition through two different pathways (Scheme 25.22).

25.2.4.3 CeO_2-Clay Composite

Another noticeable class of biomaterial is associated with hydroxyapatite [HAP; $Ca_{10}(PO_4)_6(OH)_2$] (Lu et al. 2019). This functional solid is highly recognized due to its outstanding properties such as high thermal stability, strong adsorption capability and tunable acidity/basicity (Pokhrel 2018). Accordingly, several investigations on the application of HAP as a solid catalyst or support in heterogeneous catalysis have been well executed (Fihri et al. 2017; Dobosz et al. 2016; Yan et al. 2016). In a typical study, Maddila et al. (2017b) doped ceria nanoparticles on hydroxyapatite (CeO_2@HAP) to induce the high-yielding assembly of pyrido[2,3-d]pyrimidine derivatives from the room-temperature coupling of benzaldehydes, dimethylbarbituric acid and ammonium acetate.

Honeycomb monolith (HM) is a type of solid material containing an extended matrix of long parallel and straight channels which are separated by thin walls (Govender and Friedrich 2017). This unique structural property generates a large number of void fractions and a large surface area to volume ratio. Furthermore, other major merits of honeycomb monolithic material encompass the high thermal conductivities, low pressure drops and ease of manufacturing and recyclability (Sungkono et al. 1997; Boger et al. 2004; Hosseini et al. 2020). Due to these reasons, HMs coated with metals/metal oxides are currently explored as heterogeneous catalysts in the NO_x reduction, N_2O decomposition, removal of SO_2-NO_x, syngas production, CO oxidation (Russo et al. 2007; Rico-Pérez et al. 2013; Vita et al. 2018a; Vita et al. 2018b; Davo-Quinonero et al. 2019) and organic synthesis (Gatica et al. 2016; Pratap et al. 2020). Recently, Venkatesh et al. (2015) prepared and applied the synthetic cordierite HM ($Mg_2Al_4Si_5O_{18}$) as a support to immobilize a set of cerium-based solid acids (i.e. sulphated CeO_2, CeO_2-ZrO_2 and sulphated CeO_2-ZrO_2) for the assembly of quinoxaline framework. It is disclosed that these cerium-based solid acids after coating with cordierite HM could display their supremacy over corresponding powder solid acids for the assembly of quinoxalines. In this



Scheme 25.22 Four-component assembly of substituted pyrazolones over CeO_2@SiO_2 nanocomposite

setting, high surface area, good dispersion of active sites and strong acidity of these acid-coated cordierites were acknowledged as main factors accounting for the high yield and selectivity of final products. Owing to high numbers of moderate and strong acid sites, HM-coated CeO_2-ZrO_2 was selected as the potential candidate for this synthetic paradigm, finally providing a group of quinoxalines in the range

yields of 72–89%. Strikingly, the spent catalyst could undergo six circulations with a negligible drop in the catalytic activity.

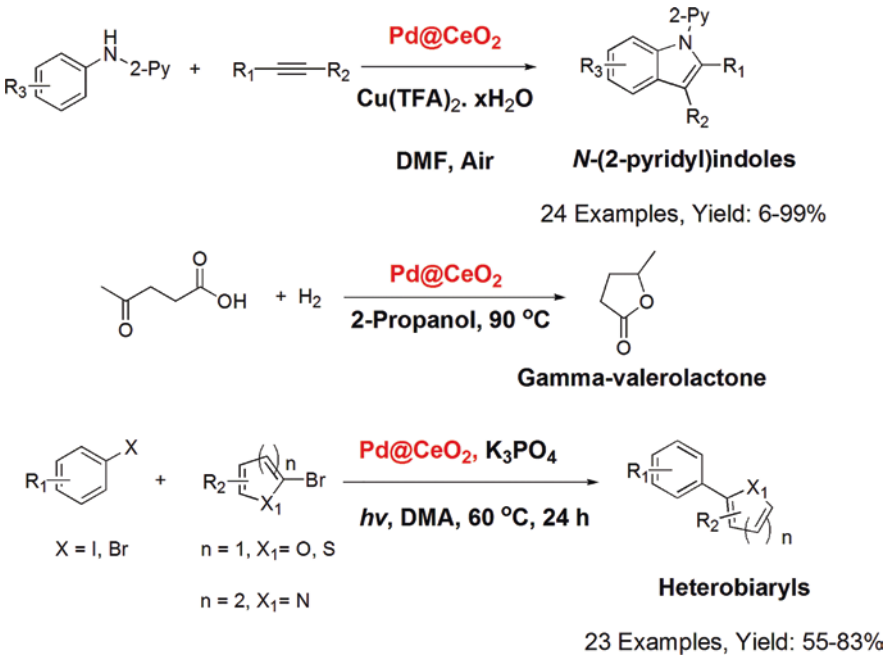
25.2.4.4 CeO_2-Carbon Template

Thanks to the unique properties (e.g. large surface area, excellent crystallinity, high physical/chemical/thermal stability and well-defined porosity), multi-walled carbon nanotubes (MWCNTs) have been exploited as versatile support in the fabrication of heterogeneous catalysts for the divergent synthesis of heterocycles (Safari and Gandomi-Ravandi 2014a, b, c; Zarnegar et al. 2015). By following this trend, Harikrishna et al. (2020) recently developed ceria-doped MWCNTs (CeO_2/MWCNTs) with 2.5 wt% of CeO_2 as a heterogeneous catalyst for the one-pot synthesis of pyridine-3-carboxamides. Under the promotion of recyclable CeO_2/MWCNTs nanocatalyst, the four-component coupling of acetoacetanilide, ammonium acetate and substituted aromatic aldehydes with ethyl cyanoacetate took place with no difficulty at room temperature. Accordingly, excellent isolated yields of pyridine-3-carboxamides (90–97%) could be delivered within a short period of time.

25.2.5 CeO_2 as Solid Support

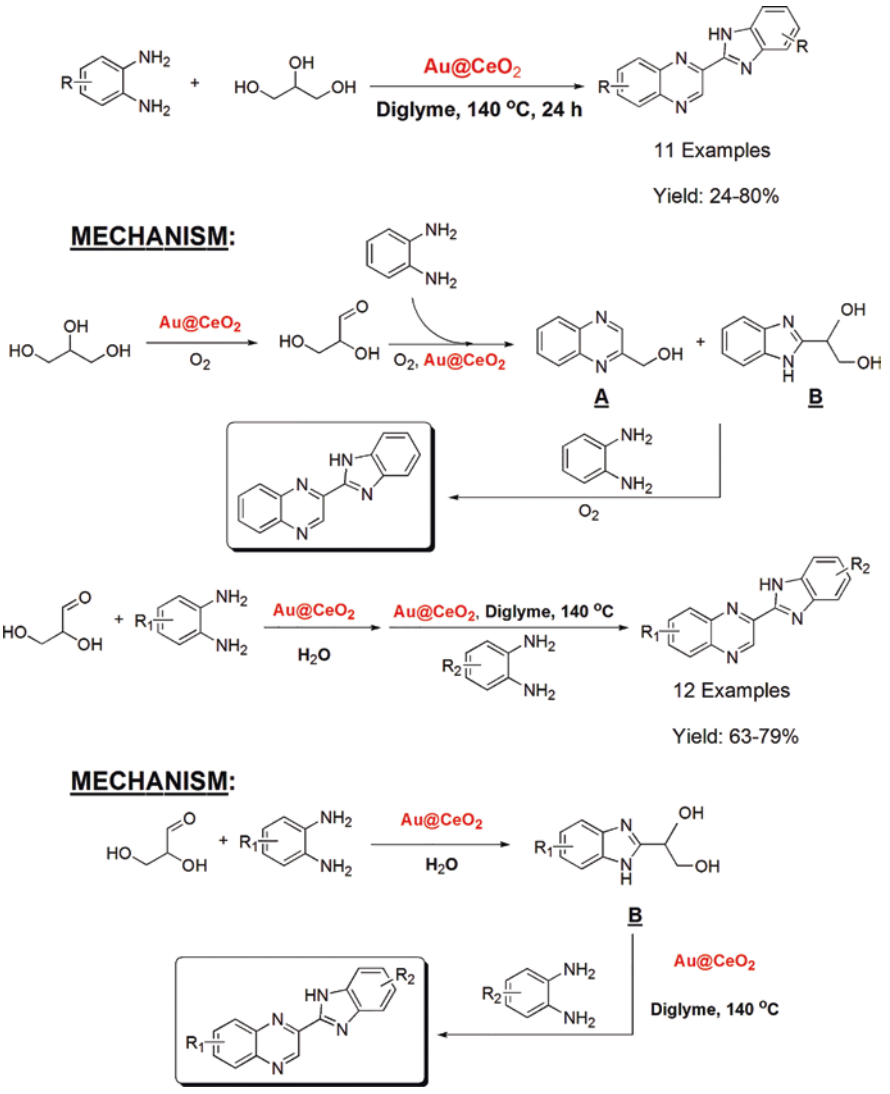
In addition to being exploited as effective catalysts in the construction of diversified heterocyclic frameworks, several research groups also attempted to utilize the versatility of CeO_2 as a solid support to immobilize palladium metal (Pd@CeO_2) to facilitate the assembly of heterocycles (Scheme 25.23). For instance, Chen et al. (2014) reported the remarkable activity of Pd@CeO_2 in the oxidative synthesis of *N*-(2-pyridyl)indole derivatives. In this study, the Pd@CeO_2 was demonstrated to outperform other commercial catalysts (e.g. Rh@C, Ru@C and Pd@C) for this oxidative C-H activation. Unfortunately, the spent Pd@CeO_2 could not be recycled well, delivering a sharp drop in the yield of annulated products after two recycling tests. Later, Zhang et al. (2017) developed a facile one-pot redox strategy to fabricate self-assembled Pd/CeO_2 hybrid catalyst with 5.82 wt% of Pd, where the high-temperature stage of calcination and reduction was avoided in the pretreatment. Thanks to the high surface area and defect sites of CeO_2, the Pd/CeO_2 catalyst was able to trigger a quantitative yield of gamma-valerolactone (GVL) from the hydrogenation of levulinic acid (LA) under mild condition (90 °C, 4 bar of H_2), which showed the catalytic superiority over commercial Pd/C (yield: 7.5%) and conventional Pd/CeO_2 derived from the precipitation-reduction method (yield: 45.3%). In another case, Ge et al. (2018) applied Pd/CeO_2 (3 wt% Pd) as an effective nanophotocatalyst to trigger the photochemical synthesis of asymmetrical heterobiaryls.

With the aim of improving the isolated yields of benzimidazoylquinoxalines from current protocols, Climent et al. (2013) established an alternative synthetic pattern where the Au@CeO_2 with 2.33 wt% of Au was exploited as a potential



Scheme 25.23 Construction of various heterocyclic structures over Pd@CeO_2 nanocomposite

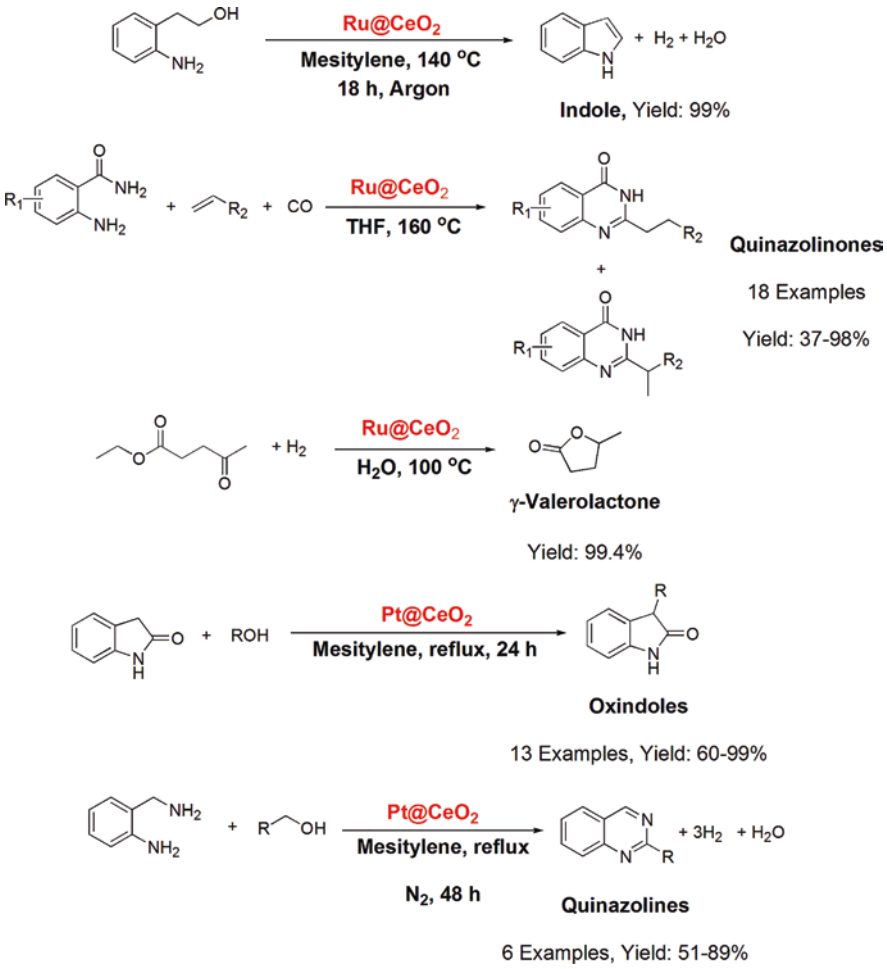
catalyst candidate. With the assistance of titled material, the trial for benzimidazoyl-quinoxalines could be attempted via two different manners (Scheme 25.24). In the straightforward approach, the oxidative coupling of the biomass-derived glycerol with 1,2-phenylene diamine was carried out in diglyme at 140 °C. In this case, two intermediates of quinoxalin-2-ylmethanol **A** and 1-(1H-benzo-[d]imidazol-2-yl) ethane-1,2-diol **B** were simultaneously generated from the coupling of 1,2-phenylene diamine with glyceraldehyde derived from the oxidation of glycerol. Afterwards, these intermediates would slowly undergo the oxidative condensation with 1,2-phenylene diamine to render the final 2-(1H-benzo[d]imidazol-2-yl)quinoxaline products (11 examples, yield: 24–80%). To expand the synthetic scope for constructing the benzimidazoylquinoxaline derivatives containing different substituents on both heteroaromatic moieties, the authors turned to deploy the one-pot two-step strategy upon starting with glyceraldehyde. In such case, 1-(1H-benzo-[d]imidazol-2-yl)ethane-1,2-diol **B** would be generated in water as the sole intermediate under the catalysis of Au@CeO_2 at room temperature, which was subsequently converted into a variety of substituted 2-(1H-benzo[d]imidazol-2-yl) quinoxaline upon oxidative coupling with substituted 1,2-phenylene diamines in diglyme at 140 °C (12 examples, yield: 63–79%). In each recycling trial, the recovered Au@CeO_2 was introduced to the calcination in O_2 at 250 °C prior to use, showing no significant loss in the original catalytic activity.



Scheme 25.24 Au@CeO_2-catalyzed synthesis of benzimidazoylquinoxalines

Furthermore, the practicality and efficiency of ceria-supported ruthenium (Ru@CeO_2) or ceria-supported platinum (Pt@CeO_2) as recyclable catalysts in the construction and functionalization of heterocycles such as indoles (Shimura et al. 2011), quinazolinones (An et al. 2018), ɣ-valerolactone (Gao et al. 2020), oxindoles (Chaudhari et al. 2014a) and quinazolines (Chaudhari et al. 2014b) have been realized in recent years (Scheme 25.25).

Another typical implementation of ceria-supported metal in the construction and functionalization of heteroarenes was introduced by Amadine et al. (2014), where



Scheme 25.25 Assembly of functionalized heterocycles over Ru@CeO_2 and Pt/CeO_2 catalyst

the ceria-supported copper nanoparticles (Cu@CeO_2) displayed the excellent catalytic activity in the *N*-arylation of indole with various aryl bromides. Although 82–89% isolated yields of *N*-arylated indoles could be achieved under optimal conditions, a considerable drop in the activity of spent Cu@CeO_2 was observed after three cycles. In this context, the reasons were likely attributed to the unavoidable oxidation of Cu^0 to Cu^{2+} and the poisonous deposition of in situ generated KBr on the surface of Cu@CeO_2. Later, Amini et al. (2016) reported the utility of robust Cu@CeO_2 nanocomposite (10 wt% Cu) to formulate a collection of 1,2,3-triazole derivatives (yield: 62–96%) from the 1,3-dipolar cycloaddition of terminal alkynes with sodium azide and benzyl halide derivatives in water.

25.3 Cerium-Based Catalysts for the Vapour-Phase Synthesis of Heterocycles

Recently, the catalysis of ceria-supported metal oxides for the vapour-phase synthesis of γ-butyrolactone (GBL) has been investigated due to the great importance and high output demand of GBL in industry (Schwarz et al. 2019). For example, Bhanushali et al. (2019) introduced the ceria supported copper ($CuO@CeO_2$) with 10 wt.% of Cu as an effective catalyst for the fixed-bed dehydrogenation of 1,4-butanediol (1,4-BDO) at 240 °C. Thanks to the high surface area, good dispersion of cooper on the ceria support and an enhancement in basicity, the $CuO@CeO_2$ could induce the dehydrogenation in an effective manner to trigger 93% conversion of 1,4-BDO and 98% selectivity of GBL. Subsequently, 10 wt% of Cu supported on CeO_2-Al_2O_3 (3:1 ratio) catalyst was able to promote the one-pot synthesis of GBL and benzyl alcohol from the simultaneous 1,4-BDO dehydrogenation and benzaldehyde hydrogenation, in which 90% conversion of 1,4-BDO and 95% selectivity of GBL were accomplished (Bhanushali et al. 2020a). Lately, 99% yield and 99% selectivity of GBL from the direct dehydrogenation of 1,4-BDO at 240 °C could be reachable in the presence of mesoporous 10 wt% $CuO@CeO_2$-Al_2O_3 (3:1 ratio) (Bhanushali et al. 2020b). In these examples, a remarkable decrease in conversion of 1,4-BDO up to 45% was unavoidable due to the coke deposition and agglomeration of copper nanoparticles after a long-time span on stream at high temperature.

Thanks to the high atom-economic, low cost and benign aspects, the vapour-phase synthesis of 3-methylindole from glycerol and aniline has drawn much interest over the past few years. In such transformation, the heterogeneous catalysts containing a large specific area along with a great number of weak acidic sites are strongly required to offer high yield and selectivity of the target product (Sun et al. 2010; Cui et al. 2013). Recently, Ke et al. (2020) applied the Cu/MIL-101 modified with CeO_2 (0.03 mmol/g) to prepare 59% yield of 3-methylindole from this synthetic paradigm. In this study, the authors stated that the addition of CeO_2 was conducive to the catalytic activity for the sake of (i) enhancing the mutual interaction of Cu and MIL-101; (ii) inhibiting the sintering of active components during the transformation; and (iii) increasing the number of weak acid sites on the surface of catalyst. Later, Qu et al. (2020) successfully fabricated mesoporous catalyst of Ag/SBA-15 modified with ZnO-CeO_2 (1 mmol/g of Ag, 1 mmol/g of ZnO and 0.05 mmol/g of CeO_2) to upgrade the yield of 3-methylindole up to 62%.

25.4 Cerium-Based Catalysts for the Synthesis of CO_2-Derived Heterocycles

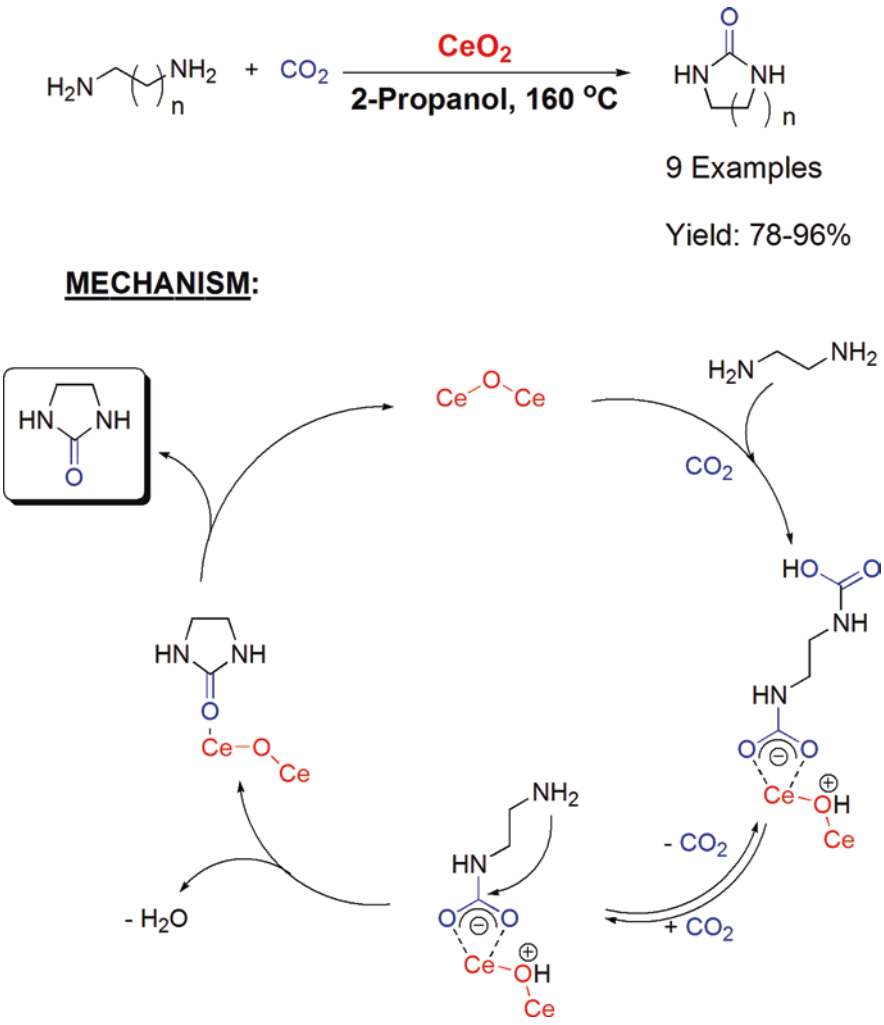
Apart from being employed as heterogeneous catalysts in the manufacture of CO_2-based products such as ureas (Tamura et al. 2016a), carbamates (Tomishige et al. 2019), carbonates (Tomishige et al. 2020) and polycarbonates (Gu et al. 2019;

Tamura et al. 2016b), cerium-based materials have been widely applied in the catalytic fixation of CO_2 towards heterocycles as well. For example, Tamura et al. (2013a) established a novel catalyst system composed of CeO_2 and 2-propanol to promote the synthesis of cyclic ureas from CO_2 and diamines. In this study, it is revealed that the presence of 2-propanol was essential to suppress the competitive formation of *N*-alkylated amines. Through the kinetic and FTIR investigations, the CeO_2-mediated cyclization is proposed to follow a cascade reaction of (i) simultaneous adsorption of diamine with CO_2 and CeO_2 to generate carbamic acid and carbamate adspecies on ceria; (ii) decomposition of carbamate species to a free amino group; (iii) annulation to cyclic urea by the intramolecular attack of amino group to the activated carbamate part; and (iv) desorption of the cyclic urea product and regeneration of CeO_2 (Scheme 25.26).

For the manufacture of CO_2-based cyclic carbonates such as ethylene carbonate (EC) and propylene carbonate (PC), Tomishige et al. (2004) reported the coupling pattern of ethylene glycol (EG) or propylene glycol (PG) with CO_2 over $Ce_xZr_{1-x}O_2$ solid solution. The authors stated that the acetonitrile as solvent helped to improve the catalytic activity and the equilibrium yield of carbonates in this reaction. Additionally, the maximal yield of both EC and PC could be obtained with CeO_2–ZrO_2 (Ce/[Ce+Zr] = 0.5) calcined at 800 °C or CeO_2–ZrO_2 (Ce/[Ce+Zr] = 0.2 and 0.33) calcined at 1000 °C. Later, Honda et al. (2014) examined the convenience of CeO_2 for the approach to five-/six-membered cyclic carbonates from diols and CO_2. It is verified that the introduction of excessive 2-cyanopyridine (2-CP) as a dehydrating agent was indispensable to overcome the equilibrium limitation, where the in situ generated water was effectively trapped by 2-CP. In the mechanistic description (Scheme 25.27), CeO_2 served as a Lewis acid to deprotonate the O-H bond of diol, thereby generating the cerium alkoxide **I** at the first stage. Afterwards, this alkoxide would allow the insertion of CO_2 to form the carbonate specie **II**, followed by the intramolecular cyclization and dehydration to result in the final cyclic carbonate.

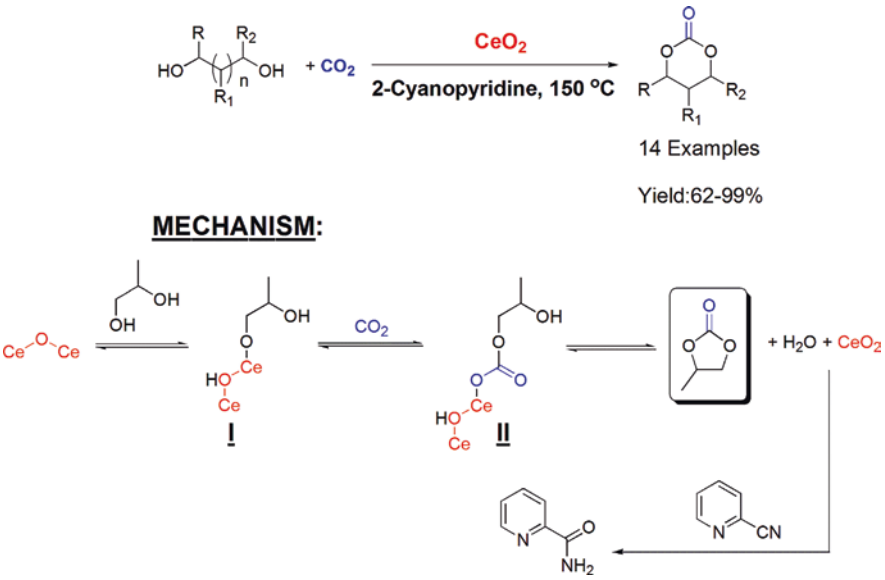
In the production of glycerol carbonate, Liu et al. (2016) carried out the CeO_2-mediated carbonylation of glycerol with CO_2 in the presence of DMF and dehydrating agent (2-cyanopyridine). For this purpose, the authors attempted three types of CeO_2 derived from the traditional precipitation (TP), hydrothermal (HT) and citrate sol-gel (SG) method for the CO_2 carbonylation. From the CO_2-TPD and H_2-TPR analysis, the basicity and oxygen vacancy density of these designed CeO_2 followed the order of nano-rod CeO_2 (HT) > nanoparticulate CeO_2 (TP) > sponge-like CeO_2 (SG). Hence, the highest yield of glycerol carbonate (78.9%) was provided under the mediation of nano-rod CeO_2 upon heating glycerol with CO_2 at 150 °C. By following the same strategy, Liu et al. (2018) applied the $Ce_{098}Zr_{002}O_2$ derived from the hydrothermal method to deliver 36.3% yield of glycerol carbonate.

To investigate the conversion of CO_2 into 2-oxazolidinones, Juarez et al. (2010) examined CeO_2 NP (5 nm) and commercial CeO_2 (40 nm) to promote the coupling of CO_2 and ω-aminoalcohols. Due to the high density of defects on the surface, the CeO_2 NPs (5 nm) displayed the best results in converting CO_2, and *N*-alkyl substituted aminoethanols into corresponding *N*-alkyl 1,3-oxazolidin-2-ones at



Scheme 25.26 Synthesis of cyclic ureas from CO_2 and diamines over CeO_2 in 2-propanol

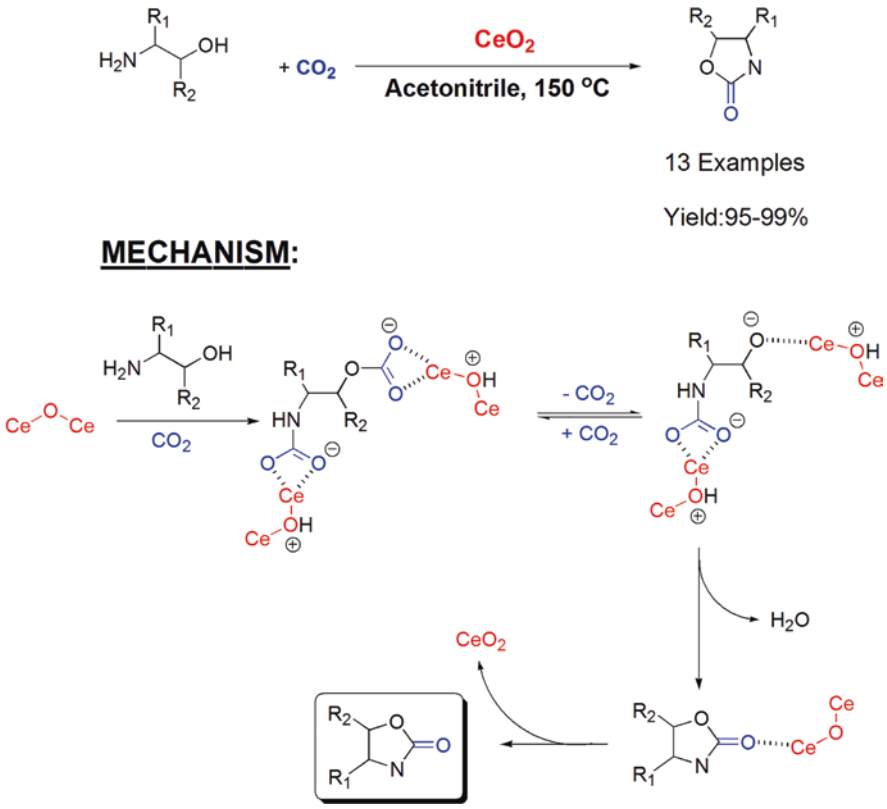
160 °C. Later, Tamura et al. (2013b) stated that a variety of aminoalcohols could be selectively converted into corresponding cyclic carbamates in high yields (88–99%) over the catalytic system of CH_3CN-CeO_2. In particular, the chiral configuration of chiral centre at the α-position of the hydroxyl group of starting aminoalcohols was kept intact after the reaction. From the kinetic studies and FTIR analyses, the mechanistic pathway leading to the generation of 2-oxazolidinones over CeO_2 is suggested to follow four consecutive steps as shown in Scheme 25.28.



Scheme 25.27 Synthesis of cyclic carbonates from CO_2 and diols under the catalysis of CeO_2 and 2-cyanopyridine

25.5 Summary and Outlook

The great importance and omnipresence of heterocyclic frameworks in natural products, bioactive molecules, pharmaceuticals and key building blocks have continuously raised the interest in developing novel, eco-friendly and sustainable protocols to improve the time/energy consumption, atom economy and selectivity during the manufacture. In this chapter, the broad practicality of cerium-based nanomaterials as both catalysts and solid supports in the synthesis and functionalization of heterocycles was summarized, where a diversity of heterocyclic skeletons containing nitrogen, oxygen and/or sulphur atom was constructed successfully under heterogeneous conditions. For this objective, well-defined cerium-based materials such as cerium oxide/mixed oxides, cerium composites and ceria-supported metals were fabricated over different procedures including co-precipitation, sol-gel, hydrothermal, wet impregnation and so on. With tunable modifications of morphology, acidity-basicity, redox properties and oxygen storage capacity, these nanocatalysts turned out to be potential heterogeneous candidates for the divergent synthesis of heterocyclic compounds. Particularly, their excellent catalytic performances were also recognized in the chemical fixation of CO_2, where valuable cyclic products of ureas, carbonates and carbamates were accomplished in great success. In such transformations, cheap, robust, easy-to-handle and recoverable nature are noticeable merits of these cerium-based nanomaterials in comparison with other benchmark catalysts. However, further improvements in this synthetic



Scheme 25.28 CeO_2-mediated coupling of CO_2 and aminoalcohols towards *N*-alkyl 1,3-oxazolidin-2-ones

strategy need to be carried out, where the development of simple, cheap and effective processes for the fabrication of cerium-based nanomaterials is strongly desired. In this manner, utilizing the latest advent of nanotechnology in controlling the size, shape and composition of final cerium oxide/mixed oxides is considered of great importance to maximize the number and strength of active sites for specific reactions. Moreover, the architecture of the solid supports and their interaction with cerium nanoparticles need to be carefully considered as well. In another aspect, the catalysis of cerium-based nanostructures in the MCR patterns should be further explored to expand the molecular complexity of heterocyclic frameworks. Last but not least, solvent-free or aqueous-phase paradigms are highly appreciated for the eco-friendly and sustainable synthesis of heterocycles.

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