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Nanomaterials for Sustainable Development

Opportunities and Future Perspectives

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ISBN 978-981-99-1634-4 ISBN 978-981-99-1635-1 (eBook)
https://doi.org/10.1007/978-981-99-1635-1

This Springer imprint is published by the registered company Springer Nature Singapore Pte Ltd.
The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

Contents

Chemical, Physical, and Biogenic Synthesis Methods for Nanomaterials

Zeenat A. Shaikh, Chetan Kamble, and Rajaram S. Mane

Abstract Through nanotechnology several concepts and phenomena are explored for technical understanding. An industrial potential of nanoparticles or nanostructures is the foundation of nanotechnology. Inorganic/organic, carbon-based, polymeric, metal organic frameworks and ceramic nanoparticles/nanomaterials etc., are envisaged in medicine, pharmaceutical, life, and engineering sciences for various applications. The aim of this chapter is to guide scholars and newly joined and experienced researchers in comprehending and learning the fundamentals of nanotechnology in addition to use of various physical and chemical synthesis methods for the production of nanoparticles/nanostructures. The particle size reduction to the nanoscale level reveals unique properties and better scientific/technical features such as increased surface area and engineered electrical and optical properties. Based on preparative parameters and bottom-up and top-down synthesis methods, the surface morphologies, structures, and physical properties of the as-prepared nanostructures are different. This chapter presents the challenges and future perspectives of aforementioned methods.

Keywords Nanomaterials synthesis methods · Top-down approach · Bottom-up approach · Biogenic synthesis methods

1 Introduction

The last century is the witness of originating nanotechnology which is booming to the next level in this century. Almost every branch of science, agriculture, medicine, and technology is directly or indirectly connected to field so called nanotechnology [1–3]. The technologies which are executed to the nanoscale level and can take to an application stage in the real world is nothing but the nanotechnology. It is described as the atomic and molecular control or reorganization of matter in the 1–100 nm size-range [4, 5]. Nanoscience is the name given to the underlying science.

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R. S. Mane et al. (eds.), *Nanomaterials for Sustainable Development*,
https://doi.org/10.1007/978-981-99-1635-1_1

The word 'nano' is coming from *nanos* (a Greek word) or *nanus* (a Latin word) whose meaning is 'dwarf' [6]. Nanotechnology is a globular tree with several branches of physics, chemistry, engineering, pharmacy, medicine and life science (Fig. 1). One should not confuse nanoscience and nanotechnology as they are more or less related to invention and incubation. Nanoscience deals with the knowledge of atoms like basic properties and arrangements at nanoscale level while nanotechnology overrides the atoms of the matter for the development of advanced useful technology [4, 7]. Because of the tremendous demand for nanomaterials in the field of engineering, medicine, electronics, the environment, and also in the defense and space sectors, researchers are trying their best to fulfill the needs [8–11]. The days are not far when nanotechnology will be going to control the living of mankind, communicating, and working fields. So, it will be interesting to discuss the basics and most important parameters of nanotechnology.

The key parameter or building block of nanotechnology is the use of nanomaterials obtained from different synthesis methods having various optoelectrochemical properties [12]. The ideal size of the nanomaterial is nearly 10^{-9} m which means one-billionth of the meter. The properties of the nanomaterials are different from the bulk materials [13, 14]. Several nanomaterials with different shapes like nanoparticles, nanorods, nanobelts, nanoribbons, and nanosheets etc., are on the record. These nanomaterials are generally characterized on the basis of their dimensions. Zero-dimensional materials include nanoparticles (NPs), one-dimensional include

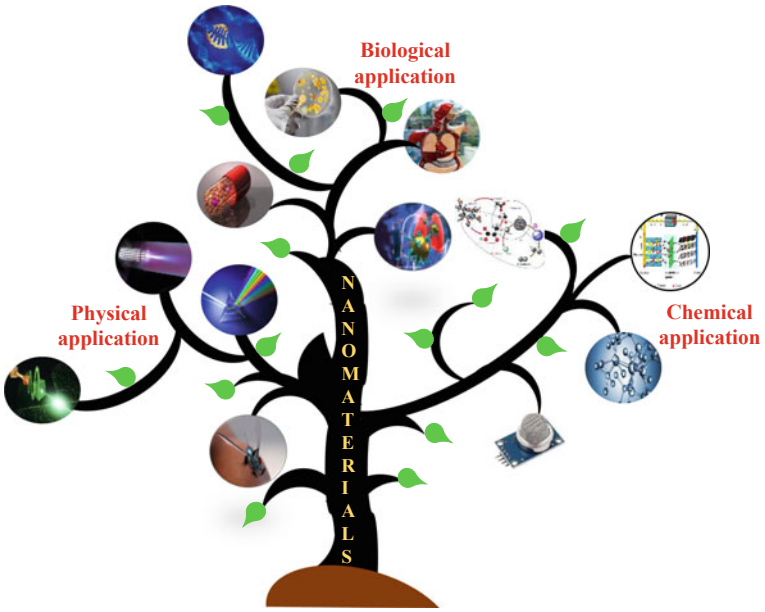

Fig. 1 Applications of nanomaterials in different fields

nanorods and two-dimensional layered graphene sheets. Three-dimensional materials include spheres, cubes, and cylinders [13, 15–18]. To synthesize these materials, several synthesis methods are used by the researchers across the world to develop nanomaterials of various sizes and shapes. A wide classification of the synthesis methods used to make the nanomaterials is presented in Fig. 2. By adopting the proper synthesis method, one can obtain desired shape, size, and physical and chemical properties of the product nanomaterial. The synthesis methods are divided into two core approaches: top-down and bottom-up. Bottom-up, also known as self-assembly, is the process of building a nanostructure by means of atom-by-atom, molecule-by-molecule, or cluster-by-cluster [19, 20]. These NPs are initially produced and then amassed into the final matter by employing either chemical or biological methods.

The bottom-up strategy has the specific advantage of increasing the probability of getting metallic NPs with fewer flaws and additional homogenous chemical compositions [1, 21]. On the other hand, in the top-down strategy, an appropriate host starting material is decreased in size with the help of the mechanical milling process (Fig. 3). The defectiveness of the surface structure is a fundamental disadvantage of the top-down method. Because of the high aspect ratio, such flaws in the surface structure can have a major influence on the surface chemistry and physical characteristics of obtained NPs [1, 22–24].

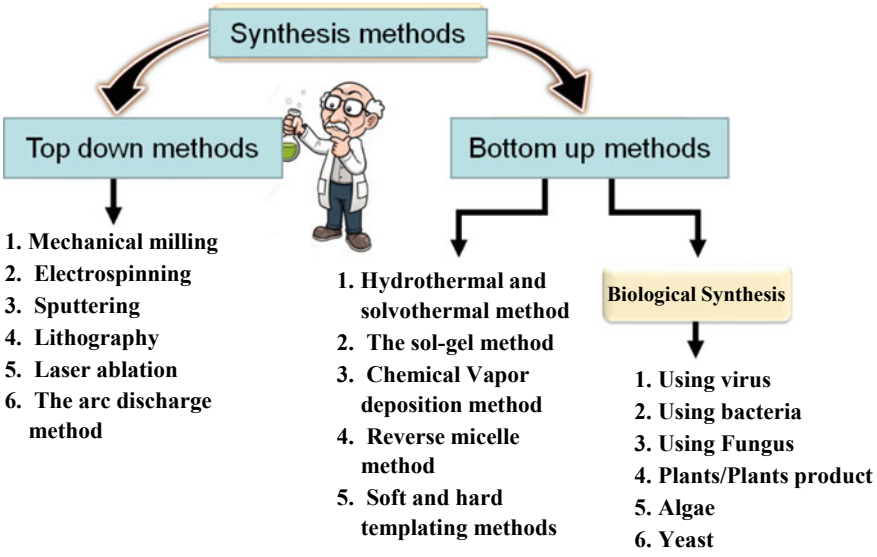

Fig. 2 Synthesis methods used for obtaining nanoparticles/nanostructures

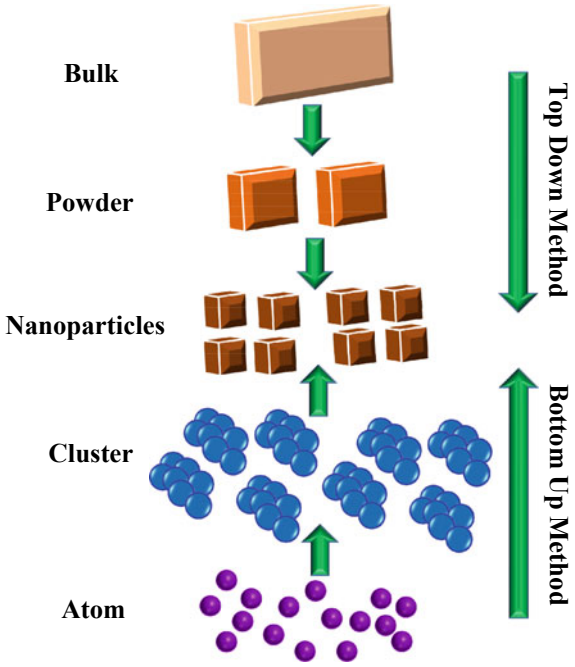

Fig. 3 Synthesis of nanoparticles from the top-down and bottom-up approaches

2 Top-Down Approach

In this, tactic mechanical model is used to synthesize the nanomaterials. Basically, these materials are crushed till the materials grasp the nanoscale level. By using the mechanical methods, one can achieve the nanomaterials of sizes less than 20 nm. This process is cheaper and offers mass scale products, but the shape of the final product is not orderly shaped. Ball milling is one of the most common and effective methods in this approach. Several physical methods fall in this category [4, 24].

2.1 Mechanical Milling

The main purpose of this method is to decrease the size of the particle to the nanoscale level and blend the particles to new phases. In mechanical milling method, a high-energy mill is used to blend the appropriate powder charge with a particular milling medium. Different types of ball millings are used for the synthesis of nanomaterials [25, 26]. In the chamber, without any restriction, the ball rolls down and influences the powder to be in nanoscale size. The mechanical milling method is the most economical because of the large-scale manufacturing with the production of desired nano-sized material [27]. The mechanical milling method has several categories like simple ball milling, Jarmill ball milling, and planetary ball milling wherein Jarmill

method is more beneficial for producing more products although the crushing process is a bit slower. On the other hand, the planetary method is quicker as the movement of the chamber is transverse and rotational [28]. The entire kinetics of mechanical milling is hanging on energy delivered to the powder through the balls while milling. There are several parameters that govern the energy transfer like types of mills, milling temperature, duration of milling, wet or dry milling, speed of milling, and ball size [29, 30]. The ball kinetic energy, milling media, and powder characteristics decide the temperature while milling. At adequate energy, an amorphous phase is anticipated if the temperature is low while high temperature leads to the formation of intermetallic phases. Furthermore, fracture of particles occurs as a result of high strain rate deformation and cumulative strain associated with ball collisions. These fractures and amalgamation measures linger throughout the progression. For the effective alloying process, an appropriate balance is essential among them. In some applications, stable state powder size distribution is attained, so the particles are often flakes type. A variety of nanomaterials and their composites can be prepared using the mechanical milling method. The carbon nanomaterials prepared from the mechanical milling method are envisaged in energy storage applications, environmental remediation, and conversion of energy [31]. Rather than this, nickel (Ni), copper (Cu), magnesium (Mg), aluminum (Al)-based alloys, and oxides/carbides of Al were also prepared [32, 33].

2.2 *Electrospinning Method*

In top-down methods, electrospinning is the simplest method that is used for the synthesis of various nanomaterials. This method helps to form the nanofibers mainly as scaffolds for tissue engineering. A variety of nanofibers of a few nanometer to micrometer dimensions were synthesized in the past [34, 35]. The setup consists of an injection pump, syringe, needle, high-voltage power supply, and collector plate as shown in Fig. 4.

The solution is pumped to the tip of the needle, and an electric field is created between the tip of the needle and the collector plate with the help of a high-power

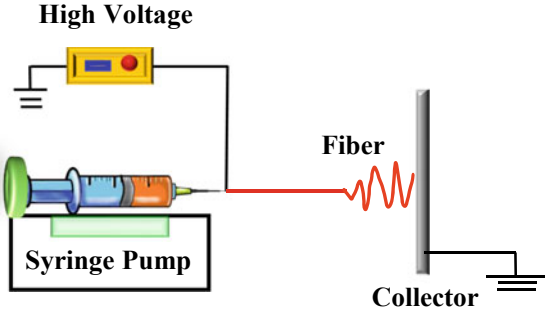

Fig. 4 Electrospinning method setup

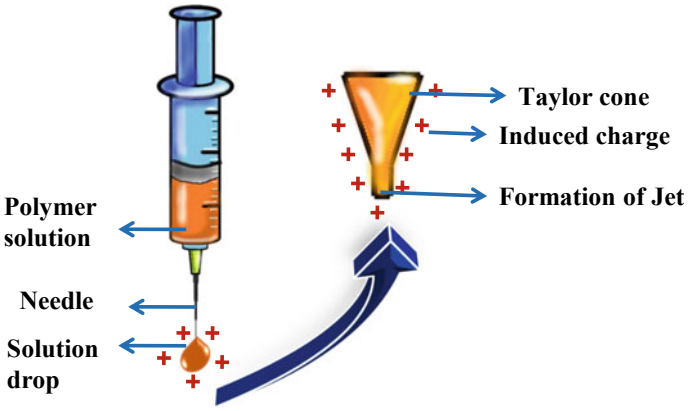

Fig. 5 Formation of Taylor cone in electrospinning

supply. Because of the force of the electric field, the surface tension in the liquid droplet is overcome, and the droplet is distorted to form the Taylor cone [35–37]. The distortion ejects the electrically charged jet toward the collector; consequently, fibers are obtained as depicted in Fig. 5. If the collector is rotating, then aligned fibers are obtained. One of the best revolutions in electrospinning is coaxial electrospinning. In this electrospinning process, two coaxial capillaries are compressed with the help of a spinneret. The two capillaries are filled with a viscous/non-viscous liquid which is used to form core-shell nano-architecture.

It is a very effective and simplest method to get core-shell thin nanofiber in bulk quantity. The nanofiber can be ranged to several centimeters [38–40]. Also, organic/inorganic and hybrid core-shell and hollow nanofibers can also be obtained. The polyacrylonitrile-carbon nanotubes prepared by Kaur et al. through the electrospinning method revealed nanofibers of 75–1500 nm in length [41]. Furthermore, Dorneanu et al. synthesized nickel oxide (NiO), zinc oxide (ZnO), and nickel oxide-zinc oxide polysulfone nanofibers (NiO–ZnO PSU). For synthesis of the aforementioned nanofibers, they used a needle of 0.8 mm diameter. The collector was kept 15 cm away from a needle. The 20 kV voltage was applied to the solution [42]. Spinel ferrite-like calcium ferrite ($CaFe_2O_4$) nanofibers were synthesized by Rafie et al. with the help of electrospinning technique using process parameters, solution parameters, and ambient conditions [43]. Although, electrospinning method endows with several advantages and disadvantages. By optimizing the as-mention parameters, one can get rid of the flaws of the electrospinning. A few limitations found for the electrospinning method are as follows:

(i) Temperature and humidity-related issues
(ii) Corner rounding and cracking of the nanofiber and
(iii) Large-scale production is difficult.

The selection of proper host materials and suitable combination routes is still challenging.

2.3 Sputtering

Sputtering, one of the popular processes for making thin nanocrystalline films, involves hitting the solid surface through high-energy particles like gas or plasma [44]. A sputtering deposition involves bombarding the target surface with energetic gaseous ions, which can cause the physical discharge of tiny atom clusters reliant on the energy of incident gaseous ions. Sputtering can be accomplished in a variety of methods, including using a DC diode, a radio-frequency diode, or a magnetron [45]. Sputtering is typically operated in an evacuated chamber in presence of the sputtering gas. Free electrons strike with gas molecules to form gas ions when a high voltage is supplied to the cathode target. The positively charged ions move rapidly in the electric field on the way to the cathode target, which they repeatedly strike, causing atoms to be ejected off the target's surface. Sputtering is appealing because the composition of sputtered nanomaterials is similar to that of the target material, with fewer contaminants, and it is less expensive than electron beam lithography [46].

The following are the primary types of sputtering:

(a) DC diode sputtering

A low-pressure plasma of argon is exploded between a substrate and target with the help of DC voltage of 500–1000 V. Positive ions of argon cause atoms to be quickly out of the target, which subsequently wanders to the substrate for condensation.

(b) RF sputtering

Instead of a DC electric field, an alternating high-frequency field is used in radio-frequency sputtering. A capacitor and plasma are linked in series with the high-frequency voltage source. The capacitor separates the DC component and maintains electrical neutrality in the plasma. The electrons and the ions are alternatively accelerating in both directions [47]. The electrons fluctuate in the plasma area, causing an increasing number of collisions with argon atoms. This results in a high plasma rate which can lead to a pressure reduction of roughly 10^{-1} to 10^{-2} Pa. This enables the creation of thin layers with a microstructure that would otherwise be impossible at greater pressures. Positive ions flow in the vicinity of the target through an overlaid negative offset voltage and are cracked by collision atoms of the target material, as in DC sputtering [48, 49]. The sputter deposition is similar to those of other sputtering processes.

(c) DC triode sputtering

In this type of sputtering, outside the plasma chamber, the target is used as a third electrode. The sputtering and plasma production processes are separated.

(d) Magnetron

While just an electric field is supplied in simple cathode sputtering, an extra magnetic field is arranged at the magnetron sputtering behind the cathode plate. The charge

carriers are diverted through a spiral path (precise cycloid orbits) due to the superimposition of the electric and magnetic fields, and they now circle over the target surface instead of moving parallel to the electric field lines. This increases the number of hits per electron by lengthening their route path [50, 51]. When the magnetic field is parallel to the target surface, the electron density is maximum, resulting in a higher level of ionization in this region.

2.4 Lithography

Lithography, a helpful technology, uses a focused beam of light or electrons to produce nano-architectures. It is a versatile and effective technology for creating nanoscale patterns. Lithography is used to manufacture precise nanomaterials on the surfaces that are highly regular in shape and size [52]. Masked lithography and maskless lithography are the two basic types of lithography. With the help of a specific mask or template, nanopatterns are transferred over a high specific surface area in masked nanolithography. Photolithography, nanoimprint lithography, and soft lithography are a few examples of masked lithography. Scanning probe lithography, focused ion beam lithography, and electron beam lithography are maskless lithography [53]. Without the use of a mask, arbitrary nanopattern writing can be performed in maskless lithography. Ion implantation through an attentive ion beam in combination with wet chemical etching can be used to accomplish 3D freeform micro-nano-fabrication.

2.5 Laser Ablation

In the laser ablation process, nanoparticles are created by striking the target material with a powerful laser beam. Due to the high intensity of laser irradiation, the source material or precursor vaporizes during the laser ablation process, resulting in nanoparticle generation [54]. The generation of noble metal nanoparticles through laser ablation is considered a green technique because no stabilizing agents or other chemicals are required. Metal nanoparticles, oxide composites, carbonaceous nanomaterials, and ceramics are also obtained using this method. Pulsed laser ablation in liquids, where surfactants or ligands are not essential, is an intriguing way of producing monodispersed colloidal nanoparticle solutions. Nanoparticle parameters such as average size and distribution can be changed by adjusting fluency, wavelength, and laser salt addition.

2.6 The Arc-Discharge Method

The earliest approach for creating multiwall nanotubes (MWNTs) and single-wall nanotubes (SWNTs) is arc discharge. Among the carbon-based materials, it creates carbon nanotubes, amorphous spherical carbon nanoparticles, fullerenes, and few-layered structures of graphene and carbon nanohorns [55]. The arc-discharge method is critical in the formation of fullerene nanoparticles. Two high phase-pure electrodes of graphite are commonly utilized as the anode and cathode in the arc-discharge process. These two electrodes are well separated by nearly 11–12 mm distance. For the vaporization of the electrode material, DC current is passed through these electrodes in presence of a helium atmosphere [56]. It is compulsory to fill the chamber with pure helium because the existence of moisture or oxygen prevents the formation of fullerene. After an arc-discharge period, at cathode, a rod of carbon is generated. With the inclusion of a metal catalyst such as Ni, Co, Fe, or Mo on either anode or cathode, this process can manufacture both MWNTs and SWNTs. Temperature, inert gas pressure, plasma arc, metal concentration, gas type, current, gas type and geometry of the system, etc., generally influence the quantity and quality of nanotubes produced, including lengths, diameters, and purity [57]. Throughout the arc-discharge procedure, distinct carbon-based nanomaterials are gathered from different sites. MWCNTs, nano-graphite particles, pyrolytic graphite, and high-purity polyhedral graphite particles are entirely recovered from anode/cathode deposits, or together electrode deposits. The interior chamber is also one of the sources to gather carbon-based nanomaterials. Single-walled carbon nanohorns (SWCNHs) of different morphologies depending on the environment were prepared. 'Dahlia-like' SWCNHs, for example, were made in an ambient atmosphere; however, 'bud-like' SWCNHs were made in CO and CO_2 atmospheres [58]. The arc-discharge approach is utilized to make graphene nanostructures quickly and easily. The conditions, under which graphene synthesized, have revealed an impact on its properties. When compared to those made with an argon arc-discharge, graphene sheets obtained with a hydrogen arc-discharge exfoliation process exhibit better electrical conductivity and thermal stability.

3 Bottom-Up Methods

3.1 Hydrothermal and Solvothermal Methods

One of the most well-known and widely used processes for producing nanostructured materials is the hydrothermal method. Nanostructured materials obtained using the hydrothermal process involve a heterogeneous reaction in an aqueous solution at high temperatures and pressures near the critical point in a closed vessel [59]. The solvothermal technique is similar to the hydrothermal technique. The only distinction is that it takes place in a non-aqueous environment. In most cases, hydrothermal

and solvothermal techniques are used in closed systems. The microwave-assisted hydrothermal approach, which combines the benefits of both hydrothermal and microwave processes, has attracted a lot of attention for developing nanomaterials of various metal oxides and chalcogenides [60]. Hydrothermal and solvothermal techniques are used for creating various nano-geometries of materials, such as nanowires, nanospheres, nanosheets, and nanorods.

3.2 The Sol–Gel Method

The sol–gel technique is a wet chemical procedure that has widely been utilized in obtaining nanomaterials of various materials. This method is used to create a variety of high-quality metal oxide nanomaterials. This process is known as a sol–gel method because the solvent precursor is turned into a sol during the synthesis of metal oxide nanoparticles which is then converted into a network structure known as a gel [61]. Metal alkoxides are commonly used as precursors in the sol–gel process for the creation of nanomaterials. The sol–gel technique used for the production of nanoparticles has multiple steps. The metal oxide is first hydrolyzed in water or with the help of alcohol to form a sol in the first step. The condensation occurs next, leading to an increase in solution viscosity and the formation of porous structures which are allowed to develop [62]. Hydroxo- (M–OH–M) or oxo- (M–O–M) bridges develop during the condensation or poly-condensation procedure, resulting in metal–hydroxo- or metal–oxo-polymer production in solutions. Poly-condensation persists during the aging process, resulting in change in the structure, properties, and porosity [63, 64]. Porosity decreases with time, and the space among colloidal molecules increases. Following the aging process, the gel is dried, in which water and organic compounds are extracted. Finally, nanoparticles are obtained through air calcination. The sol–gel process is used to create both films and powders. The nature of the precursor, hydrolysis rate, aging period, pH, and molar ratio between H_2O and the precursor are the parameters that influence the final product quality produced using the sol–gel process [65]. The sol–gel method is cost-effective and offers several other benefits, including the homogeneous nature of the obtained product material, low processing temperature, and the method's ease of use in producing complex and composite nanostructures.

3.3 Chemical Vapor Deposition Method

In the production of carbon-based nanomaterials, chemical vapor deposition (CVD) is essentially required. The chemical reaction of vapor-phase precursors forms a thin coating on the substrate surface in CVD process. Whenever a precursor has acceptable volatility, high chemical purity, good evaporation stability, eco-friendly and economical, non-hazardous and has a long life, it is considered perfect for CVD.

Furthermore, its decomposition should not leave any contaminants behind. When making carbon nanotubes by the CVD process, for instance, a substrate is put into the oven and heated to higher temperatures. As a precursor, a carbon-containing gas (like hydrocarbon) is gently introduced into the system [66]. The breakdown of the gas produces carbon atoms that reunite to form carbon nanotubes on the substrate at higher temperatures. However, the catalyst used can have a big impact on the form and type of nanomaterials produced. Nickel and cobalt catalysts produce multilayer graphene in CVD-based graphene production, although a Cu catalyst produces monolayer graphene. Ultimately, CVD is a great way to make high-quality nanomaterials, and it is especially skilled at producing two-dimensional nanomaterials [67].

3.4 Reverse Micelle Method

The reverse micelle approach can also be used to create nanomaterials with specific shapes and sizes. Normal micelles form as a result of an oil-in-water emulsion, with hydrophobic tails aiming at a core containing trapped oil droplets. In the case of a water-in-oil emulsion, however, reverse micelles form when the hydrophilic heads point at a water-containing core. The reverse micelles' core functions as a nanoreactor for NPs production [68]. It serves as a testing ground for nanomaterials. The size of these nanoreactors may be regulated by adjusting the water-to-surfactant ratio, which has an impact on the size of the nanoparticles manufactured using this process. On reducing the water concentration smaller water droplets occur. As a result, the reverse micelle approach is a simple way to make homogenous NPs with exact size control. The reverse micelle approach produces NPs that are incredibly tiny and monodispersed in nature. The reverse micelle approach is used to make magnetic lipase-immobilized NPs [69].

3.5 Soft and Hard Templating

To make nanoporous materials, the soft and hard template processes are frequently employed. A soft template is a traditional approach for creating various nanostructured materials. Because of its simple implementation, relatively mild experimental conditions, and the production of materials with a variety of morphologies, the soft template approach has several advantages. Soft templates, like block copolymers, flexible organic molecules, and anionic, cationic, and non-ionic surfactants, are generally used to make nanoporous materials through a soft templating process [70]. Hydrogen bonding, Van der Waals, and electrostatic forces are the most prevalent interactions between the soft templates and the precursors. The 3D-ordered mesoporous structures are synthesized using soft templates of 3D specially structured liquid crystalline micelles. The production of mesoporous solids such as lamellar (MCM-50), cubic (MCM-48), and hexagonal (MCM-41) structured mesoporous

silicas employing alkyl-trimethyl ammonium surfactant can be a typical example of it [71, 72]. In general, two methods named cooperative self-assembly and 'real' liquid–crystal templating are used to synthesize ordered mesoporous materials using a soft templating method. Surfactant and precursor concentrations, surfactant to precursor ratio, surfactant structure, and ambient variables are strongly influenced by the mesoporous material architecture generated from 3D organized micelles. The pore diameters of nanoporous materials can be tuned by changing the surfactant carbon chain length or adding supplementary pore-expanding agents [73].

The soft template approach is used to make a variety of nanostructured materials, including mesoporous N-doped graphene, porous alumina, single-crystal nanorods, and mesoporous polymeric carbonaceous nanospheres. Nano-casting is another name for the hard template process. To produce nanostructures for necessary applications, well-designed solid materials are employed as templates, and the solid template pores are filled with precursor molecules [74]. The hard template must be chosen carefully to create well-ordered mesoporous materials. Such hard templates should maintain in a mesoporous material during the precursor conversion, and they should be easily removed without affecting the nanostructure developed. As hard templates, a variety of materials including carbon nanotubes, carbon particles, carbon black, colloidal crystals, wood shells, and silica are explored [75]. The synthetic approach for generating nanostructures *via* templating methods involves three basic phases. The proper original template should be generated or selected in the first phase. The template mesopores must then filled with a specific precursor to turn them through an inorganic solid. To create the mesoporous duplicate, the original template is erased in the last stage. Unique nanostructured materials such as nanostructured metal oxides, 3D nanostructured materials, nanorods, nanowires, and many more nanoforms can be generated utilizing mesoporous templates [76]. From this brief explanation, it is clear that soft and hard template approaches can be used to create a wide range of unique structured nanomaterials.

4 Biogenic Processes

Chemical processes are often low-cost for mass production, but they have downsides such as using toxic, harmful, hazardous solvents, the product getting soiled because of the precursor chemicals and also, it produces harmful by-products. As a result, there is a growing requirement to obtain a high yield, cheap, harmless, and ecologically friendly metallic nanoparticles using alternative manufacturing processes. As a result, the biological tactic of nanoparticle manufacturing becomes imperative. Viruses, bacteria, fungi, plants/plant products, algae and yeast, etc., are only some of the biological resources accessible in nature that could be used to make nanoparticles [77]. It is worth noting that unicellular and multicellular organisms are acknowledged to create inorganic minerals, either intracellularly or extracellularly. Extracellular and intracellular extracts from the xylotrophic basidiomycetes *Pleurotusostreatus, Grifolafrondosa, Ganoderma lucidum and Lentinus edodes* were used to make Si,

Table 1 Biosynthesis of nanoparticles by micro-organisms

Name of microorganism	Synthesized nanoparticle	Morphology	Location/Organelle	Reference
Marine alga, Sargassum wightii Greville	Au	Planer	Extracellular	[79]
Yeast cell	Au–Ag	Irregular polygonal	Extracellular	[80]
Escherichia coli	Au	Triangles, hexagonal	Extracellular	[81]
Enterobacter sp.	Hg	Spherical	Intracellular	[82]
Aspergillus fumigatus	Ag	Spherical	Intracellular	[83]
Bacillus cereus	Ag	Spherical	Intracellular	[84]
Neurospora crassa	Au and Au–Ag	Spherical	Intracellular and extracellular	[85]

Se, Ag, and Au NPs using aqueous solutions of Na_2SiO_3, Na_2SeO_3 $AgNO_3$, and $HAuCl_4$ [78]. The extract type and the fungus species mainly influence on the shape, size, and aggregation properties of the NPs. The phenoloxidase activity of the fungal extracts is strongly related to the bioreduction of metal-containing substances and the production rate of Ag and Au NPs. The activity of phenoloxidase is not required for the biofabrication of Se and Si nanoparticles. Some of the regular metal biosynthesis prepared from microorganisms are given in Table 1.

4.1 Bacteria-Assisted Synthesis

Prokaryotic bacteria are the most widely studied bacteria among natural resources for manufacturing metallic NPs. The relative simplicity of management is one of the motives for 'bacterial preference' for the synthesis of NPs. In the initial experimentations, Slawson et al. discovered that *Pseudomonas stutzeri* AG259, a silver-resistant bacterial strain obtained from silver mines, have collected Ag NPs within the periplasmic region [86]. Inorganic compounds are generated by micro-organisms potentially intracellularly or extracellularly. Researchers have investigated bacteria extensively for the generation of metallic nanomaterials among micro-organisms as given in Table 2.

Table 2 Bacteria-assisted synthesis of various nanoparticles

Name of bacteria	Synthesized nanoparticle	Morphology	Location/Organelle	Reference
Arthrobacter nitroguajacolicus	Au	Spherical	Intra extracellular	[87]
Pseudomonas stuzeri AG259	Ag	Triangular, hexagonal, and spheroidal	Periplasmic space, intracellular	[88]
Rhodopseudomonas capsulata	FeS	pH-7-spherical, pH-4 triangular nanoplates	Extracellular	[89]
E. coli	CdS	Spherical, elliptical	Intracellular	[90]
Ureibacillus thermosphaericus	Ag	Spherical	Extracellular	[91]

4.2 Fungus-Assisted Synthesis

Fungi are a pleasing middle step in the investigation of metallic NPs because of their endurance, the ease with which they can scale up and metal bio-accumulation capability. Because fungi are exceptionally resourceful secretors of extracellular enzymes, therefore, a significant synthesis of enzymes is quite simple. Economic feasibility and simplicity of processing biomass are two more advantages of adopting a green technique of fungal mediated for the production of metallic NPs. The Bhainsa and D'Souza revealed extracellular Ag NPs production *via* the filamentous fungus *Aspergillus fumigatus*. It is worth noting that the synthesis is completed quickly [88]. As soon as the Ag^+ ion comes into contact with the cell filtrate, Ag NPs are formed. The comparison of different NPs syntheses using fungi-assisted method is given in Table 3.

4.3 Plant-Assisted Synthesis

While micro-organisms such as bacteria, fungi, yeasts, and actinomycetes are still being investigated and analyzed in the production of metallic NPs, using sections of complete plants for comparable NP biosynthesis procedure has a fascinating and underexplored potential. In a different experiment, plant extract from lemongrass (*Cymbopogon flexuosus*) has been utilized to make nanoprisms of Au. Extracellular production of Ag NPs have been described by reducing aqueous Ag^+ ions with a geranium leaf extract (*Pelargonium graveolens*). In comparison with previous investigations on the manufacture of Ag NPs with the help of bacteria or fungi, this plant extract reduces Ag^+ ions quite quickly [83]. Table 4 summarizes the available information on the synthesis of NPs using plant extract.

Table 3 Fungi-assisted synthesis of different nanoparticles

Name of fungi	Synthesize of nanoparticle	Morphology	Location/Organelle	Reference
Fusarium oxysporum	Au–Ag compound	Spherical	Extracellular	[92]
Botrytis cinerea	Au	Spherical, pyramidal, hexagonal, triangular, and decahedral	Extracellular	[93]
Aspergillus flavus	Ag	Isotropic	Surface of cell wall	[94]
Verticillium luteoalbum	Au	pH-3 spherical, pH-5- spherical, triangular, hexagons, spheres and rod, pH-7–9- small spherical, and irregular-shaped particles	Intracellular	[95]

Table 4 Plant-assisted synthesis of different nanoparticles

Name of plant extract	Synthesized nanoparticle	Morphology	Location/Organelle	Reference
Annona squamasa	Pt	Spherical	Peel extract	[96]
Chenopodium album	Au and Ag	Quasi-spherical	Extracellular	[97]
Magnolia kobus and Diopyros kaki	Au	Spherical, triangle, pentagons, and hexagones	Leaf extract	[98]
Beetroot	Ag	Spherical	Beetroot extract	[99]
Garcinia mangostana	Cu	Spherical	Extracellular	[100]
Lemon grass	Al_2O_3	Spherical	Leaf extract	[101]

4.4 Algae-Assisted Synthesis

The ability of algae is to absorb metals and decrease metal ions making it an excellent candidate for synthesis of metallic NPs, where both live and dead dried biomass are used. Algae are well-known for their ability to hyper-absorb heavy metal ions which can be restructured into more flexible forms. There are limited reports on the synthesis of metallic NPs using algae as a 'biofactory'. Singaravelu et al. used an organized technique to investigate Sargassum wightii's manufacture of metallic NPs [102]. This is the first time marine algae were employed to generate very stable extracellular Au NPs in a short amount of time compared to other biological techniques. Algae from the *Rhodophyceae, Phaeophyceae, Cyanophyceae, and Chlorophyceae* families are normally used to synthesize Au, Ag, and other metallic NPs using intracellularly

Table 5 Algae-assisted synthesis of various nanoparticles

Name of algae species extract	Nanoparticle type	Morphology	Reference
Turbinaria conoides	Au	Spherical and triangular	[103]
Cyanobacterium Oscillatoria limnetica	Ag	Quasi-spherical	[104]
Bifurcaria bifurcata	CuO	Elongated and spherical	[105]
Ulva fasciata	ZnO	Spherical	[106]

Table 6 Yeast-mediated synthesis of various nanoparticles

Name of yeast extract	Synthesize of nanoparticle	Morphology	Location/Organelle	Reference
Saccharomyces cerevisiae	Ag	Spherical	Extracellular	[108]
Yarrowia lipolytica	Au	Hexagonal and triangular	Cell wall	[109]
Sachharomyces cerevisae	TiO_2	Spherical	Extracellular	[110]
Sachharomyces cerevisae	MnO_2	Spherical and hexagonal	Intracellular and extracellular	[111]

and extracellularly. The various species of algae and their metallic synthesis are summarized in Table 5.

4.5 Yeast-Mediated Synthesis

Similar to algae, there are very few reports available on synthesis of the metallic NPs using yeast. Kowshik et al. synthesized Ag NPs of sizes ranging from 2 to 5 nm using Ag-tolerant yeast species MKY3. The majority (N99 percent) of the Ag was precipitated extracellularly as elemental NPs [107]. Table 6 summarizes the biosynthesis of metal NPs using yeast.

5 Challenges and Future Perspectives

Various conceptual and practical research on nanotechnology and nanomaterials are being studied. The efficiency with which materials may be modified at the nanoscale for varied uses will determine future technology. The creation and efficient application of nanomaterials, however, presents numerous difficulties. The following list includes some of the major difficulties:

(a) Nanomaterials' intrinsic properties can be degraded, and their effectiveness can be affected by flaws. For example, one of the recognized finest materials is carbon nanotubes. The tensile properties of carbon nanotubes can, however, be significantly reduced through contaminants, interrupted tube lengths, flaws, and unpredictable configurations.
(b) A further significant difficulty is finding cost-effective ways to synthesize nanomaterials. The manufacturing of high-quality nanomaterials typically includes special and challenging environmental conditions, which restricts their use in mass production. The production of 2D nanomaterials makes this problem even more critical. The majority of low-cost production techniques are used on a big scale; however, they typically result in low-quality, defective items. Controlled synthesis of nanomaterials is still a difficult task.
(c) Performance in pertinent domains can significantly be harmed by the aggregation of NPs at the nanoscale level, which is an underlying problem. The majority of nanomaterials begin to aggregate as they come into contact. Agglomeration may occur as a result of ionic interaction, physical interaction, or greater surface energy.
(d) Except for graphene, relatively little experimental testing of 2D ultrathin materials has been performed, even though they represent a remarkable family of nanomaterials with promising theoretical features. One of the biggest problems with 2D ultrathin materials is their stability and production. It is projected that their fabrication and proper implementation will receive more attention in the future.
(e) Both use of nanomaterials in industry and the rate at which nanoscale materials are prepared are on the rise. Furthermore, the field of nanotechnology investigation has a very broad scope; when new nanomaterials with intriguing properties are explored, new fields will be invented in the future. One of the key worries about nanomaterials that cannot be disregarded is their toxicity, which is currently not well-known and is a substantial worry in light of their home, workplace, and environmental appliances. It is uncertain to what extent compounds made of NPs can cause cellular toxicity. The scientific community must work to close the information gap between the explosive growth of nanomaterials and the potential for harm in living organisms. For the framed structure and implementation of nanotechnology, a thorough understanding of how NPs interact with organisms, tissues, and protein is essential.

Nanotechnology breakthroughs are connected to the future of modern technology. The development of nanomaterial-based engineering techniques is making the goal of producing clean energy. They have produced novel types of solar and hydrogen fuel cells, served as effective catalysts for hydrogen production, and have demonstrated good hydrogen storage capabilities. These materials have proved promising outcomes. Nanomedicine holds a bright future for nanomaterials. Therapeutic compounds can be delivered *via* nanocarriers.

6 Conclusions

When a material's dimension falls between 1 and 100 nm, it is called a nanomaterial. Nanomaterials are synthesized using two different approaches. Top-down approaches include mechanical milling, electrospinning, sputtering, lithography, laser ablation, and arc-discharge technologies. Bottom-up procedures are solvothermal and hydrothermal, sol–gel, CVD, reverse micelle processes, and soft and hard methods etc. Nanomaterials have several distinct characteristics that set them apart from their bulk counterparts. To obtain the intended consequences as a result of regimented nanostructures, more emphasis is being placed on manufacturing nanomaterials with regulated morphologies and nanoscale dimensions. Some commercial items have already been introduced using nanotechnology. Much further advancement is expected, with nanomaterials being incorporated into the next-generation technologies to meet future high-energy demands, as well as playing a larger role in biosensors and nanomedicine to combat existing and novel diseases. The majority of nanomaterials are being developed for laboratory use, and significant work is necessary to bring them before commercial marketing. Another key difficulty in current nanotechnology is identifying substitutes for endangered and limited-resource materials in nanomaterial synthesis. Forty-four of the 118 elements will encounter supply constraints in the next years. Critical elements include precious metals, phosphorus, and rare-earth elements. It is vital to lessen reliance on endangered and crucial elements. In batteries, for example, efforts are currently underway to substitute crucial lithium ions with more abundant metal ions. Carbon-based nanomaterials are a good alternative for large-scale synthesis for a variety of applications due to the widespread availability of carbon sources. Core-shell morphologies are beneficial in decreasing the use of key elements in a variety of applications. With a deeper understanding and quick development of nanotechnology, future difficulties of modern society can be solved to some level.

Acknowledgements The author stated the Department of Science and Technology, New Delhi, for the financial assistance granted under the INSPIRE Program (No. DST/INSPIRE Fellowship/2016/IF160613, Registration No: IF160613) (India). The sciences, engineering, and research board (SERB) under the NPDF scheme-SERB/NPDF/PDF/2020/001333 is acknowledged by the authors.

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Biosensor: Tools and Techniques for Characterization and Analysis

Sambhaji S. Bhande and Shivaji Bhosale

Abstract Recent advances in developing low-cost and highly efficient biosensors are under intense investigation for developing highly sensitive and specific operations. However, the basic research is still undergoing to refine the sensing strategies and analytical instrumentation and procedures to develop new applications in numerous fields for rapid detection and development of biosensors. As a material scientist, one must need to focus on the detection and development of biosensors, and hence, they need to be characterized starting from their materials and their compositions to their activities/response to the specific application for the development of biosensor applications. This chapter intends to provide brief and specific applications of biosensing devices developed in the laboratory and possible ways to characterize them. Various spectroscopic characterization techniques, electrochemical measurements, electrochemical impedance spectroscopy, FT-IR, zeta potential, surface plasmon resonance spectroscopy, and dynamic light scattering are used in the complete analysis of the biosensor from its synthesis to potential applications which can serve as an introductory part for those who are new to this field as well as the people working in this field.

Keywords Biosensor · Characterization techniques · Nanomaterials · Biosensing device

1 Introduction

Nano-sized and nano-dimensional materials that reveal considerably innovative and enhanced physical, chemical, and biological characteristics, phenomena, and functioning have attracted great attention in rising technology and research during the

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R. S. Mane et al. (eds.), *Nanomaterials for Sustainable Development*,
https://doi.org/10.1007/978-981-99-1635-1_2

last few decades. Nanotechnology is an emerging multidisciplinary field with several applications such as materials science, mechanics, optics, pharmaceuticals, plastics, energy, aerospace, and so forth. Because of their potential uses for attaining certain processes and activities, nano-phasic and nanostructured materials are also gaining a lot of attention from textile and polymer researchers and manufacturers. The underlying principle of nanotechnology is that the characteristics of materials change substantially when their sizes are decreased to the nanometer scale; yet, measuring nanoscale materials is a difficult operation that necessitates extensive sophisticated equipment techniques. Advanced approaches are being used in the fabrication of nanostructured and nano-phasic materials. Furthermore, it is a developing sector that presents several problems to scientists and technicians. Thus, nanotechnology has stimulated an increase in research activities focused on the discovery and development of innovative nano-characterization procedures to enable greater control of the shape, size, and dimensions of materials in the nano-range. This chapter briefly discusses the key characterization strategies employed in the current investigation.

2 X-Ray Diffraction

The X-ray diffraction (XRD) technique is considered one of the most versatile, non-destructive [1] analytical techniques which reveals information about the structural properties of the materials which are influenced by the crystallographic nature of the films [2]. XRD studies were carried out to study the crystallographic properties of the semiconducting, conducting, and insulating materials prepared which is based on observing the scattered intensity of an X-ray beam hitting a sample as a function of incident and scattered angle, polarization, and wavelength or energy. Whether a component is present in its pure condition or as one constituent of a mixture of substances, it always generates a distinct X-ray diffraction pattern.

This knowledge serves as the foundation for the chemical analysis diffraction technique. The benefit of X-ray diffraction analysis is that it reveals the existence of a material rather than its individual chemical constituents. Diffraction analysis is beneficial when it is important to determine the state of the chemical combination of the elements involved or the specific phase in which they are present. When compared to conventional chemical analysis, the diffraction approach is quicker, uses a lot smaller sample, and is non-destructive. Each scatterer re-radiates a small proportion of its intensity as a spherical wave in response to the incoming beam (from the upper left). If scatterers are set symmetrically with a spacing d, these spherical waves will only be in sync (add constructively) in orientations where their path-length difference $2d\sin\theta$ equals an integer multiple of the wavelength λ.

In this kind of scenario, an incoming beam is deflected by an angle 2θ, resulting in a reflection spot in the diffraction pattern. Crystals are regular atomic arrays, while X-rays are electromagnetic radiation waves. X-rays are scattered by atoms, typically through electrons. An X-ray impacting an electron creates secondary spherical waves. This is referred to as elastic scattering, and the electron is the scatterer. A regular

scatterer array generates a regular array of spherical waves. Through destructive interference, these waves cancel each other out in most directions. This approach also reveals phase composition, lattice parameters, particle size, and lattice strain. The XRD method relies on diffraction, which is regulated by Bragg's law [3]. Diffraction often occurs when waves interact with a periodic structure. It is critical to understand that for diffraction to occur, the wavelength of the wave should be about equal to the repetition distance of the periodic structure. Inter-atomic lengths are measured in angstroms. Since X-rays have wavelengths of the same order, they are employed to study crystals. When an X-ray beam strikes a crystal, it interacts either constructively or destructively with the parallel plane of atoms, depending on the path difference. When the waves satisfy Bragg's law, [4, 5].

$$n\lambda = 2d \sin \ominus \tag{1}$$

where "n" is an integer denoting the order of reflection, "λ" is the X-ray beam wavelength, "d" is the inter-planar spacing, and "⊖" is the incidence angle. A diffractometer is used to perform X-ray diffraction. We utilized a Rigaku Geiger-Flex diffractometer with Cu k radiation ($\lambda = 1.54$) for this work. A diffractometer comprises essentially an X-ray source, a monochromatic, a slit, a specimen container, and a detector [6]. Figure 1 depicts an XRD system design. The X-ray source consists of a tube with a tungsten filament that works as a cathode and a copper (Cu) target as an anode. A large potential difference (30 kV) allows the filament to release electrons, which are then accelerated to interact with the cathode, producing X-rays. The beam's size and form may be changed via slits. When the beam is diffracted at an angle of 2⊖, the detector records its intensity. In a typical ⊖-2⊖ scan, the detector travels by 2⊖ and the specimen moves by an angle ⊖. Crystallographic information from a comparatively broad region of the sample may be obtained using the X-ray diffraction method. It needs little sample preparation and is non-destructive. Using clay, the sample is attached to the holder. It is crucial to install the sample carefully so that it is tilt-free and in the sample holder's plane. It is critical to understand that the XRD method only uses surfaces aligned to the specimen surface to generate the signal. There is only one set of planes aligned with the surface for a single-crystal sample. As a result, an XRD scan of a single crystal ought to show just one peak and higher-order peaks from the same family. Multiple planes from various grains will be aligned to the sample surface in the scenario of a polycrystalline film. As a result, the XRD scanning of a polycrystalline sample will show many peaks that correspond to different planes. A sample that is amorphous will have a broad diffused signal at a 20° angle. The XRD method has drawbacks even though it offers simple and rapid information regarding crystallographic orientation and phase composition. It is significant because it only provides texturing information in the growing direction. It becomes challenging to identify material using an X-ray if the amount is smaller than 10% of the total weight. It could be difficult to identify particles or precipitates of nanoscale diameters.

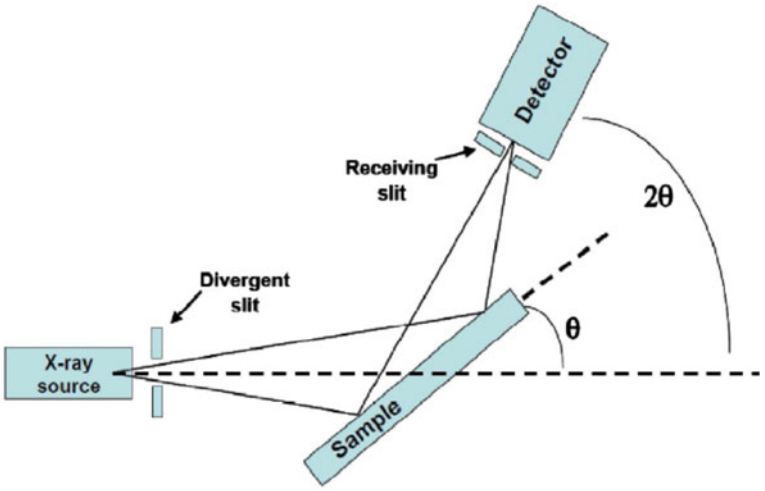


Fig. 1 Schematic illustration of the XRD $\Theta - 2\Theta$ scan

Limitations of XRD to porous structures:

(a) A highly smooth surface is required, which is challenging to achieve with huge grain sizes.
(b) Grinding is necessary to reduce the particle size, although doing so might damage the sample itself.
(c) Mesostructured materials have a limited number of higher-order peaks in their diffractograms, making it challenging to determine their internal structure without the help of further characterization techniques.

3 Scanning Electron Microscope

The topology and morphology of specimens are studied using the scanning electron microscope (SEM), as opposed to the methods discussed above. To photograph the surface properties, the secondary scattered electrons (in-elastically released electrons) are detected when the high-energy electron beam sweeps the surface. Widely employed in the study of materials, the SEM is a potent instrument for analyzing and understanding the microstructures of materials [7, 8]. The interactions of an incoming beam of electrons and the solid object are the foundation of the SEM concept [9, 10]. The specimen may emit a variety of emissions as a result of the electron bombardment, including X-rays, visible photons, Auger electrons, backscattered electrons, secondary electrons, and others.

3.1 Secondary Electrons

When an incoming electron hits an electron in a specimen atom, the electron is knocked outside its orbital shell and the atom is ionized. Because incident electron loses minimal energy after each collision, many collisions are conceivable, and this process can be repeated until the incident electron no longer has enough strength to release secondary electrons. Each released secondary electron has a relatively low kinetic energy (< 50 eV) that is independent of the incident electron energy. Such secondary electrons can elude being caught by the detector if they are created near sufficient to the sample surface (< 10 nm). As a result, secondary electron scanning is intrinsically tied to sample topography.

3.2 Backscattered Electrons

The incoming electrons will bounce or scatter "backward" out of the sample as backscattered electrons if they hit the nucleus of surface atoms. These electrons often have an energy of 50 eV or more compared to the first incident electrons. Backscattered electron pictures can be utilized to identify variations in sample atomic number since the generation of backscattered electrons changes directly with atomic number.

3.3 Auger Electrons

A vacancy is left in the electron shell of an ionized atom as a consequence of secondary electron production. Electrons from the same atom's higher-energy level outer shell can drop down and fill this hole. The atom now has an excess of energy, which can be reduced by releasing outside electrons or Auger electrons. Auger electrons can be used to determine the composition of a target sample since they have a characteristic energy that is specific to the component through which they are released. Only short sample depths (< 3 nm) yield Auger electrons, which have low kinetic energy.

3.4 Characteristic X-Rays

The incoming electron beam's interactions with the surface of the specimen also result in the production of X-rays. The process of moving electrons around to fill shell deficiencies can also result in surplus energy that can be released in the shape of an X-ray instead of Auger electrons, which is identical to the Auger electrons

generation process. X-rays have a distinctive energy that is specific to the elements from which they originate; hence, they can reveal a sample's composition. In this investigation, X-ray analysis and secondary electron imaging were the main methods employed for SEM sample characterization. This method offers both a deep field and excellent spatial resolution. The method also uses modest accelerating voltages, which minimizes sample radiation damage. For effective imaging, an ideal surface, and signal resolution, the specimen's electrical conductivity and electrical grounding are critical. A thin layer of conducting material, mostly gold as well as other metals or carbon, is placed onto the specimen surface in the scenario of insulating materials to prevent charging. The electron column, the detecting system, and the viewing system are the three separate components that make up an SEM. A design of a straightforward scanning electron microscope is shown in Fig. 2. The same scan generator controls two electron beams at the same time: one for the incident electron beam and one for the cathode ray tube panel. Line by line, the incident beam is swept across the sample, collecting, detecting, and amplifying the signal from the secondary electrons that occur. This signal is then used to regulate the second electron beam's intensity. As a result, changes in brightness representing the surface topography of the specimen will be displayed on the cathode ray tube display as a depiction of such intensity of secondary emission of electrons from the scanned region of the sample. Due to this technique, the SEM image's magnification may be changed by merely altering the size of the area that is being examined on the specimen surface.

Energy-dispersive X-ray spectroscopy coupled to either of the aforementioned electron microscopy methods allows for qualitative and precise quantitative elemental analysis. Inner shell electrons from the exposed sample's atoms are ejected by the main electron beam, and when these electrons relax, element-specific X-rays

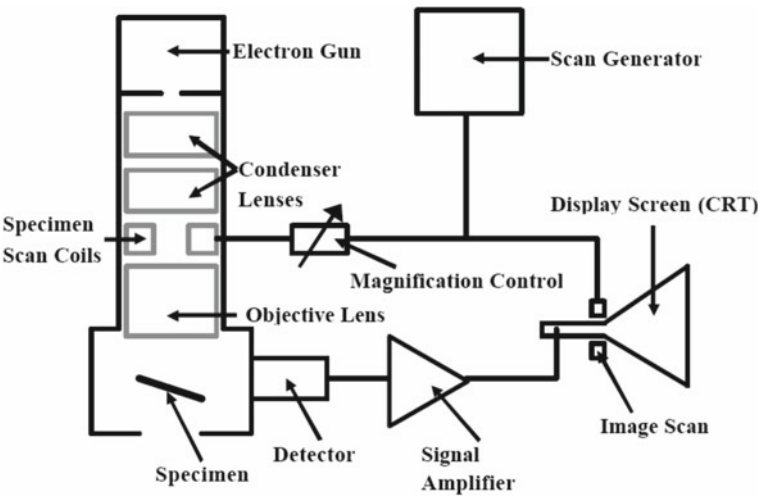


Fig. 2 Schematic diagram of a scanning electron microscope

are released, allowing for the analysis of the ensuing X-ray spectrum. Element identification and a relatively precise element composition may both be determined by calibration. The disadvantage of SEM in the context of porous materials is the loss of comprehensive information about a crystalline structure where the coating is required due to the aggregation effects of the metal particles.

4 Transmission Electron Microscope

A similar concept underlies transmission electron microscopy (TEM), which aims to provide a comprehensive picture of materials in the sub-micrometer area with a resolution of 0.2 nm [11, 12]. In TEM, a very thin electron-transparent material is passed through a high-energetic electron (> 100 kV) to create a magnified picture that is then projected onto a fluorescent screen or even a CCD camera using a series of electromagnetic lenses.

The characterization of nanocomposites has made extensive use of the TEM method, one of the most potent methods in materials research [13, 14]. It can analyze these nanocomposites' structural features, such as grain size and form, crystallinity, and chemical changes, at a resolution as low as the nanoscale level. Modern TEM's sophisticated design makes it possible to view atoms, their motions, and even lattice flaws.

Since electrons have a nearly 104-fold greater interaction with matter than X-ray photons do, it is conceivable to learn the structural details of crystals as small as a few nanometers in size that X-rays would not be able to reveal. Denser regions and regions containing heavier elements look darker in the resultant TEM picture as a result of enhanced electron scattering, and further diffraction contrasts are produced by scattering from crystallographic planes [15]. Individual crystal characteristics and crystal flaws may therefore be determined from a micrograph, along with component identification and an understanding of the atomic arrangement [16]. The general representation of TEM is shown in Fig. 3.

Following are the six fundamental parts that make up a typical TEM.

4.1 An Illumination Source

An electron source, which is typically employed in all TEM, consists of a filament that emits electrons either by thermal heating (a thermionic filament) or by applying a strong electric field to a metal filament tip, resulting in field-emission electrons (referred as field-emission filament). The field-emission filament gives a steadier source with better resolution and a longer lifetime than that of thermionic filament, but it is significantly more costly and necessitates a higher vacuum.

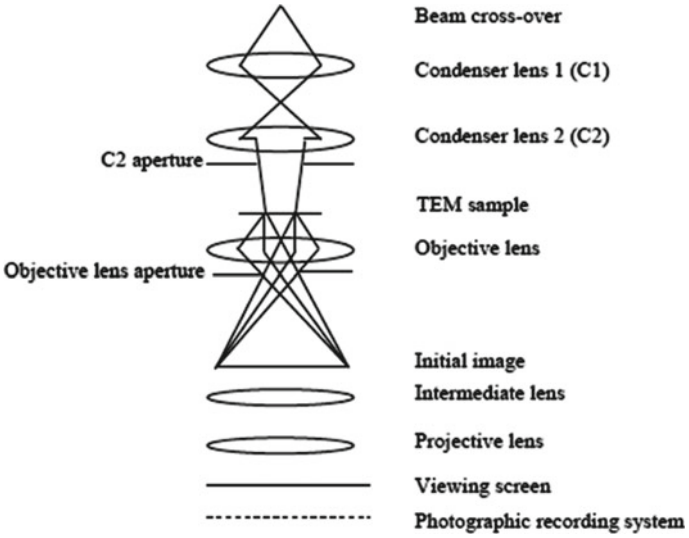


Fig. 3 Schematic diagram of a transmission electron microscope

4.2 Electrodes

One of these is the cathode, which accelerates the electrons produced by the filament to high energy, anywhere from a few hundred to more than a million volts. Most TEM equipment is operated between energies of 100 kV and 400 kV, while a greater voltage can result in a higher resolution. This will lessen sample damage and equipment expense while still obtaining the shortest feasible electron wavelength.

4.3 An Optical Apparatus

This is made up of a number of electromagnetic lenses, including the condenser, objective, projective, and intermediate lenses. These lenses aid in the focus of the electrons, resulting in a tiny probe beam and the formation of sample pictures. The core of the microscope is the objective lens. The main drawbacks to the TEM instrument's resolution are its inherent spherical and chromatic aberrations.

4.4 A Sample Chambers

The sample is inserted here, immediately in front of the objective lens. The chamber must be roomy enough to allow for the large range of tilting required for both the chemical analysis and the crystal orientation inspection of the samples.

4.5 Camera(s)

Typically, a video/scanned camera that is positioned underneath a phosphor screen where its pictures are visible is used to capture photographs of the samples. By raising the screen, the film is exposed to the camera to capture the images. However, the use of charge-coupled device cameras, which capture digital images that can be downloaded onto computers, has rapidly supplanted this recording technique.

4.6 Vacuum System

A vacuum system keeps the TEM operating at a very high vacuum. A typical example of such a system is one that combines mechanical and diffusion pumps.

In order to use a TEM to analyze materials, the sample should typically have a diameter of less than 3 mm and an area of interest that is thin enough for electrons to pass through. As a precursor to any analysis employing different TEM methods, it is crucial to create a suitable TEM specimen (including imaging, EDX, and others). In addition to being challenging to prepare, such as mechanical/electrochemical refining and ion sputtering, which may produce a lot of artifacts in and on the sample and lead to incorrect information, it is also challenging to thin the bulk specimen down to the appropriate thickness (often less than 100 nm).

4.7 Limitations

(a) Mesoporous materials' organization and structure are incredibly sensitive to the circumstances of preparation. As a result, the majority of them frequently have local fluctuations and/or intergrowths (domains).
(b) TEM is solely utilized to offer crucial information on the local specifics of the materials, whereas XRD provides structural features of the bulk material.
(c) In addition, investigating thick materials or samples made up of many layers is challenging, and the high working voltage frequently results in radiation damage.

5 Atomic Force Microscope

It was designed in 1986 by Binning et al. [17]. Both conducting and non-conducting substances may provide three-dimensional topographical pictures with AFM in any setting. The components of an AFM include a flexible cantilever working as a probe with a sharp tip, a piezoelectric scanner, a split photodiode cantilever deflection detection system, AFM electronics, and feedback loop, as well as a cantilever and sample containers (shown in Fig. 4). The force of contact between the cantilever tip and sample surface, as determined by the measurement of cantilever deflection, is used to characterize any substrate by AFM [18, 19].

A tip is employed in AFM to image. Typically, silicon or silicon nitride (Si_3N_4) is used to create it. It moves toward the sample at various inter-atomic distances (of around 10 Å). The tip is joined to the end of the spring cantilever and is typically 3–15 microns long. The cantilever has a length of between 100 and 500 microns. The cantilever bends negatively or positively depending on whether the tip, which is attached to the cantilever, is far enough away from the surface to interact with it through attracting and repulsive forces. A laser beam is used to identify this bending.

The cantilever's spring constant, along with the separation between the tip and the surface, determines how much force is created between the tip and the surface. Hooke's law can be used to represent this force.

$$F = -k \cdot x \tag{2}$$

where F = force, k = spring constant, and x = cantilever deflection.

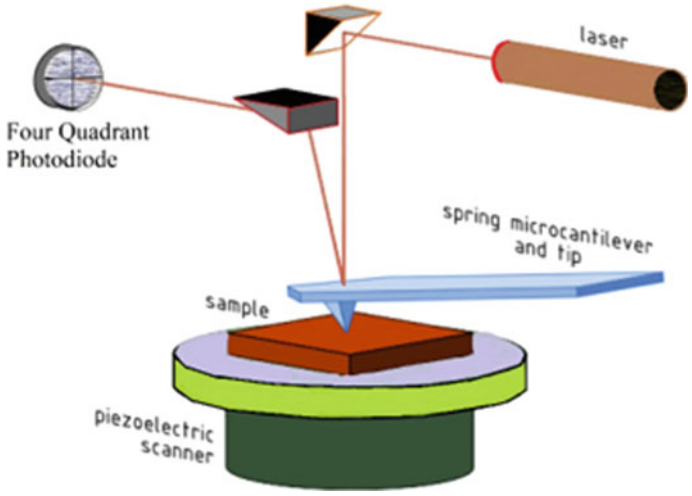


Fig. 4 Simple ray representation of AFM

Cantilevers bend and their deflection is measured if the cantilever's spring constant is smaller than the surface. The tip glides up and down as it traverses the sample topography in accordance with the sample's surface characteristics. The interactions of numerous forces, including electrostatic, magnetic, capillary, and Van der Waals forces between the tip and the sample, are the causes of these variations.

A picture of the topography is created after measuring the tip's movement. On the back of the cantilever, a laser beam is concentrated. It can be redirected to a photodiode detector with four quadrants. This position-sensitive photodiode allows for exact measurement of the cantilever's bending. The cantilever deflects in accordance with fluctuations in the atomic forces between the samples, allowing the detector to measure the deflection. As a result, the image that was produced is a topographical representation of the specimen surface.

The different modes in which AFM works can be classified as follows.

5.1 Static Mode

The easiest way to use an AFM is in static mode, often known as contact mode. This mode allows the probe to remain in constant touch with the sample while scanning the surface in 2D and producing a picture as it "drags" over the sample. The most typical static mode design is to use continuous force or deflection feedback. The cantilever deflection serves as the feedback parameter in this mode. The user regulates how little or much the probe interacts with the sample by adjusting the cantilever deflection, which is correlated to how firmly the tip presses against the surface. In addition, the error mode also employs the static mode. A steady force is used to operate in this mode. The deflection signal added to the surface structure, however, then improves the topographical image even more. The deflection signal in this mode is also known as the error signal since it represents the feedback parameter; whatever characteristics or morphologies that occur in this channel result from the feedback loop having to boost in order to maintain the constant deflection set point. Height (also known as z topography) and the deflection signal are the two pictures that are produced in static mode with constant force. As long as the force can be regulated below 100 pN, the static mode can be a helpful, straightforward imaging mode, particularly for strong samples in the air that can withstand the high loads and torsional stresses imposed by static mode. Surprisingly, however, more fragile samples in liquid can also benefit from the static mode's simplicity.

5.2 Dynamic Mode

The dynamic force mode is characterized by the cantilever oscillating at a high frequency at or near the resonance. The most typical dynamic mode is the so-called amplitude modulation mode (AM-AFM). The feedback parameter in AM-AFM is

the oscillation's amplitude; in other dynamic modes, the feedback parameter can be frequency or phase (modulation). Dynamic force mode, intermittent contact mode, tapping mode, and amplitude modulation mode are all applicable. The dynamic mode has a number of significant advantages as an image mode. In contrast to static imaging modes, the cantilever interacts with the specimen as the probe "taps" along the surface because it functions at resonance, which results in a less harsh engagement with the surface. This helps to maintain the tip's sharpness. Additionally, the torsional forces in between probe and the sample are reduced in this type of contact. These forces are accentuated in static imaging mode.

6 Selected Area Electron Diffraction

A crystallographic experimental technique known as the selected area electron diffraction (SAED) pattern may be used within a TEM to analyze crystal defects and identify crystal structures [20]. Comparable to X-ray diffraction, but different in that it may analyze regions as tiny as few hundred nanometers, whereas X-ray diffraction normally examines regions that are around centimeters in size. One of the most widely utilized experimental methods in the domains of solid-state physics and material research is the SAED. The electron beam illuminates a sizable portion of the sample in SAED, but not all of the lighted region contributes to the pattern. Following the sample, an aperture places a limit on the diffracting region. Only that portion of the aperture—which is in a plane conjugate to the sample—contributes toward the diffraction pattern. Two types of interactions between the sample and the beam happen when a sample is added: (a) elastic scattering and (b) inelastic scattering. Electrons are diffracted into well-defined paths at set angles with regard to the incident electrons if the sample is crystalline, as we will assume for the time being. This elastic scattering then takes the form of Bragg reflection. As a result, in SAED, the diffraction pattern is made up of a collection of distinct spots, each of which is spaced off from the direct beam by a vector dictated by the crystal structure.

6.1 Inelastic and Diffuse Scattering

It is not necessary for electrons scattered in a sample by inelastic or diffuse scattering mechanisms to fall in positions directly according to the incident beam's direction. As the name "diffuse" implies, they can be dispersed in all directions. The area contributing to an SAED pattern is not simply defined by the size of the area-selecting aperture. There is also a fundamental constraint connected to the objective lens's spherical aberration coefficient [8–15]. Although this limit will be determined by both the objective lens's characteristics and the camera's length (the range of diffraction angles included in the pattern), the smallest area that can be investigated using SAED is typically thought to be one meter in diameter. A thin crystalline sample is exposed

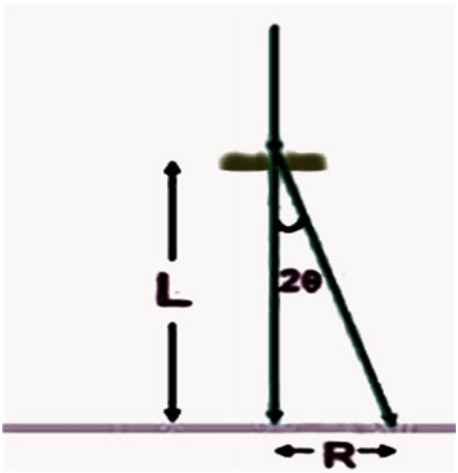
to a parallel high-energy electron beam in a TEM. Since TEM samples are typically only 100 nm thick and electrons have an energy range of 100–400 kV, the sample is easily penetrated by the electrons. Depending on the sample's crystal structure, a portion of these will be scattered at specific angles, while the remainder will pass through the material undisturbed. The electron beams will all be stopped by inserting a specified area aperture strip, which is positioned below the sample holder on the TEM column, with the exception of the small portion that passes through to contribute to a diffraction pattern on the screen. The diffraction pattern that results is then captured on photographic film or with a CCD camera. Single crystals, polycrystals, and amorphous materials are the three forms of solid matter that can affect diffraction patterns;

(a) Atoms are aligned in an organized lattice to form single crystals. Spot patterns are created by an electron beam traveling through a single crystal. The type of crystal structure, such as FCC or BCC, as well as the "lattice parameter" (i.e., the separation between adjacent (100) planes) can be identified from the diffraction spots. Additionally, the single crystal's orientation can be identified since the spot diffraction pattern will revolve predictably around the center beam spot if the single crystal is twisted or flipped.
(b) Materials with polycrystalline structure contain a lot of tiny single crystals. A polycrystal's smallest single crystals will randomly distribute among all of the potential orientations. Therefore, a polycrystal will generate a diffraction pattern similar to that generated by a beam traveling through a number of single crystals with different orientations. As a result of numerous spots being very close to one another at different rotations around the center beam spot, a series of concentric rings are created. Each circle represents a unique set of Miller indices, such as a plane. Additionally, the kind of crystal structure and the "lattice parameter" can be ascertained from the diffraction rings. However, because the ring pattern does not vary, it is impossible to determine the orientation of a polycrystal by tuning or flipping the polycrystal.
(c) Atoms in amorphous materials are not placed in ordered lattices, but rather at random locations. Amorphous materials are hence totally disorganized. On the fluorescent screen, there will be fuzzy rings of light that represent the electron diffraction pattern.

Using the following equations, a significant phase of the nanomaterial can be determined by indexing the diffraction pattern:

The Bragg law for small angles roughly corresponds to

$$\lambda = 2d\theta. \tag{3}$$



From the figure,

$$R/L = 2\theta. \tag{4}$$

Therefore,

$$R/L = \lambda/d \tag{5}$$

$$\lambda L = Rd, \tag{6}$$

where L is the image recording's TEM camera length. The amount of $L\lambda$ is frequently referred to as the microscope's "camera constant". On the diffraction pattern, "R" denotes the radius of every ring or the separation between a diffraction spot and the direct beam spot, and "d" stands for the phase's lattice constant. In most samples, in between the Bragg peaks, the diffuse scattering has no structure (simply a reduction in intensity as we move away from the elastic peaks). However, there is a pattern in the diffused scatter of some samples with specific types of disorder that can provide information about the sample's state [21–29].

7 Energy-Dispersive X-Ray Spectroscope

The composition of the sample affects the energies and relative abundances of the X-rays that are produced when electrons of the right energy impact a sample. The term "microanalysis" refers to the process of using this phenomena to determine the elemental composition of microscopic volumes (between one and several hundred

cubic micrometers) [30]. Chemical characterization is the primary use of energy-dispersive X-ray spectroscopy (EDX or EDS), an analytical instrument. It is a sort of spectroscopy that depends on examining a specimen through interactions among light and matter, in this case through studying X-rays [31]. X-rays are produced when a high-intensity beam of electrons (in a TEM or SEM) collides with the substance to be studied. The elemental makeup of the specimen surface may be identified and studied using these X-rays, which can be detected using a Si-Li detector and calibrated in relation to cobalt metal emission (6.925 keV). Its ability to characterize is largely a result of the fundamental idea that every element in the periodic table has a distinct electronic structure and, consequently, a distinct reaction toward electromagnetic waves [32, 33]. Figure 5 depicts the schematic representation of the X-ray emission mechanism. First, an electron is ejected out of an inner shell of a sample atom by an electron from, let us assume, a scanning electron microscope. An electron from the atom's higher-energy shell then fills the ensuing vacancy. This vacancy-filling electron is forced to surrender part of its energy, which manifests as electromagnetic radiation, in order to "drop" to a lower-energy state. Therefore, the energy of the radiation that is released is precisely equivalent to the difference between two relevant electronic states. For inner shells, such energy difference is quite considerable; hence, the radiation manifests as X-rays.

The pulse is then translated into a numerical value in relation to the incoming X-ray energy by an analogue to a digital converter. Once the signal has been allocated to a certain energy channel, it is counted as one. The result of counting is an energy-dispersive spectrum. The initial vacancy's shell is used to label each of the emission lines connected to X-rays that an atom emits, such as K, L, and M. The electron shell that fills the gap is often denoted with a Greek letter subscript. K radiation, for instance, is radiation that develops when an electron out from the highest shell fills a hole in the K-shell. An electron from K implies a vacancy in the K-shell that has been filled from the two shells above.

The order and energy of X-rays are governed by a few fundamental laws:

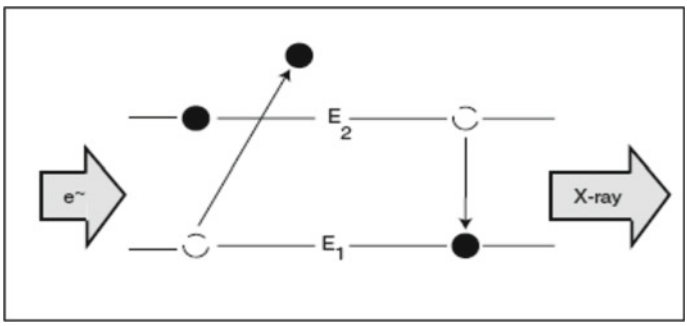


Fig. 5 Electronic transitions among inner atomic shells serve as the foundation for X-ray micro-analysis. An orbital electron from a low-energy shell is displaced by an energetic electron out of an electron column (E1). In order to fill the vacancy, an electron from such a shell with a higher energy must first lose energy. The lost energy manifests as radiation with the energy signature E2–E1

(a) The lower line series has more energy for a given element; such that, the overall energies of the K lines are higher than that of the L lines.
(b) The elements in such a line series with more atoms radiate X-rays with higher energy. Thus, the energy of the oxygen K lines is greater than that of the carbon K lines.
(c) The structures of the lower line series are simpler than those of the higher line series; for example, the K lines are simple, but the L and M lines become more complicated and begin to overlap.

Almost a real-time visual depiction of the chemical analysis may be obtained from the EDX spectrum, which can be recorded over brief time intervals and shown practically instantaneously. While quantitative analysis uses peak intensities to calculate the relative quantity of the elements in a sample by comparing them to other elements in the spectra or to values, the qualitative analysis uses distinctive peaks in the spectra to identify the components present in a sample. It has a dynamic range from the smallest detection limit to 100% with relative accuracy of 1–5% across the entire range, is sensitive to very low concentrations, and has minimum detection limits that are frequently less than 1% and below 0.1% in the best circumstances. In most circumstances, the method is essentially non-destructive, and sample preparation requirements are quite low [34].

8 X-Ray Photoelectron Spectroscope

One of the most popular surface analysis tools in use today is the X-ray photoelectron spectroscope (XPS), which is more accessible to researchers due to its user-friendly design. A surface-sensitive analytical method called X-ray photoelectron spectroscopy bombards a material's surface with x-rays and then measures the kinetic energy of the electrons that are released. The surface sensitivity and capacity to extract information about the chemical states of the sample's constituent components are two of this technique's key strengths that make it effective as an analytical approach. Almost every material, including plastics, textiles, and semiconductors, has had its surface studied using XPS, which can detect all elements with the exception of hydrogen and helium. Every material has a surface, and it is these surfaces that affect how different materials behave. Surfaces and surface contamination affect several factors, including surface wettability, adhesion, corrosion, charge transfer, and catalysis. For this reason, researching and comprehending surfaces is crucial.

8.1 Working Principle

In XPS, the sample is exposed to soft x-rays with energies below 6 keV, as well as the kinetic energy of the released electrons is measured (Fig. 6). The full transmission

of x-ray energy to an electron at the core produces the photoelectron that is released. The mathematical representation of this is

$$h\nu = \mathrm{BE} + \mathrm{KE} + \Phi_{\mathrm{spec}}. \tag{7}$$

It simply says that the *x*-energy ray's Energy (*hv*) is defined by the binding energy (BE) of an electron, its kinetic energy (KE), which is released, and the constant value of the spectrometer's known as work function (Φspec). The element and orbital in which the photoelectron was emitted are noted on photoelectron peaks. For instance, "O 1 s" refers to electrons that leave an oxygen atom's 1 s orbital. The sample should emit any electrons with binding energies lower than the energy of the x-ray source so that they may be seen using the XPS method. An electron's binding energy is a characteristic of the material and is unaffected by the x-ray source that ejected it. The binding energy of photoelectrons does not change when tests are conducted with various x-ray sources, but the kinetic energy of the photoelectrons that are released does, based on the energy of the X-ray used [34–36].

Finding out the chemical environment of the atoms in a sample is one of XPS's key advantages over other methods. The element's oxidation state and closest neighbors are two aspects of this chemical environment that have an impact on the photoelectron peaks' binding energy (and the Auger peaks).

Figure 7 depicts the logical parts of an XPS instrument. A region of a sample is illuminated by X-rays, which causes electrons to be expelled from it at a diversity of energies and orientations. The electron optics, which can be a group of electrostatic or magnetic lens units, gather a percentage of the released electrons determined by the rays that can be focused onto the analyzer entry slit and passed via the apertures. Electrons with a certain beginning kinetic energy are measured by adjusting voltages for such lens system which focus onto the entry slit that needed starting energy electrons and slows their velocity such that its kinetic energy upon going through

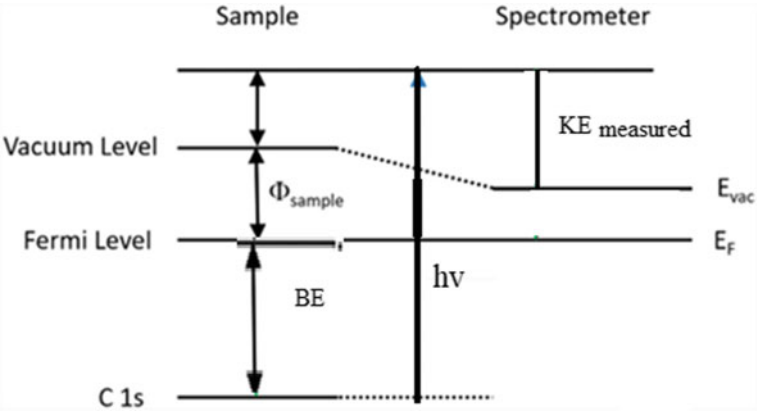


Fig. 6 Fundamental XPS equation is graphically illustrated in the energy level diagram

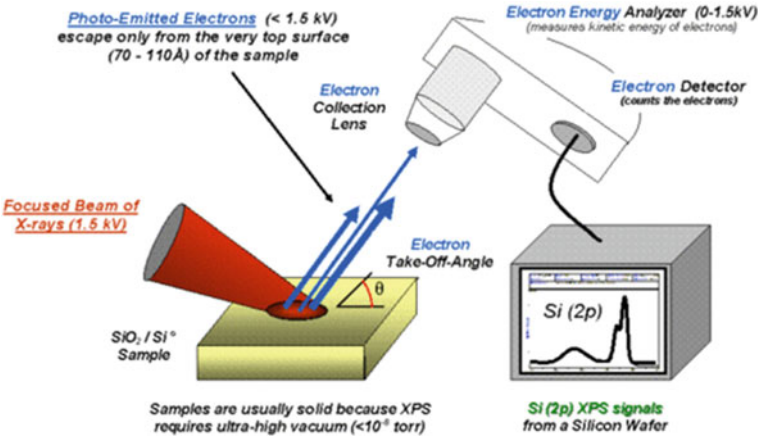


Fig. 7 Diagram depicting the instrumentation of the X-ray photoelectron spectrometer (Figure taken from the public domain: https://en.wikipedia.org/wiki/X-ray_photoelectron_spectroscopy)

the electron collecting lenses equals the required pass energy of the analyzer. It is important to scan the voltages supplied to these lenses in order to obtain a spectrum spanning a variety of initial excitation energy. The set of lens functions is the prescription for these lens voltages. Typically, the acquisition system's configuration files provide information on these lens functions. These lens functions are crucial to a spectrometer's ability to efficiently sample electrons, and an instrument's performance might suffer if the lens functions are not appropriately calibrated. It is vital to describe an instrument using a suitable transmission function for every one of the lens modes as well as energy resolutions since even in well-tuned equipment, the collection efficiency differs across the various operating modes.

9 Ultraviolet/Visible Absorption Spectroscope

Light in the visible and nearby near ultraviolet (UV) bands is used in ultraviolet/visible spectroscopy or UV/VIS. Molecules have electronic transitions at these wavelengths [37]. In this method, the sample being studied is illuminated, with part of the light being absorbed by the specimen. The sample must thus be thin enough for some light to pass through it. Another consideration is that the sample needs to be mounted on a support material that is transparent for the light wavelengths being employed, such as quartz. The valence electrons of the material are driven from its ground states to higher-energy excited states whenever visible or ultraviolet light is absorbed by the substance (Fig. 8). In electronic transitions, the orbitals' energies have fixed values. It is noted how much the starting and final intensities differed. The Beer–Lambert law, which is used to plot wavelength versus absorbance in a spectrum, defines absorbance as

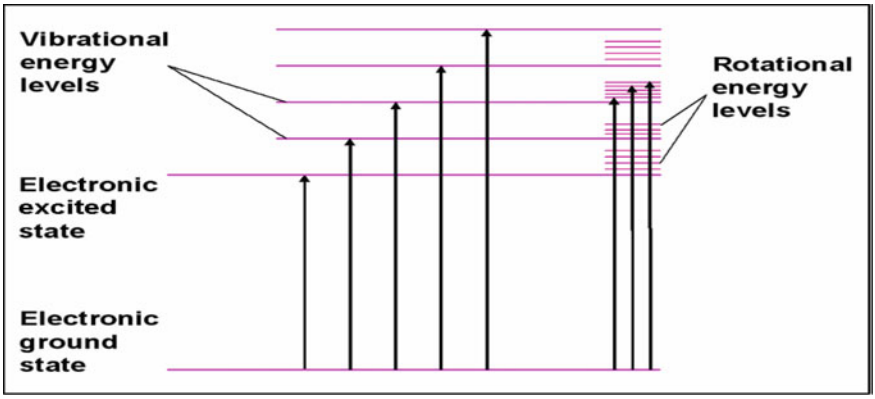


Fig. 8 Example of how electronic transition happens when light is absorbed

$$A = -\log_{10}(I/I_0), \tag{8}$$

where A is the determined absorbance, I_0 is the intensity of the incoming light at a certain wavelength, and I represents the transmitted intensity. The typically measured range of absorbance upon that vertical axis of most spectrometers is between 0 (100% transmittance) and 2 (1% transmittance). Maximum absorbance is indeed a characteristic value with the prefix λ_{max}.

The least energy between the filled-in valence band and the vacant conduction band in a crystal is the band gap. The E_{04} band gaps and also the Tauc optical band gap are the two most widely used definitions. When the absorption coefficient is equal to 10^4 for a photon, the E_{04} band gap is calculated. Extrapolating from a plot of $(\alpha E)^{(1/2)}$ against photon energy, one may get the Tauc gap. The magnitude of the Tauc optical gap is given by the intersection of this line with the energy axis [38, 39]. The absorbance variations of the thin film that was deposited were observed in this work using a UV/visible spectrophotometer (Cary 100, Japan). The reference film of glass was used to monitor the absorbance of the deposited nanocrystalline thin film.

10 Electrochemical Impedance Spectroscope

Early on in the twentieth century, electrochemical impedance spectroscopy (EIS) tests were performed largely to gauge the capacitance of a mercury electrode, which is an ideal polarizable electrode. An electrochemical method first appeared in the late 1960s, but measurements of the whole impedance spectra were not achieved until about the 1970s, when potentiostats had gained broad use. For comprehending electrochemical systems, the EIS is a potent tool. Briefly stated, this approach includes determining the cell impedance in response to a tiny (−5 mV amplitude) AC signal at any constant DC potential, at frequencies generally ranging from 5 kHz to 10 Hz (thus

the term impedance spectroscopy) [40]. It is possible to evaluate and qualitatively assess a number of processes, such as the charge transport in the electrode and electrolytes, interfacial charging at the surface films or the double-layer, charge transfer processes, and the mass transfer effects, if any, using a measured cell impedance as in the form of real and imaginary components and phase angle. These various processes involve various time constants, and as a result, the characteristics of these processes will manifest in the EIS spectrum at various frequencies [41]. An electrochemical cell (the system being studied), a potentiostat/galvanostat, and a frequency response analyzer (FRA) make up a standard electrochemical impedance experimental setup. FRA is a single-sine approach that involves applying the working electrode with a modest AC wave of 5–15 mV of a chosen DC bias voltage and measuring the AC current that results. By scanning the frequency and calculating the impedances using the AC voltage and current data at specified frequencies, this procedure is repeated. As seen in Fig. 9, the electrochemical cell in an impedance analysis can have three electrodes. The electrode being studied is typically referred to as the working electrode, and the electrode required to complete the electrical circuit is referred to as the counter electrode.

Typically, a liquid electrolyte is submerged behind the electrodes. There may be no electrolyte or solid electrolyte in solid-state systems. For conventional electrochemical applications, a cell with three electrodes is most frequently used [42]. To correctly calculate the working electrode's potential, a third electrode referred to as the reference electrode is needed. Since it is impossible to determine the precise potential of a single electrode, all potential measurements in electrochemical systems

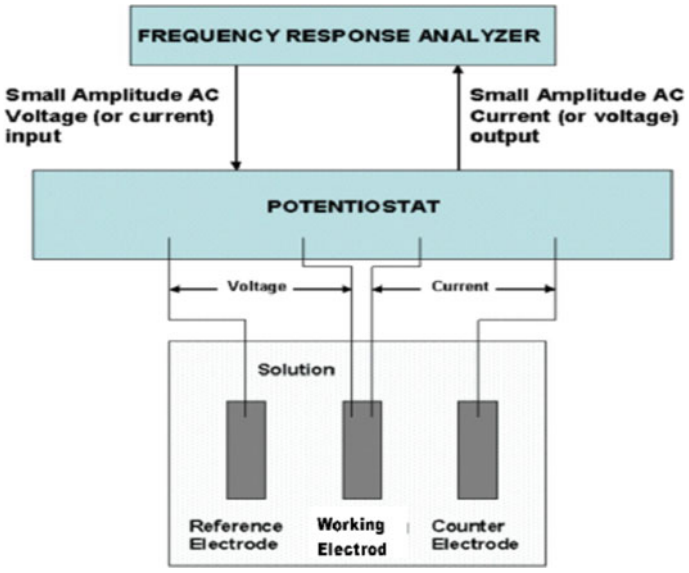


Fig. 9 Three-electrode configuration for EIS measurement

are made in relation to a reference electrode. Therefore, the reference electrode should be reversible and its potential should not change during the measurement.

The majority of corrosion experts have tried to use different analogue circuit element combinations to investigate impedance spectra. The following can be used to outline the arguments in favor of this method:

(a) Corrosion of alloys and similar conductive materials is an electrochemical degradation process driven by kinetics and thermodynamics.
(b) In real-life complicated and frequently poorly described systems that are typically encountered, this chemistry is frequently challenging to understand.
(c) Analogous circuit components let corrosion practitioners fill up knowledge gaps.
(d) Because of this bridging, electrochemical impedance spectroscopy can predict corrosion rates and processes in systems with limited information.

Capacitor, resistor, and inductor are common components in the particular circuit components.

Corrosion is an electrochemical reaction involving molecules and ions, which is one aspect that cannot be emphasized enough. The elements of similar circuits offer a means of simulating and explaining the corrosion process. They are not a part of the actual corrosion process. A parallel combination of a resistor and capacitor in series with a resistor in series as an illustration of a straightforward circuit can simulate a very passive alloy (such as titanium in water). This circuit is illustrated in Fig. 10a [43].

As seen in (Fig. 10b), a Nyquist plot results from plotting the real component of impedance versus the imaginary part. Nyquist representation has the benefit of providing a fast summary of the data and allowing for some qualitative conclusions. To avoid distorting the curve's shape when plotting results in the Nyquist format, the real and imaginary axes must be equal. When interpreting the data qualitatively, the curve's form is crucial. Losing the data's frequency dimension is a drawback of the Nyquist representation. The frequencies on the curve can be labeled as one method of solving this issue. The advantages of these techniques embrace the following [44]:

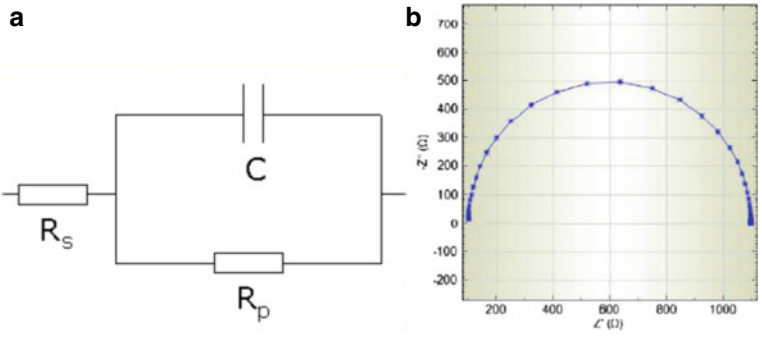


Fig. 10 **a** Electrochemical equivalent circuit and **b** a typical Nyquist plot where Rp is polarization resistance and Rs is solution resistance

(a) Since the applied polarization is low enough to preserve linear polarization circumstances—that is, conditions where polarization rises linearly with current—and since the rate equations are simplified as a result, it is non-destructive.
(b) Quick and simple measuring techniques that are currently feasible thanks to the development of computer-controlled equipment like potentiostats and frequency response analyzers and the corresponding software, which greatly simplify data collection and subsequent analysis.
(c) This method is simple to use and can be managed the simplest using a laboratory computer.

On the other hand, the weakness of this approach is mostly due to the difficulty in interpreting the data, imagining an appropriate electrical equivalent circuit to represent the electrochemical system, and quantitatively calculating the pertinent electrical parameters that would assist and comprehend the response of the system. This method has been used in the past with many electrochemical systems. In particular, it has been used to comprehend how (neutral) molecules and passive films adhere to electrode surfaces, evaluate the effectiveness of corrosion inhibitor coatings, and track the performance of energy conversion technologies like batteries and fuel cells. This method for non-destructively estimating the level of charge in batteries has been employed effectively in several systems. This method has been used to assess the ionic conductivity of electrolytes or thin polymer films as well as the rates of electrochemical processes, such as corrosion currents. This method allows researchers to look into the surface films that have an impact on the lithium primary cell's voltage delay and shelf-life properties.

11 Fourier Transform-Infrared Spectroscopy

The FT-IR analysis of synthesized samples was done to confirm metal–oxygen bond stretching vibration.

11.1 Working Principles

Infrared electromagnetic radiation is absorbed in this process, resulting change in the vibrational energy of molecules. Every molecule will typically be vibrating in some way, usually by stretching and bending. The energy that is absorbed will be used to alter the associated energy levels. It is an effective and powerful tool for determining inorganic and organic compounds with polar chemical bonds (like OH, NH, CH, etc.) and good charge separation [45].

11.2 Instrumentation and Working

Fourier transform-infrared spectrometer is shown in Fig. 11. source (a red-hot ceramic material), a monochromatic grating, a thermocouple detector, and cells made of sodium chloride- or potassium bromide-containing materials, among other components. The light of monochromatic is dispersed in this process. However, this sort of fundamental IR measuring architecture is now out of date. Fourier transform-infrared (FT-IR), a more recent approach, has been used in place of the old one. The instrument parts for this method are identical to those of the preceding one, and it uses a single, undispersed beam of light. In FT-IR, the sample is illuminated by an undispersed light beam, and the detector concurrently detects absorbance across all wavelengths [46]. This data is subjected to an automated mathematical operation known as the "Fourier transform" in order to acquire absorption information across every other and every wavelength. The FT-IR apparatus has two mirrors, one fixed and one mobile, with or without scanning the sample, in order to do this, sort of computation interference of light pattern is necessary. A relatively new advancement in the way data is gathered and transformed from an interference pattern to a spectrum which is known as Fourier transform-infrared spectroscopy (FT-IR).

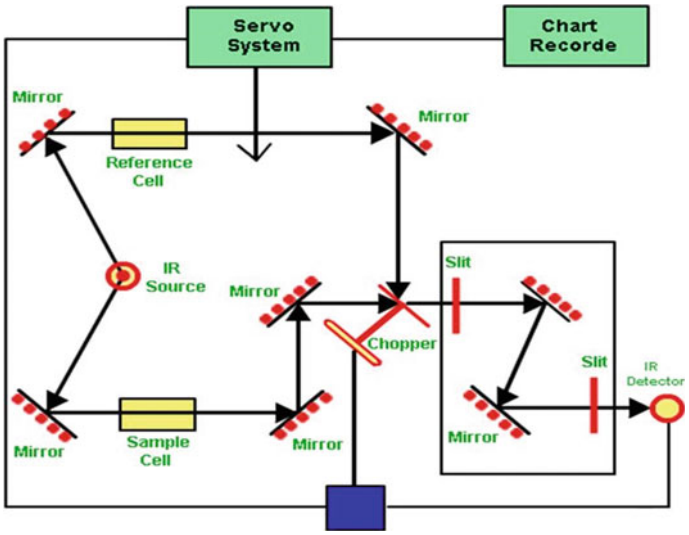


Fig. 11 Schematic representation of the FT-IR spectrophotometer

12 Zeta Potential

The charge that forms at the boundary between the solid surface and its liquid medium is known as the zeta potential. In other words, an important fundamental characteristic that is known to influence stability is known as zeta potential, which is a measurement of the strength of the electrostatic interaction between particles. This millivolt (mV) potential can develop as a result of many causes. This might involve the surface ionogenic groups dissociating and the surface area being selectively adsorbed with solution ions. The concentration of counterions adjacent to the particle surface increases as a result of the net electric charge at the particle surface, which also affects the ion distribution in the vicinity of the particle. The potential of a particle measured at its sliding plane while it is being affected by an external electric field is known as the zeta potential. It represents the potential discrepancy between the aqueous, inorganic, or organic layer surrounding the electrophoretic mobile particles at the sliding plane and the electric double layer surrounding them. A particle in solution creates its electric double-layer surface, which consists of two layers, instantly. The inner layer, or the Stern layer, is made up of particles with opposing charges that are strongly connected to the center of the core particle. A diffusive layer made up of both molecules and ions with opposing and similar charges makes up the next and outermost layer. The particles travel to the opposing electrode when the sample is exposed to an electrical field. While in the electrical field, a hypothetical plane within the diffuse layer serves as the interface between the layer of the surrounding dispersion and the moving particles. The zeta potential is present at this particle–fluid interface, and this plane serves as the typical shear plane [47, 48]. Charged particle electrophoretic mobility in an applied electric field is used to quantify the zeta potential. As a result, the area of the particle–liquid interface forms an electrical double layer. It can be used to enhance the formulation of dispersions, emulsions, and suspensions because its measurement provides an in-depth understanding of the causes of dispersion, aggregation, or crystallization and emulsification.

12.1 Zeta Potential in Electrophoresis

According to the definition of electrophoresis, it is the movement of charged polyelectrolytes or colloidal particles submerged in a liquid under the effects of an external electrical charge (shown in Fig. 12). In this scenario, the electrophoretic velocity, v_e (ms^{-1}), is the speed of the electrophoresis, and the electrophoretic mobility, u_e ($m^2\ V^{-1}\ s^{-1}$), is the velocity magnitude divided by the electric field strength. If the particles are moving in the direction of a lower potential, the mobility is positive; otherwise, it is negative. Thus, we obtain the equation $v_e = u_e\ E$, where E is the electric field that is applied externally. In the electrophoresis case, the formula for zeta potential is as follows: $\varepsilon_{rs} =$ relative permeability of electrolyte solution, ε_0 is the electric permittivity of vacuum, ζ *represents zeta potential,* and η is the viscosity.

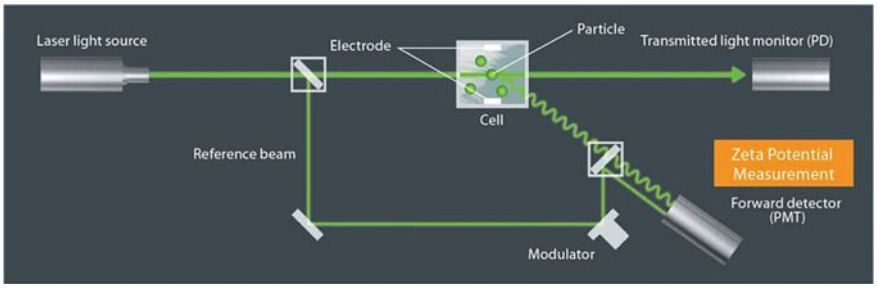


Fig. 12 Ray diagram of laser Doppler electrophoresis representing its mechanism (courtesy: Horiba Scientific)

$$u_e = \varepsilon_{rs}\varepsilon_0\zeta\eta - 1 \tag{9}$$

$$v_e = \varepsilon_{rs}\varepsilon_0\zeta\eta E - 2 \tag{10}$$

Colloid particle stability behavior with regard to zeta potential.

Zeta potential	Stability of the particles
0 to ± 10	Speedy coagulation
10 to ± 30	Initial stability
30 to ± 40	Modest stability
40 to ± 60	Good stability
Greater than ± 61	Outstanding stability

13 Surface Plasmon Resonance Spectroscopy

In order to create the most effective and widely used optical biosensor, surface plasmon resonance (SPR) sensing has emerged as one of the most adaptable approaches.

In addition to being widely used in the identification of chemical and biological analytes, SPR biosensors have emerged as a key instrument for examining the kinetics of biological molecule interactions [49]. In addition, by combining the SPR method with an imaging system, one may easily perform high-throughput and real-time tag-free biosensing in two-dimensional (2D) microarray analysis and parallel monitoring of many biomolecular interactions. Oscillations in charge density at the interface in between metal and a dielectric produce the visual phenomena known as the SPR. At the interface of the research media, such collective oscillation of the metal's electron gas produces extremely strong and tightly contained electromagnetic fields. The SPR is also responsible for other phenomena, such as the vivid hues

of metallic colloids, which corresponds to the entire reflection in thin metal sheets, and diffraction abnormalities in metal gratings. In recent years, these phenomena have captured the interest of researchers, deepening our understanding of the interaction between light and metal. We can distinguish between two main classes of SPR sensors based on whether the surface plasmon resonance is spreading or localized. The surface plasmon polaritons (SPPs), which are detectors relying on moving surface plasmons in thin metallic sheets and gratings, make up the first category. The second category consists of metal nanostructure-based sensors. Metal nanostructures show charge density oscillations that result in extremely strong and restricted electromagnetic fields, just as flat metal films and gratings. The term localized surface plasmon resonances (LSPRs) is frequently used to describe these excitations. It has been widely utilized in recent years to measure the specificity, affinities, and kinetic characteristics of the binding of macromolecules, including protein–protein, protein–DNA, receptor–drug, as well as cell/virus–protein bindings [50]. Four practical SPR sensing methods, including intensity, wavelength, angle, and phase investigations, have received a lot of attention to date [51]. The shift of the SPR dip is converted into a change in reflectivity in the linear section of the SPR angular/spectral response curve in the intensity probing SPR. The SPR spectral profile can be acquired in the wavelength investigation mode by scanning the incident wavelength or by examining the reflected beam with a spectrometer. The SPR angular spectrograph may be continuously scanned in the angular investigation mode to track the shift of the SPR dip. By identifying the phase difference in between the signal beam and the reference beam, the SPR phase shift may be determined in the phase investigation mode.

The surface plasmon resonance (SPR) biosensor provides unique real-time and label-free measuring abilities with high detection sensitivities, making it an effective tool for exploring the kinetics of inter biomolecular reactions (Fig. 13). SPR technology had also been widely commercialized over the last several decades, and significant technical work has been done to constantly enhance its performance. The advancement of SPR techniques is concentrated on the identification of the samples' portability, sensitivity, and speed. In order to detect chemical and biological ionic species with high throughput, real-time, and high sensitivity, numerous attempts have been done. The significant improvements in nanotechnology have led to several novel concepts incorporating nanoscale structures in SPR sensing that have surfaced more lately. In order to monitor interactions between tiny molecules, new SPR approaches have emerged that are based on the aforementioned concepts.

14 Dynamic Light Scattering

For determining the size of particles in suspensions and emulsions, dynamic light scattering (DLS) is indeed a trusted and accurate measuring technique. It is based on Brownian particle motion, which explains why smaller particles move more quickly in a medium than bigger ones. The size distribution may be seen from the information on diffusion speed included in the light dispersed by the particles. Dynamic light

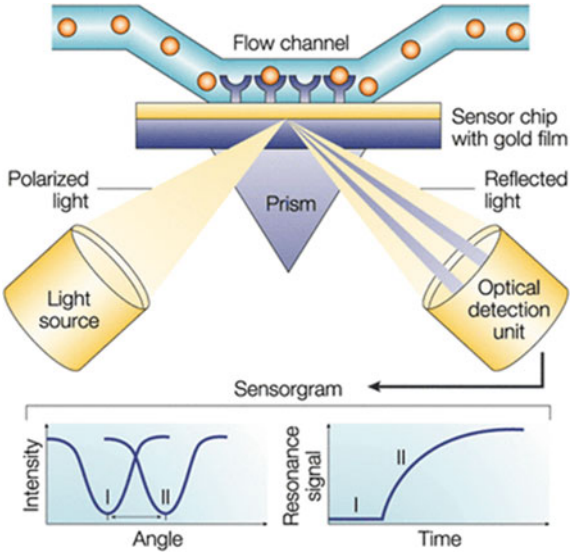


Fig. 13 Sketch diagram representing an SPR sensor. (Image taken from Twitter Creative-Biolabs @creativebiolabs dated May 21, 2021, ProteOn™ XPR36 protein interaction array system)

scattering enables the analysis of particles in a size range from 0.3 nm to 10,000 nm. Laser diffraction (LD) techniques often reach their limits for particles smaller than 100 nm due to the weak signal and the low angular variance in the scattering signal. It is a technique suited to the analysis and characterization of nanoparticles. Other few advantages include measurements of both highly concentrated and highly dilute samples, and the ability to determine zeta potential, molecular weight, and concentration, which is inbuilt into many analyzers of today's modern instrumentation. The dynamic light scattering technique measures motion optically by recording the scattered light signal at a fixed angle thus giving an advantage of non-destructive sample characterization. A coherent, monochromatic light source (LASER) is used to illuminate the particles, and the light reflected by that of the particles is then captured on camera. The analysis of the light dispersed as a result of light's interaction with matter provides details on the sample's physical properties. Typically, a monochromatic beam is focused onto the sample in light scattering tests, and a detector subsequently captures the dispersed light at a specific angle. When comparing the more uniform light scattering through each angle for tiny particles (Rayleigh theory) with the variations in the light scattering across various detection angles from bigger particles (Mie theory).

When light is detected using static light scattering, its intensity is averaged over time, and from this we may determine the molecular weight of the particle as well as its radius of gyration (R_g). However, dynamic light scattering (DLS) allows for the determination of the diffusion coefficient (D), which itself is related to the particle's hydrodynamic radius (R_h) via the Stokes–Einstein equation by monitoring the variations in light intensity over time as a result of particle Brownian motion [52].

$$D = \kappa_b T / 6\pi \eta R_h \tag{11}$$

where Boltzmann constant is κ_b (1.380×10^{-23} kg · m^2 · s^{-2} · K^{-1}) and T and η represent absolute temperature and viscosity of the medium, respectively.

Particle diffusion is influenced by temperature, medium viscosity, and particle size, as seen in Eq. (11). DLS calculates the amount of light that has been dispersed over time. When the intensity is interrelated over time, the scattered intensities are initially comparable, but with time they become less similar as a result of the movement and aggregation of the particle. The photon correlation then deteriorates at early stages of the experiment, and the diffusion is quicker for tiny particles. The closeness of the intensities over time does, however, endure for longer durations since massive particles diffuse relatively slowly; hence, the photon correlation takes longer to fade. With regard to time spans (on the n_s and μ_s timeframes), a digital correlation monitors intensity fluctuation and associated correlation. A normalized integration of such intensities at the start and a delayed time τ make up the measured parameter [53, 54].

$$g_2(\tau) = \langle I(t) \cdot I(t+\tau) \rangle / \langle I(t)2 \rangle \tag{12}$$

Figure 14 depicts a DLS instrument's fundamental configuration. The sample within a cuvette is targeted by a laser with a single frequency. The incoming laser light is dispersed widely if there are any particles in the sample. The Stokes–Einstein equation uses the signal from the scattered light, which is monitored over time at a certain angle, to calculate the diffusion coefficient and particle size. A gray filter is frequently positioned in between the laser and the cuvette to reduce the incoming laser light. The user can manually set the filter parameters or the instrument will automatically modify them. When measuring turbid samples, the detector would not be able to handle the number of photons. In order to get an adequate yet manageable signal at the detector, the laser light is attenuated.

For measuring particle size, modern DLS equipment has two or three detection angles. Depending on the sample's turbidity, side scattering (90 degrees) or backscattering (175 degrees) is preferable. Aggregation can be observed at a forward angle of 15°. The dispersed light signal's temporal variation is significant since it provides insight into the motion of the particles. The fluctuations are caused by the fact that

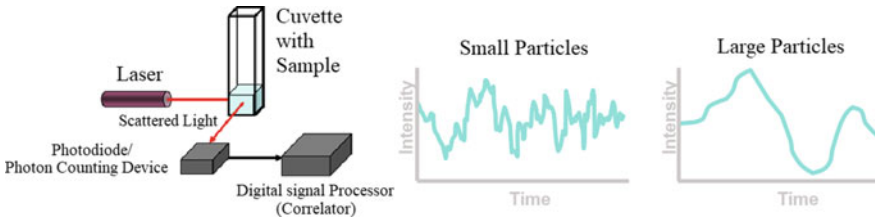


Fig. 14 Representation of the DLS instrument with a ray diagram and important components along with an intensity-time graph with particle size

the particles scattering the light move relative to each other, resulting in constantly changing interferences within the total scattered light. As a result of the particles' position or velocity being dependent on time, the light dispersed by them contains a few small frequency changes. Measured over time, motion causes a distribution of frequency shifts. These shift frequencies can be determined by comparison with a coherent optical reference. In dynamic light scattering, the shift frequencies are on the scale of 1 Hz to 100 kHz, which can be easily measured.

15 Nuclear Magnetic Resonance

NMR spectroscopy is a physicochemical investigation technique based on the interaction of radiofrequency radiation delivered externally with atomic nuclei. Nuclear spin, an inherent feature of atomic nuclei, changes as a result of the net energy exchange that occurs during this interaction. A physicochemical method known as nuclear magnetic resonance (NMR) spectroscopy is used to determine a molecule's structural information. Isidor I. Rabi's 1938 demonstration of the physical phenomena of magnetic resonance serves as its foundation. The very first efficient and effective studies of NMR in condensed matter were acquired separately in the 1940s by two research teams. For pioneering contributions to the discipline of magnetic resonance, the two leading researchers of these teams, Stanford University's Felix Bloch and Harvard University's Edward M. Purcell, shared the 1952 Nobel Prize in Physics [54–57]. Ever since, NMR has advanced alongside other fields of technology, including rapid Fourier transform-capable computers/workstations, effective spectrometer management, and reliable high superconducting magnets. Due to the characterization technique's restrictions and technical shortcomings, NMR was only very infrequently employed for solid materials up until the previous decade. However, the enhancements in magnetic angle spinning (MAS)-induced spectrum resolution have made NMR a crucial tool for examining the local structure of solid materials. By using magnetic field gradients, NMR may deliver spatial information. NMR spectroscopy developed in the modern age with developments in many other disciplines, but may not be confined to mathematics, physics, and informatics. Superconducting magnets and computers were both introduced into NMR equipment in the 1960s, which allowed for a significant increase in sensitivity as well as the creation of novel NMR experiments and apparatus. As a result, researchers have created several cutting-edge approaches to examine complicated systems, including membrane proteins, metabolically highly complicated materials, and even biological tissues. One of the most effective methods for determining the structures of chemical species as well as for researching molecular dynamics and interrelations is NMR spectroscopy [58, 59].

As nuclear spin behavior is the focus of NMR, nuclear spin is described by a quantum number (I), which changes depending on the isotope under consideration. NMR spectroscopy can only identify atomic nuclei with $I \neq 0$. (NMR-active nuclei, such as ^{1}H, ^{2}H, ^{13}C, and ^{15}N). These magnetic nuclei that exhibit NMR activity

behave like small magnets or magnetic dipoles and can align with applied magnetic fields from the outside. The gyromagnetic ratio (γ), whose value varies depending on the isotope, is a constant that describes the force emitted by the small magnets [60–63]. Every element's nucleus is charged; therefore when protons and neutrons inside the nuclei do not couple up, the total spin of the nucleus produces a magnetic dipole along the spin axis. The size of this dipole, also known as the nuclear magnetic moment, is a fundamental characteristic of the nucleus. The internal geometry and structure influence how charges are distributed in the nucleus symmetrically. $I = 1/2$ is the spin angular momentum number for spherical distributions, such as the 1 s hydrogen orbital. This means that the magnetic moment magnitude in a certain direction can have two equal and observable values that correspond to the spin quantum numbers + 1/2 and − 1/2. Accordingly, any nucleus submerged in a magnetic field H along the z-axis may be regarded as oriented either alongside the field ($I_z = -1/2$) or just against it ($I_z = +1/2$). The synchronization along the field is a good energy state. Energy disparity (ΔE) between the states grows linearly with the applied magnetic field (H), or $\Delta E = \gamma \hbar H$, where $\hbar = h/2\pi$ and h is Planck's constant, γ = proportionality constant (gyromagnetic), which varies depending on the kind of nuclei (^{1}H, ^{2}H, ^{13}C, etc.). Higher spin numbers are also found in nuclei with non-spherical charge distributions, such as the hydrogen 3d orbital. The alignment of magnetic dipoles of NMR-active nucleus in S (S = 2I + 1) orientations or spin states, relative to the field, occurs in response to the application of an external magnetic field (B). Quantum mechanics has a limit on this alignment. The nucleus in question rotates with frequency n and may be expressed as follows:

$$v = \mu \beta_N \beta_0 / hI \tag{13}$$

where μ represents the nucleus magnetic moment and β_N as nuclear magneton constant. The gyromagnetic ratio (γ) can be expressed as

$$\gamma = 2\pi \mu \beta_n / hI. \tag{14}$$

By simplifying the above equation, we get

$$v = \gamma \beta_0 / 2\pi. \tag{15}$$

When some NMR-active nuclei align with an external magnetic field, their nuclear spins can take on two distinct orientations (B0). The least energy level of the nucleus is related to one orientation (parallel to the externally applied magnetic field), while the greatest energy level is connected to the opposite orientation (antiparallel to the externally applied magnetic field) (Fig. 15a). The gyromagnetic ratio (Eq. 14) and the magnetic field both alter the disparity between energy levels (E), which has an impact on the technique's sensitivity.

When radiofrequency is used to irradiate nuclei, magnetic resonance is produced. Nuclear spins' orientations shift as a result of these transitions between energy levels. The magnetic vector (μ) connected to the nuclear magnetic dipoles as a result of

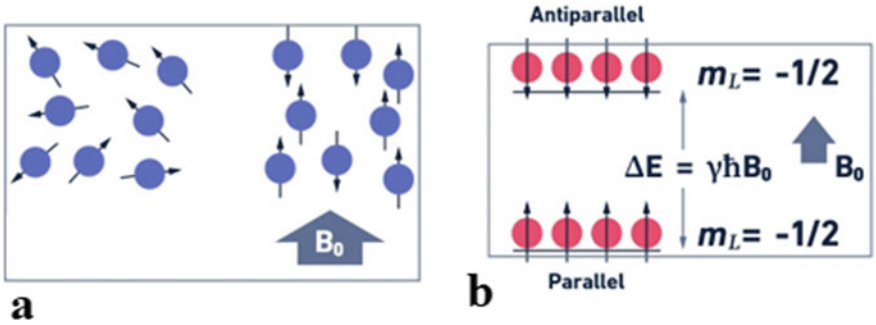


Fig. 15 Sample's nuclear spin orientations (parallel and antiparallel) in accordance with the path of an externally applied magnetic field B0 (left panel). The two potential energy levels in nuclei with $I = 1/2$ and the dispersion of nuclear spin populations in those levels (right panel)

this precession movement has a component parallel to the magnetic field (μ_z) and other perpendiculars to the magnetic field (μ_{xy}), with the latter consisting of a net zero value in the absence of external disturbances. Since the magnetic field is too strong in the z direction, it is simply not possible to analyze the signal in an NMR experiment. As a result, the z component's magnetization must be transferred toward the xy plane. In order to do this, a magnetic pulse perpendicular to B_0 is delivered that has frequencies near the Larmor frequency in order to resonate nuclear spins, which produces a nonzero μ_{xy} component. Following this pulse, there occurs a relaxation phase, and the μ_{xy} component eventually regains its overall zero value (Fig. 16b). This relaxation causes energy to be released as radiofrequency, creating the distinctive signal known as free induction decay (FID), which is detected by the detector. This FID is then converted into an NMR spectrum, which is a graph of intensities vs frequencies [64, 65]. Distinct spin states have distinct energy levels, and photons of RF frequency can bridge these levels. Promotions between spin states (Fig. 16) take place whenever the incident frequency precisely matches the resonance frequency. Furthermore, the excited nuclei might relax into lower spin states by a process known as spin flipping [66]. The two most common processes for relaxing excited nuclei are spin–lattice and spin–spin relaxation. They are both non-radiative processes. An excited nucleus' energy is transferred to an electromagnetic vector during spin–lattice relaxation (like a polar solvent molecule, the intramolecular group goes through vibrational–rotational processes). In contrast, more energy is added to a comparably relaxed nucleus during spin–spin relaxation. The excited nucleus may possibly re-emit the extra energy in addition to this. The pace of relaxation controls the effective excitation. Sharp spectral lines are produced and the average half-life of relaxation is extended (to around 1 s) due to inefficient energy transfer, which can happen in non-viscous fluids with randomly oriented molecules, for example [67].

Three primary parts make up an NMR spectrometer: a superconducting magnet, a probe, and a sophisticated electronic apparatus (console) run by a workstation (Fig. 17).

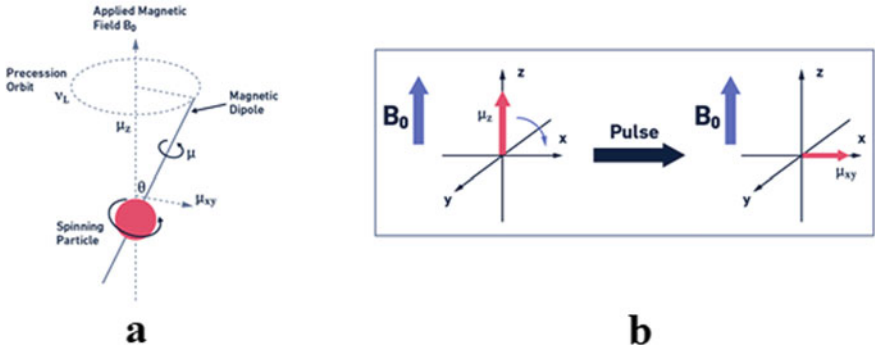


Fig. 16 Nuclear spin dynamics when an external applied magnetic field is present (**a**). Diagram of a fundamental NMR experiment, in which the introduction of a magnetic pulse causes the magnetization to move to the *x*–*y* plane (**b**)

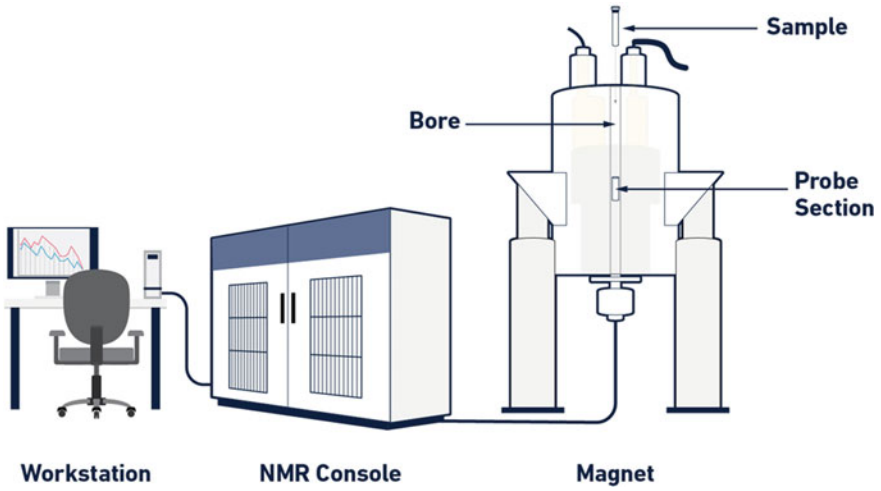


Fig. 17 NMR spectrometer's general layout and essential parts

The creation of a powerful magnetic field by the magnet causes the atoms in the sample to align their nuclear spins. Since today's NMR spectroscopy magnets are made of superconducting materials, they must operate at very low temperatures (around 4 K). NMR spectrometers have a cooling system built into them as a result, which consists of many layers of thermal isolating materials, and inner jacket filled with liquid helium, a second jacket filled with liquid nitrogen, and a cooling fan (Fig. 18). The instrument's most important component, the "probe", is a cylindrical chamber encircled by the superconducting magnet. The sample is inserted into the probe, coming into contact with the magnetic field. In addition, the probe has a number of magnetic coils positioned all across the specimen (Fig. 18). Numerous

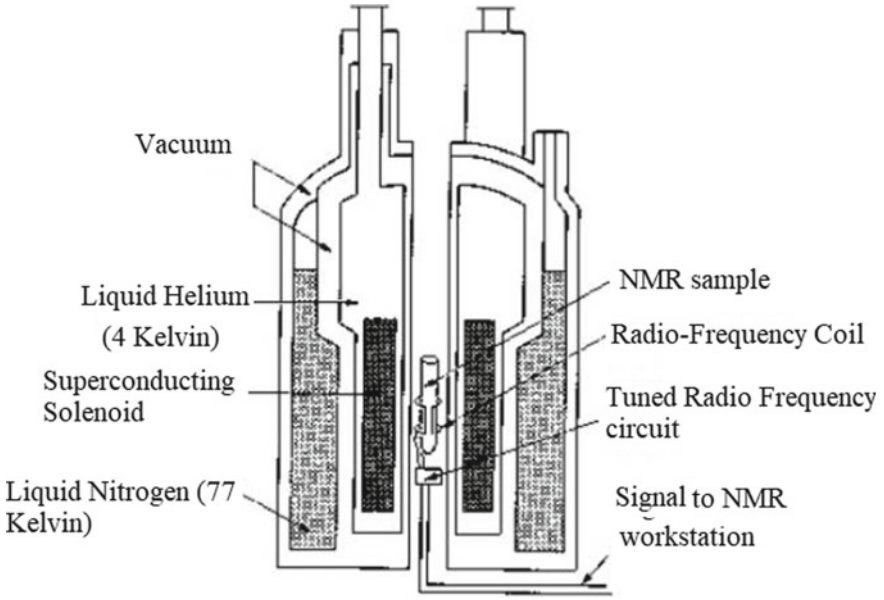


Fig. 18 Cross-sectional view of internal components of an NMR spectrometer

uses exist for these coils. On the one hand, they are utilized to irradiate the radio frequency pulses and to find and gather the NMR signal the specimen emits. In addition, they also allow for the regulation of magnetic field uniformity and the implementation of pulse gradients, which are employed in several NMR research [63, 65, 68].

Last but not least, the spectrometer's electronic system regulates all experimental settings and enables workstation-based setup and change of any NMR experiment parameter. Data collection and subsequent mathematical translation into an NMR spectra are also handled by this system. The spectrum has a number of peaks with varying intensities that are related to the chemical shift, which is calculated from the Larmor frequencies of the various atomic nuclei in the specimen [69].

16 Challenges and Future Perspectives

Tools for clinical analysis, food safety, and environmental analysis that have long been used include enzymes and antibodies. Biosensors have only been used in a few number of applications, despite the high promise and high hopes in the early 1980s. A range of biosensor platforms with varying application have been created, including wearable, implantable, and also most lately, ingestible biosensors, with the diversity of biomolecules that have been used both as the biological recognition layer and as analytes. Biosensors have been developed and applied in many scientific

and technical fields, with a focus on the food business, environmental monitoring, and healthcare and medical fields. Research on biosensors has greatly profited from the use of innovative materials and technologies, similar to other scientific and technical domains. One such example is nanotechnology, which consistently leads to the development of biosensor systems that are more effective. The most typical nanomaterials for use in sensors include graphene, carbon nanotubes, quantum dots, and gold nanoparticles [70]. Nevertheless, despite the extensive scientific and technological advancements recorded in the field of biosensors, a discrepancy between these advancements and the number of commercially accessible products based on biosensors is plainly visible. Such a gap has likely been caused by the challenges of mass-producing sturdy and dependable devices with excellent specificity, sensitivity, and most importantly, repeatability. All application sectors face these difficulties, including the medical industry, which while having the greatest number of commercially accessible devices still lacks items that can match the demands of portable, affordable, quick-response, disposable, and environmentally friendly applications.

The use of biosensors as advanced analytics in critical scientific and technical fields is a scenario that is highly exciting, but there are still issues that pose significant obstacles to the profession. Enhancing biosensors' precision, sensitivity, and specificity as well as repeatability and scalability of production in order to create disposable, inexpensive, and highly effective devices, surface-based biosensors provide a wide range of options, from huge flat surfaces to extremely rough surfaces like nanoparticles and quantum dots. This makes the tuning of nanomaterial surface layers for sensing a difficulty even today. A bigger surface area opens up a wide range of opportunities for sophisticated detection techniques, but it also presents a number of difficulties, one of which is the difficulty in precisely measuring the structure and makeup of the surrounding environment as well as adsorbed molecules. When used in situ (in an aqueous buffered environment), surface analysis is most reliable for biosensor applications. However, this method of designing and fabricating biosensing surfaces has additional technical difficulties related to interfacial characterization. Although in situ optical or probe microscopy examinations of the interface can produce nanometer-resolved surface assessments, they are nevertheless subject to the subjectivity of the region chosen for research. It will eventually be necessary to employ many strategies in order to thoroughly investigate the effectiveness of the biosensors. In order to improve the surface area, accessibility, and grain boundaries of the connected probes [71, 72], nanostructured metal surfaces have been utilized.

Utilizing SEM, TEM, and AFM, a great deal of research has been done on the monolayer-coated electrode surface [73, 74]. These techniques offer clarity that is suitable with numerous electrochemical techniques, from the micro to the atomic level. In comparison with optical approaches, the AFM's area of view is quite tiny. Scanning probe techniques can show how the initial layer of probe molecules that have been adsorbed on the surface atoms coordinate with them under normal imaging settings. It may be possible to obtain additional information from later layers by carefully manipulating the imaging circumstances. The molecular layer covering the electrode surface will ultimately determine how well the electrochemical biosensor

performs analytically, allowing for improved insight and control over the features of the probe interface and an increase in the measurement's sensitivity and selectivity.

Ex situ surface examination techniques (such as SEM, TEM, AFM, and XPS) are often utilized, however doing so removes the data from the aqueous environment, which makes them more difficult to interpret. The surface can be drawn out in terms of the chemical environment and probe design because many in situ technologies are sensitive to these less-than-perfect circumstances. The creation of strategies that guide us in the direction of desirable configurations may result in biosensors that are more dependable, robust, and capable of functioning better.

Optical spectroscopic techniques have long been used to characterize the metal surface in situ. Recent developments and an increased understanding of optical spectroscopy, instrumentation, and surface-enhanced methods have made it possible to characterize surfaces that have undergone molecular modification. Important molecular-specific information, such as the composition and activity at the interface, is provided by these measurements. Chromophore-containing monolayers can be studied in situ using electro-reflectance techniques [75]. Depending on electron transfer kinetics that is connected to optical changes, electro-reflectance studies may discriminate between the various components on a surface. Chemically detailed information about the molecular makeup of the interface at various potentials may be obtained using in situ infrared spectroscopy. IR spectral response, a non-destructive and label-free technique, has good surface sensitivity and may disclose molecule direction, protein conformation, and functioning. Key information about the activity taking place at the interface may be gleaned from the thorough assessment of peak locations.

Potential or charge upon that electrode surface can induce alterations in the molecular adsorbate's properties, which can be seen using potential modulation methods. SPR has been employed often for the investigation of probes immobilized on surfaces, particularly for the evaluation of binding kinetics and non-specific adsorption in actual solutions [76, 77]. SPR offers a means to quantify surface-bound aggregates since it is sensitive to areas that are 100 nm or less from the electrochemical surface (depending on the evanescent wave decay length). To conclude this chapter has given an overview of different characterization techniques and their fundamental operational modes for operating to get desired characteristics of particular biosensors and nanomaterials in general. The challenges discussed must be overcome to have better biosensors that will be portable, low-cost, fast response, disposable, and importantly in everyone's reach.

17 Conclusions

The aim of this chapter is to facilitate the comprehension of the work by an inexperienced as well as an experienced reader in various characterization techniques that can be employed in the study of nanomaterials for various applications and in particular biosensors and, in some way, to include a general description of a group

of basic characterization techniques in a clear way. For that, the principles on which the different techniques are based are presented. We have highlighted the applications of each characterization approach through this thorough overview, highlighting their benefits, drawbacks, and limits, as well as outlining how they might be utilized successfully for the particular application. It is common for a researcher to employ more than one approach to thoroughly and accurately assess even a single attribute in order to provide a complete picture of the range of properties related to a nanomaterial. This chapter will serve as a reference, assisting the scientific community in better comprehending the different techniques and the science underlying them by outlining the function of each approach in a comparative manner. This will enable researchers to select the most appropriate methodologies for their characterization and to more accurately evaluate how they are being used.

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Nanomaterials for Toxicity Constraints and Risk Assessment

Abhishek Kumar Jain, Divya Chauhan, Nitin Gupta, Rudra Pratap Singh, Ankit Kumar Singh, and Vipendra Kumar Singh

Abstract Nanotechnology is one of the quickest developing fields dealing and controlling matter within approximately 1–100 nm in size dimensions. These small and unique sizes of nanomaterials (NMs) enable them to use in various novel fields including biomedical, consumer products as well as industrial products. Recent scientific reports demonstrate that the assembly and utilization of NMs are increased in consumer products. Extensive use of NMs has enhanced the exposure frequency of NMs in our daily life. Therefore, the toxicity constraints and risk assessment of NMs found in the living environment is an area of hike in scientific concern. The information and data provided in this chapter are acquired from the literature. It shows that NMs determined in our surroundings may also have conceivable toxicological results. However, the recent studies on the toxicological effects of NMs are non-identical. These studies can be applied in-vivo, in-vitro, and in-silico test systems, diverse sources of test NMs, and various techniques for the characterization of NMs

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R. S. Mane et al. (eds.), *Nanomaterials for Sustainable Development*,
https://doi.org/10.1007/978-981-99-1635-1_3

under experimental conditions. Therefore, available information is hard to illustrate. More studies on NMs related to toxicity, biological interaction, and impact on human health are expected. The available test methods for risk assessment of NMs require verification. Therefore, basic information is not presently accessible for risk assessment of various NMs that might be carried in different industrial and consumer products, or these NMs may enter into the environment and market in near future. Established and accurate test methods are required for the risk assessment of NMs. Therefore, in the lack of well-optimized and validated test methods, any concrete regulatory testing conditions for NMs are presently premature. In the present chapter, we wrap up the physicochemical characteristics, route of nanomaterial exposures, and various test methods used for the risk assessment of nanomaterials on human health.

Keywords Nanotechnology · Nanomaterials · Risk assessment · Human health · Toxicity

1 Introduction

Nanomaterials (NMs) are the understanding and control of matters such as nanoparticles (NPs) of 1–100 nm dimensions [1, 2]. Due to size variation, these NMs have different shapes and display special physicochemical and biological attributes that are non-identical from comparable materials of relatively larger size and mass [3, 4]. The small size and high volume to the surface area of NMs are affiliated with the prospective for excellent stability, physicochemical and biological activity, and greater strength [5–7]. Therefore, NMs have a vast range of applications and thereby become a billion-dollar industry worldwide by manufacturing the mat commercial levels such as quantum dots (QDs), metal oxide nanomaterials (MONMs), fullerene, carbon nanotubes (CNs). NMs are consistently used in various applications in different fields of human interest such as water treatment [8], health sector [9], food and nutrition industry [10–12], drug delivery [13–15], production and engineering sector, as well in our everyday life [16]. Despite this, NMs are also used extensively in the food industry to: enhance colour and texture for nutrition fortification, enhance barrier properties of packaging materials, enhance bioavailability, and enhance food preservations [17, 18]. NMs permit us to make functional systems and devices by directing matters at the atomic and molecular levels. Due to nanosize, lightweight, and lowest demands of power, excellent sensitivity and high specificity are appropriate refinements seen in the design of the sensor. Due to their huge utility for diagnosis as well as treatment, NMs have been thoroughly utilized in biomedical science and personal care products [19]. As per the data of 2014, more than 6214 institutes and/or organizations from 32 nations have utilized NMs in approximately 1814 consumer items. Approximately, 42% of the items belonged to the health sector [19]. The “nanodata base” is a catalogue of economically or commercially listed items containing NMs manufacturing of approximately 3000 items in

the consumer market of Europe. As per the data of the repository, most of the NMs are (approximately 2000) utilized in the health sector with approximately 900 items belonging to the category of cosmetics and personal care items. The most thoroughly utilized NPs for these purposes include NPs of silver (Ag), titanium, and silicon [20, 21]. The growth in the application of NMs can immediately lead to the expanded presence of NMs in our surroundings and consequently, at once increase human exposure. There is a crucial public interest in better interpretation of the negative health impact of NMs existing in our environment. Despite these huge developments in the field of nanotechnology, the concern about whether NMs endow side effects has been initiated in the form of an agenda. The synergy of NMs, i.e. smaller size and higher surface area, with the microenvironment of cells and tissue can exhibit severe toxicity that is incapable to be generated with chemically similar and greater counterparts in living organisms.

2 Physicochemical Properties of NMs Related to Toxicity

NMs have exceptional features relative to their greater counterparts which transmit their useful properties; ironically, they may also grant them a distinctive mode of action of toxicity. Overall, toxicity from NMs has been thought to come from their size, shape, surface area, and composition, and so forth as discussed in the following parts and illustrated in Fig. 1.

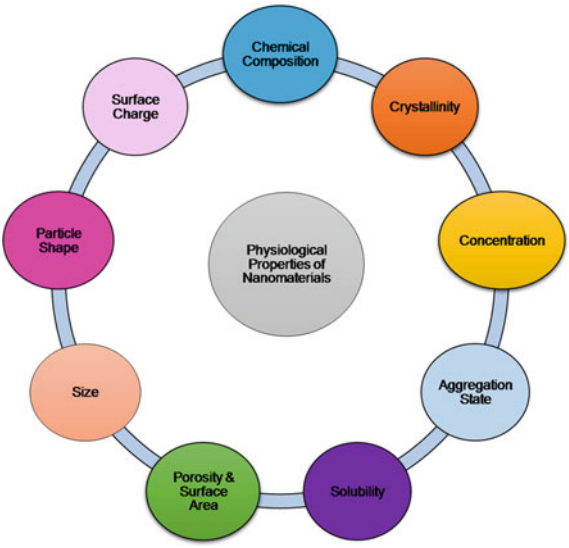

Fig. 1 Physicochemical properties of NMs

2.1 Effect of Surface Area and Size

Surface area and size of the NMs are crucial for their interaction with cellular systems. Reducing the dimensions and size of materials leads to an exponential enhancement in the surface-by-volume ratio, thereby creating the surface area of NMs more reactive individually and to its adjacent setting. NMs surface area and size govern how the biological system reacts to distribute as well as eliminate the NMs [22, 23]. Several biological processes such as cellular uptake, endocytosis, and efficiency of nanoparticle processing in the pathway of endocytic signalling are associated with the size of NMs [24, 25]. Different scientific groups have recently assessed in-vitro toxicity of NMs of diverse sizes utilizing different types of cells, exposure times, and different culture settings [26, 27]. However, in-vivo assessment of NMs is challenging due to their more sophisticated nature in the living systems and requires further detailed information on the NMs [28], though various researchers have calculated their cytotoxicity concerns in living systems applying different animal models. The toxicity of NMs associated with size can be ascribed to its potential to enter into the living systems [29] and then alter the composition of different macromolecules, thereby hampering the essential functions of biological systems [30]. In addition, the surface areas of these NMs are that exhibit toxic illustrations such as inflammatory responses in the lung and other epithelial cells in animal models [31]. With a gradual decrease in the size of particles, the surface area also changes which causes a concentration-dependent gradual increase in deoxyribonucleic acid (DNA) damaging and oxidation potentials of these NPs [32] much higher as compared to the larger particles with the same mass concentration [33]. Various studies associated with toxicity have documented that NPs smaller than < 100 nm (in dimensions) cause severe respiratory health impacts as compared to larger size particles of the same compound [33, 34]. Another study also revealed that instillation of 80 nm particles of Ir192 caused bioaccumulation in the liver of rats with an increase of 0.1% of the total amount, while the smaller sized particles (15 nm) showed an increase of bioaccumulation to an increase of 0.3–0.5% [35]. The size of NMs also enhances oral cytotoxicity. In general, the oral cytotoxicity enlarges with the reducing size of NPs. Oral cytotoxicity of NPs of copper (Cu) can be enhanced by reducing its size. But large sized particles are the least toxic even at their higher concentrations [36].

2.2 Effect of Shape

The shape of NMs is one of the crucial parameters in which there is limited absolute information with regard to its connection with cytotoxicity. Recently, designing NMs has fascinated much attention and led to the production of NMs with different shapes such as wire, rod, sheet, sphere, rings, tubes, fibres, and planes. Also, unique geometrical shapes like cubes and squares can be constructed. Recently, shape-associated cytotoxicity has been reported for various NPs such as silica, allotropes, gold, carbon

nanotubes, and titanium [37–39]. Generally, a shape associated with NMs cytotoxicity affects the membrane wrapping activity in-vivo at the time of phagocytosis or endocytosis [40]. The impact of the shape of gold (Au) NPs on the cellular uptake in animal models has been proposed where a spherical shape has resulted in a 375–500% greater cellular uptake capacity as compared to rod-shaped NPs [38]. Rod-shaped NPs of single-walled carbon nanotubes (SWCNTs) can block K^+ ion channels several times more potent in comparison to spherical carbon fullerenes [41]. It seems that endocytosis of spherical NMs is easier and quicker as compared to wire or rod-shaped NMs [42]. The shape associated with the cytotoxicity of silica is noticeable by the fact that silica (amorphous form) is utilized as food additives, but crystalline silica is carcinogenic to human health [37]. Likewise, another study has also demonstrated that the uptake of nanorods of gold (Au) is slower as compared to spherical ones [38].

2.3 Effect of Aspect Ratio and Surface Charge

The aspect ratio is the ratio of length to width (or diameter) of NPs under investigation. Nanotubes of carbon are excellent examples of NPs having a greater aspect ratio. The aspect ratio of NMs is directly associated with cytotoxicity, the more the aspect ratio the more the toxicity of the nanoparticle [43]. NPs of silica of 70 nm diameter and identical chemical structure and surface charges but non-identical aspect ratio (5 and 1.5) demonstrate different levels of toxicity in-vivo [44]. The multi-walled carbon nanotubes (MWCNTs) which have a greater aspect ratio leave a more severe toxic response. Due to the high aspect ratio, MWCNTs could cause diseases such as asbestosis [45]. Studies have shown that the TiO_2 fibre with a length of 15 mm is severely toxic as compared to fibre with a low aspect ratio fibre (5 mm in length) and induce an inflammatory reaction by alveolar macrophages in the rodent model [39]. The cytotoxicity of fibres with a greater aspect ratio is directly associated with their plasma shelf life. The fibrous NPs that are adequately soluble in the fluids of the lungs can pass out in a matter of months, later on; the non-soluble fibres are likely to persist in the lungs continually. Other studies also noticed that a greater aspect ratio of SWCNT generates severe pulmonary toxicity as compared to spherical NPs [46]. Further, long sized MWCNT enhances inflammation of the wall of the abdominal post-intra-abdominal infusion, whereas no inflammatory reaction was recognized in the case of small sized MWCNT [47]. Therefore, as the complexity of these mechanisms progressively untangles, they would support the application of a safer nanotechnology-based set-up.

2.4 Effect of Surface Charge

Surface charges on NMs also cause a significant role in the cytotoxicity of NMs as it enhances cellular uptake [48]. In the recent past, different studies have been completed to determine the correlation between the surface charge on NMs and the cellular toxicity of various NPs. The surface of NMs regulates a lot of characteristics of materials like the integrity of the blood–brain barrier, binding of plasma protein [49] colloidal nature as well as adsorption of NPs [50, 51]. Negatively charged and neural NMs show low cellular uptake as compared to positively charged NMs. Furthermore, negatively and neutrally charged NMs have displayed an enhanced platelet aggregation and haemolysis for generating huge cellular toxicity to the system [52]. Various studies have demonstrated that positively charged NPs of polystyrene produce high toxicity as compared to negatively charged polystyrene in HeLa (cervical cancer) cells [53]. Negatively charged NPs do not have a severe impact on the cell cycle checkpoints, whereas positively charged NPs activate cell cycle checkpoints and enhance DNA damage [53]. In other model systems such as bacteria, the negatively charged NMs of silica, gold, and silver cause low and non-significant levels of toxicity, but the positively charged NMs of these metals cause severe toxicity [54]. Additionally, positively charged NPs of silica (Si) (Si–NP–NH_2) have caused severe toxicity as compared to negatively charged and neutral NPs of Si which demonstrate nominal cytotoxicity [54].

2.5 Effect of Composition and Crystalline Structure

The composition and crystalline characteristics of NMs may lead to cytotoxicity. The composition of carbon materials causes lung inflammation and injuries in the epithelial cells of rats as compared to NPs of titanium dioxide (TiO_2). The composition of these NMs presents huge side effects as compared to their bulk counterparts [55]. Metallic NPs of iron can induce cytotoxicity of carbon NMs which is due to enhanced oxidative stress and reactivity [55]. Crystal structure of NMs can also affect the cytotoxicity of NMs; recently, it has been noticed that NPs of rutile TiO_2 enhance lipid peroxidation, severe DNA damage, and micronuclei formation without light; however, the NPs of anatase with similar chemical composition and size did not cause these effects [34]. NMs can alter crystal structure post-interaction with dispersion mediums such as water molecules or others. But the NPs of ZnS are more organized in occupancy with water (H_2O) molecules by reordering their crystal structure and become more similar to the structure of a bulk zinc oxide (solid ZnS) [56].

2.6 Effect of Concentration and Aggregation

The concentration and aggregation of NMs also affect their cytotoxic potential. Generally, the aggregation states of NMs rely on the surface change composition of NMs and size among others. Nanotubes of carbon are mostly bio-accumulated in different organs such as the spleen, livers, and lungs without manifesting toxicity but enhance toxic effects because of accumulations of NPs aggregates for chronic durations [57]. Agglomerated NMs such as carbon nanotubes have more severe effects as compared to well-dispersed nanotubes of carbon and increase the fibrosis of pulmonary interstitial [58]. It has been well documented that higher doses (concentration) of NMs, decrease the cytotoxicity.

2.7 Effects of Physical Properties

NPs have a relatively greater ratio of surface atoms and are also determined by their geometry. The ratio of NMs is also related to their porosity, roughness size, and smoothness of the surface. For example, NMs of Si (porous) have greater biocompatibility as compared to the non-porous silica NMs, additionally; the haemolytic activity of the Si (porous) is lower than Si (non-porous) [59]. The effect of defects found in the structure of NMs on pulmonary toxicity could be analysed [60, 61]. Surface defects of NMs generated reactive oxygen species and enhanced cytotoxicity in animal models [60, 61]. Other studies also demonstrate a great cytotoxicity level of nanosheets as compared to nanowires as well as nanospheres; this cytotoxicity is due to extensive defects on their surface generating surface reactions [62]. By altering the electrical characteristics, impurities may alter the cytotoxicity potential of NPs, whereas the finding of other studies illustrates that the toxicity generated by zinc and copper oxide particles is directly associated with their purity [63]. Zinc oxide containing aluminium impurities has more severe toxicity; this is because of induced electric charge leading from induced impurities. The roughness of the surface enhances non-specificity that increases cellular uptake of NMs [60, 62–64] and is useless in the reaction rate of NPs with cell systems. Particles may also cause toxicity by creating disorders in the plasma membrane as well as generating a transient hole in the plasma membrane [65].

2.8 Effect of Media/Solvents

Conditions of medium/solvents are well documented to influence NMs agglomeration state and dispersion which gradually have an impact on their particle size thereby affecting the cytotoxicity. The NPs of ZnO, TiO_2, or carbon demonstrate a much greater size in phosphate buffer saline as compared to water as NMs show

distinct diameters in biological systems [66, 67]. Consequently, the adverse effects of NMs display a huge variation based on the composition of the medium in which NMs are suspended. The same NMs demonstrate different toxic phenomena when dissolved in different mediums [68, 69]. The dispersing agent may enhance the characteristics of the solution of NPs formulations in addition to their physicochemical properties. Medium and/or solvents may also severely affect the cytotoxicity of NPs.

3 Classification of NMs

The International Organization for Standardization (ISO) has defined "nanomaterial" as a "material with any external dimension in the nanoscale or having an internal structure or surface structure in the nanoscale" [70] and "NPs" as a "nano-object with all three external dimensions in the nanoscale" where nanoscale is defined as the size range from approximately 1–100 nm [71]. These definitions, based on the size of NMs may be sufficient from an evaluation of risk assessment standpoints. NMs can be broadly classified into four groups such as: (a) inorganic-based NMs, (b) organic-based NMs, (c) carbon-based NMs, and (d) composite-based NMs as shown in Fig. 2.

Broadly, inorganic-based NMs consist of various metal and metal oxides such as metal-based inorganic NMs are gold (Au), aluminium (Al), copper (Cu), silver (Ag), iron (Fe), cadmium (Cd), lead (Pb), and zinc (Zn), while the examples of metal oxide-based inorganic NMs are magnesium, aluminium oxide ($MgAl_2O_4$), titanium dioxide (TiO_2), copper oxide (CuO), silica (SiO_2), cerium oxide (CeO_2), iron oxide (Fe_2O_3), iron oxide (Fe_3O_4) and zinc oxide (ZnO), etc. Example of carbon-based

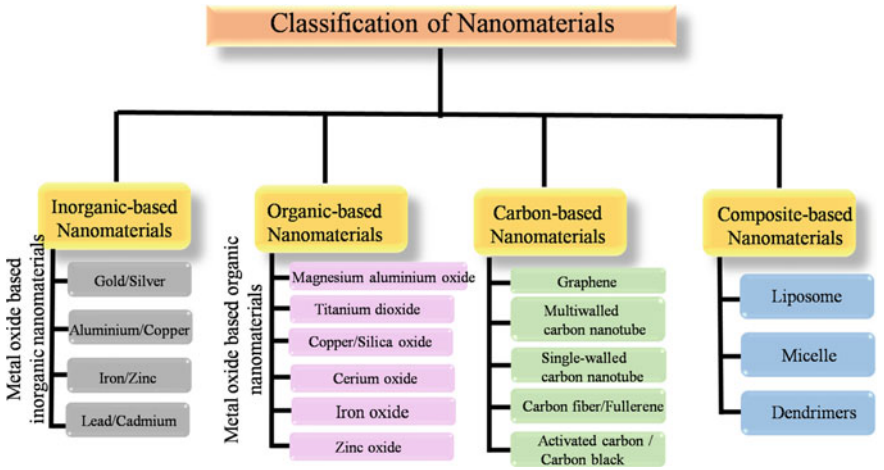

Fig. 2 Schematic classification of nanomaterials

NMs is graphene, multi-walled carbon nanotubes, single-walled carbon nanotubes, carbon fibre, fullerene, activated carbon, and carbon black. The example of organic-based NMs constructed from organic NMs prohibits carbon materials, for specifying cyclodextrin, liposome, micelle, and dendrimers. The composite NMs are combinations of metal oxide-based, carbon-based, metal-based, and/or organic-based NMs, and these composite NMs have sophisticated structures such as a metal–organic structure.

3.1 Types

Metal chalcogenides are inorganic compound that involves at least one molecule of chalcogen anion and one more electropositive metal element. The elements situated in the group of VIA in the periodic table are known as chalcogens. The term metal chalcogenides are most simply engaged for tellurides, selenides, and sulphides, rather than the oxides and polonium compounds. The metallic properties of the elements change in the periodic table in group VIA, going to top to bottom. Thus, the highest metallic potentials of polonium (Po) and extremely strong non-metallic potential of oxygen (O_2) have constructed them fully different from the rest three chalcogens (Te, Se, and S). Due to this nature, the class of chalcogenides reveals semi-metallic properties. A lot of metal chalcogenides exist with different compositions and different structures like Cu_2Se, Ti_2S, CaTe, and Na_2S. This diversity of chalcogenides is associated with the orbit of transition metals [16–18]. Non-metallic potentials of the chalcogens help in the formation of plentiful metal chalcogens. Specifically, transition metals containing empty orbitals can help in the shaping of various non-stoichiometric compounds like In_3Se_2, $Cu_{1.97}S$, Ta_2S, In_4Se_3, InSe, Cu_2S, and Ta_3S. Thus, the chalcogenides are very broad and diverse in nature, and they can be classified in various ways [19]. These are tellurides, selenides, sulphides as well as double, triple, quartet, and multiple chalcogenides in terms of elements [72].

3.2 Metal NPs

Metallic NPs have enchanted researchers and scientists for the last few decades and are at present most thoroughly utilized in the field of biomedical science and engineering. They are a centre of interest due to their vast applications in nanotechnology. The major advantage of metal NPs can be modified and synthesized with lots of functional groups, which enable these NPs to easily fuse with ligand, drugs, and antibodies of interest and thus creating a huge opportunity in the field of biotechnology, the field of target drug delivery, magnetic separation, as well as pre-concentration of target analytes and carrier for drug and gene delivery and also helps in imaging at diagnostic levels. In the recent past, a lot of imaging procedures have been

developed such as computerized tomography (CT) scan, positron emission tomography (PET) scan, magnetic resonance imaging (MRI), ultrasound, surface-enhanced Raman spectroscopy (SERS) as well as optical imaging assist in image several disease conditions. These imaging procedures vary in both instrumentation and techniques and more critically demand a contrast factor containing distinctive physicochemical properties. This has influenced the discovery of different nanoparticulated contrast materials like gold, silver NPs, and magnetic NPs for their utilization in these imaging techniques. In addition to the utilization of numerous imaging methods in nanocages and tandem newer multifunctional nanoshells have been established. Mody et al. [73] have reviewed the therapeutic and diagnostic imaging applications of various metallic nanoparticles such as nanocages, nanoshells, magnetic nanoparticles (Fe_3O_4), gold and silver nanoparticles etc.

3.3 Metal Oxides/Hydroxides

Metal oxides/hydroxides are crucial and extensively defined solid catalysts. Metal oxides are treated as heterogeneous catalysts, exercised for redox and acid–base reactions in various groups of metals such as transition metals which have fascinated much concentration due to configured outer electrons. They are used thoroughly in several reactions which involve dehydration, oxidation, isomerization, and dehydrogenation. The oxides of transition metals, for example, WO_3 [74], Nb_2O_5 [74], and TiO_2 [75] have more thoroughly been utilized as heterogeneous acid nanocatalysts. The mesoporous nature of these transition metal oxide NPs favours the substrate material's inner side of the metal pores for the catalysed reactions. These metal oxides (mesopores) are investigated for their unique structural characteristics such as variable pore size, stability, and excellent surface area. Recently, mesoporous metal oxide (CeO_2) was utilized for a breakdown of methanol and demonstrated a high transformation ability from 13 to 96% (non-mesoporous CeO_2) [76]. The synergistic association of Mn (IV) and Mn (III) along with the hematite phase has been shown to generate active oxidation of formyl furan acid to furan dicarboxylic acid [77]. Metal hydroxides are hydroxides of different metals. They are generally strong bases. Metal hydroxide is composed of metallic cations and hydroxide anions. Few metal hydroxides like alkali metal hydroxide ionize fully when dissolved, whereas several metal hydroxides are weak electrolytes and partially dissolve in an aqueous solution. Recently, nickel hydroxide was utilized as a Bronsted base for the oxidation of alcohol. The catalytic system effectively oxidized both primary and secondary alcohols (86%) to their carbonyls [78].

3.4 Polymeric NPs

Polymeric NPs (PNPs), colloidal organic compounds, are produced from polymeric materials with nanosize from 1 to 1000 nm. PNPs are composed of active pharmaceutical elements that are adsorbed/within polymers (macromolecular substances). At present time, PNPs have heightened more interest in the field of polymeric materials due to their multifaceted utilization [79]. Due to quantum size effects, PNPs alter their cytotoxicity which is associated with toxicity, oxidative stress, and genotoxicity. Nanodiamonds have become an idea of current research consequent to their fascinating characteristics. Recently, these PNPs have been utilized to eliminate heavy metals. These PNPs composite materials reveal exclusive properties such as optical and thermal properties, excellent electrical conductivity, and better mechanical strength. Nanofluidics is extensively utilized in controlled and sustained drug delivery due to their nature of biodegradability and biocompatibility [80, 81]. Poly-lactic-co-glycolic acid (PLGA) NPs are developed to synthesize nanomedicine (peptide-based) for controlled delivery of genes intruded by ultrasound waves [82]. Additional study has also described that PNPs lead to the alteration of the chemical structure of semiconducting polymer by photoacoustic amplification [83]. New fluorescent NMs, encouraged from the area of polymeric drug delivery vehicles and leading fluorophores, can fuse advanced brightness with low toxicity and biodegradability.

3.5 Metal–Organic Frameworks

Metal–organic framework NPs, also known as porous coordination polymers, are one of the important components of the science of NMs, and their position in catalysis is fitting pivotal. The exceptional richness and variability of their structures provide engineering synergies between functional linkers, metal nodes, encapsulated substrate, or NPs for activating MOF-based nanocatalysts. Pyrolysis of MOFs nanoparticle compounds form distinctly porous P- or N-doped graphitized MOFs derived NMs that are instantly utilized as dynamic catalysts uniquely in photo and electrocatalysts [84].

3.6 Hybrid NPs/Nanocomposites

Inorganic or organic-based hybrid NMs can be classified into two groups as per the binding potential. The binding potential of these hybrid NMs is responsible for the various types of interaction between organic as well as inorganic-based elements [85, 86]. Hybrid NMs belonging to class one interact weakly by electrostatic hydrogen bonds or van der Waals forces between organic and inorganic molecules. Hybrid

NMs belonging to class two are held together by strong bonds like ionic or covalent interactions. The progress of hybrid NMs (class two) with strong and stable binding interaction has been leading in the last few years [87, 88]. These hybrid materials (class two) carrying covalent bonds can be applied to synthesize entirely novel NMs from functionalized alkoxide, easily define organic–inorganic interfaces and minimum phase [88]. These organic/inorganic-based hybrid NMs or their hybrid conjugate such as metal nanoparticles (MNPs) carbon nanotubes, ceramic and natural polymers can enhance the processability and biocompatibility of the native materials, and the characteristics of NMs can be altered by the surface polymer [89]. Hybrid NMs reveal the properties of both organic as well as inorganic NPs. These hybrid NMs can be utilized in numerous biomedical products such as phototherapy, drug delivery, biomedical imaging as well as image-guided therapy [90, 91]. In the recent past, lipid-chitosan-based hybrid NMs are developed to be used as carriers for the successful delivery of cisplatin [92]. The authors have mentioned the excellent biocompatibility of the NMs because of the mixture of phospholipid S75 (74% phosphatidylcholine with soybean) and chitosan (natural polymer). Distinct ratios of chitosan/lipid were evaluated to obtain the ideal characteristics, which were attained at the ratio of lipid polymer (20:1). The upgraded formulation has demonstrated 89.2% drug-carrying potential with a mean size of 200 nm. Further therapeutic efficacy of the formulation was evaluated in A2780 cells treated with various doses of blank and drug-loaded cisplatin NMs. Rezaei et al. [93] have reported that hybrid NMs of micelles enhance the drug delivery of cisplatin in the MCF-7 cell (breast cancer) line, without any significant toxic effects. Amorphous and highly porous hybrid nanogels have displayed crucial dexibuprofen release in hydrated solutions. These formulations are biocompatible and nontoxic in nature.

4 Route of Exposures

The major paradigm in the field of toxicity is focused on the exposure—a dose–response relationship. As stated in this fundamental principle, external exposures contribute a chance for agents to invade the body. It is universally studied that no adverse effect can take place without exposure. The word "exposure" can be described as a chance for external agents such as NMs or environmental chemicals to enter the body. Hence, exposure to aerosols of NMs (inhalation) may not or (may) have detrimental effects on the respiratory system. In addition, exposure to NMs by dermal route may have significance for the skin. This segment is designed to give short information concerning the probable route of exposure to NMs either in consumer, occupational or medical/diagnostic settings. It is well reported that prime concerns linked with potential respiratory tract responses to inhaled NMs happen majorly under workplace or occupational conditions. The concerns about the ingestion of NMs probably take place as unintentional oral exposures or food ingestion when encountering consumer items. The numerous routes of NMs exposure (as shown in Fig. 3) that may occur via the subsequent entrance of entry are briefly defined below.

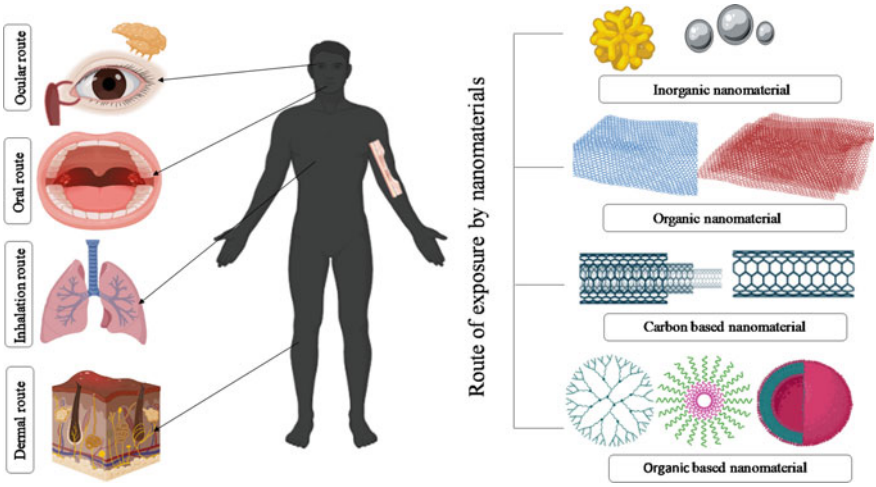

Fig. 3 Outline for route of exposure by NMs

4.1 Inhalation Exposures

Most of the exposures of NMs and toxicology research studies and evaluations with NMs so far have concentrated on inhalation exposures which are investigated to take place mainly in workplace environments. As a consequence, NMs such as agglomerates or aggregates are inhaled into the respiratory system wherein; they settle onto the outer wall of epithelial cells of alveoli and eventually may or may not move from pulmonary/interstitium regions of the capillary. It is difficult that inhaled NMs could ultimately get systemic circulation via this way, whereas the possibility is considered to be rarely possible or negligible [94, 95]. Most of the in-vivo studies demonstrated that inhaled NMs affect the cellular components within the anatomical compartments of the respiratory tract [96]. Inhalation is the most thoroughly studied route of exposures of nanomaterials. Recently, various screening assays have been established and delineated on an acute exposure of inhalation toxicity method to evaluate and categorize the cytotoxicity of thirteen different types of nanomaterials of metal oxides [97]. Therefore, rats were exposed to 0.5–50 mg/m^3 concentration of aerosols of various test materials for approximately five consecutive days. The observation/recovery time is set from quickly following exposure to two or three weeks after exposure. The assay for investigation such as analysis of bronchoalveolar (BAL) and assessments of histopathology associated with pulmonary clearance or deposition and conversion of NMs into extra-pulmonary organs.

4.2 Skin (Dermal Exposures)

Lademann and colleagues have decided based on recent studies of penetration pathways and penetration kinetics of materials applied topically such as NPs of TiO_2 that there is an inadequacy of corroboration illustrating that NMs less than 100 nm are capable to penetrate dermal components of skin into living tissue under ordinary conditions [98, 99]. Nanoparticles of TiO_2 (commercial product) with the size of 100 nm, often utilized in the product of sunscreen, it was established that subsequent exposures of dermal, these NMs are detected exclusively on the upper surface of the skin. Generally, the skin involves a huge surface area and is involved in two important segments. Large components are classified as the more distal dermal components and epidermal components, which lie beneath the epidermis and have a finite vascular supply. Studies described that no NMs were detected in the innermost layer of the stratum corneum, even with subsequent application of long-term exposures. Other studies related to skin biopsies demonstrated that NMs may also penetrate the openings of hair follicles. The importance of this information is that topically applied NMs did not infiltrate beyond the region of epidermal into the dermal surface which consists of a blood supply and hence could not get to the systemic circulations. Hence, in normal skin, it is unexpected that dermal exposure of NMs can go through the different layers of skin and successively enter the vascular component and give the crucial systemic exposure of the body to NMs. Indeed, it remains to be established whether skin exposed to NMs can go through the inner layers under settings wherein the surface of the skin may be irritated or skin lesions like cold sores, eczema, psoriasis, or extreme sunburn [99].

4.3 Oral Exposures

Ingestion of oral exposure of NMs is another entry wherein ingested NMs can invade the body. Exposures of inhaled NMs via the gastrointestinal route take place after food intake or subsequent pulmonary clearance as well as swallowing. Various sources of ingested items such as food pigments or supplements and flavour enhancers and the probability of numerous unintended, nonedible remnants like components of food and drink containers as well as nanosilver-coated toothbrushes are the some common sources of NMs [100, 101]. The major route for food consists of NMs involving the subsequent organs such as the large intestine, small intestine stomach, and oesophagus. Absorption and uptake of NMs rely upon various factors such as the type of NMs and physicochemical properties including dispersibility, size, and change of the NMs. Only a small amount of NPs are absorbed but excreted from the tract of gastrointestinal. One more pathway for NMs to move the gastrointestinal tract (GI) route may occur; subsequently, inhalation exposure of pulmonary clearance of NMs by the airways of a muco-ciliary escalator may result in swallowing of the "cleared", inhaled NPs, which can then move through the GI tract. Several studies

have described that oral exposures to NMs can bring absorption through the Peyer's patches (epithelial cells) in the gut-related lymphoid tissue [36]. Another study also suggested that oral administration of NMs may be absorbed across the GI tract via the lymph nodes, finally migrating to the spleen and liver tissues [102]. As compared to these studies, high-dose exposures (acute) of oral gavage to nanosized or pigment grade TiO_2 NPs in rodent models did not result in uptake into the circulation post-exposure of 48 h or 72 h [103].

4.4 Ocular or Eye Exposures

Eye exposure or ocular exposure of NMs is easily evident and can be reduced in the site or workplace by the wearing of goggles or safety glasses. The probability of such an event is rare in occupational settings or the workplace, and therefore, ocular exposure has been poorly studied.

5 In-Silico Assessment of NMs Toxicity

Computer-based in-silico modelling is relatively a novel field that integrates experimental procedures, providing an excellent technique to help in better understanding phenomena at the atomic level [104–106]. In the subject of nanotechnology research, in-silico-based modelling has been used to explore unique and safer NPs [106, 107]. Since 2006, Organization for Economic Co-operation and Development (OECD) has organized the Working Party on Manufactured Nanomaterials (WPMN), intending to design relevant policies to verify the safe utilization of NMs and avoid the possible risks of NMs toxicity [108]. However, the risk evaluation of an extensive type of different NMs is an inadequate and costly technique. Therefore, in-silico tools, like computational strategy and bioinformatics have grown as extensive tool that permits estimating the potential risks of NMs. At present, various nanospecific databases can be utilized to analyse the risk assessments of NMs like Nano Databank, NanoMILE, ModNanoTox and Online Chemical Modeling Environment (OCHEM) [109]. To review the nanomaterials as unique pharmaceutical drugs aimed at the prevention and cure of various diseases, the structural and physicochemical characteristics of the NMs must be analysed via in-silico methods. Molecular dynamics (MD) simulations, quantitative structure–activity relationship (QSAR), and molecular docking studies are three distinctive classes of computational techniques. In this segment, we outline the different types of in-silico modelling and their application in risk assessments of NMs.

5.1 Molecular Docking

Molecular docking studies are a reliable technique for computational simulations as well as assessment of biomolecules interaction with chemical molecules on the structural basis of 3D understanding. In brief, molecular docking research is a simulation-based prediction tool that predicts how drugs or NMs interact with enzymes or proteins (large molecules). In the initiation of docking, every possible conformation and orientation of all ligands are developed as per the original shape of the active site in the structure of the protein. Subsequently, perform scoring functions to relatively predict suitable interactions between the docked ligand and protein. Post-docking, the docking scores, computed by the scoring functions, are utilized to order all correctly fitted ligand molecules in their active sites. These active sites can be utilized to explain the excellent affinity of ligand for selected protein molecules. A better score of docking denote that the ligand has excellent intermolecular interactions such as hydrophobic interactions, hydrogen bonds, and electrostatics for a given molecule and illustrate the excellent affinity as a powerful association. The molecular docking studies put the ligand into the docking site of the crystal structure of the protein molecules that are acquired from the Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB). The application of every docking study is based on the algorithm of the conformational search like Monte Carlo (MC) [110], incremental construction (IC), and the genetic algorithm (GA) [111]. The desired protein associates with the ligand molecules (docked ligand) and further creates a protein–ligand complex that may increase or decrease the biological activity in the experimental conditions [112]. Therefore, the docking approach can be used to analyse the relationship of the protein with desired chemicals such as NMs. Thus far, molecular docking has applied the crystal structure of the protein to demonstrate the toxic potentials and probable risks associated with various NMs [5, 113–116]. Computational approaches have also been utilized to assess the cytotoxicity of various types of NPs such as Mn_2O_3, Ag, Au, Fe_3O_4, ZnO, CuO, TiO_2, and Fe_3O_4 [117]. Therefore, molecular docking analysis between proteins and NMs has acquired attention in the field of NMs science as one of the alternative techniques that are sufficient to predict the cytotoxic potential [118].

5.2 Quantitative Structure–Activity Relationship (QSAR) Assay

The QSAR assay is a computer-based method and one of the reliable tools that can be utilized as an alternative method to predict the cytotoxicity of different NMs. This technique helps to minimize the cost related to resources, manpower, and time in assessments of NMs [119]. QSAR modelling works based on mathematical algorithms and knowledge of machine learning; therefore, it is a reliable technique for predicting the toxicity or biological activity of NMs. The general principle of

the QSAR model is to describe suitable functions that have a feasible relationship between biological activity and chemical structures. The QSAR can further outline the biological as well as physicochemical knowledge to forecast the impacts of toxicity of NMs. As per the molecular descriptors dimensions utilized for the generation of the model, QSAR assay can be divided into various classes of modelling like 1D, 2D, 3D, 4D, and 5D etc. [120]. Out of these, 2D and 3D-based QSAR works are utilized to analyse the lots of NMs and other environmental chemicals [121–123]. The 1D-QSAR system permits for the establishment of interactions for 1D descriptors (structural fragments, log P, fingerprints and pKa) along with biological interests [124]. To date, the 2D-QSAR assay has been extensively investigated in several works for medicinal chemistry or toxic chemicals [125]. The physicochemical characteristics of a 2D-QSAR model consider different variables such as polar surface area, topological indices, geometric parameters as well as molecular fingerprints. The absence of steric characteristics is a demerit of 2D-QSAR. To resolve this issue, the 3D-QSAR technique utilizes the 3D characteristics such as electrostatic field and steric surrounding the desiring molecules and utilizes chemometric assay to set up a correlation between the structural characteristics and the activity of molecules [126]. As per the uses of a variety of machine learning algorithms, QSAR models creation can be mainly divided into two groups such as linear and nonlinear systems. The linear systems carry partial least-square (PLS) methods, principal component analysis (PCA), as well as multiple linear regression (MLR) systems, whereas the algorithms of nonlinear regression involve artificial neural network (ANNs), support vector machine (SVM), and random forest (RF). 3D QSAR is more appropriate than 2D-QSAR because it utilizes statistical tools like the PCA methods, PLS analysis, ANN algorithm, and cluster analysis for model creation [127]. At present, the QSAR tool is most thoroughly used in toxicology, chemical regulations, regulatory decision making as well as risk assessments. Therefore, recently researchers have practised QSAR models to investigate the potential risk assessment of NMs involved in uses and manufacturing as shown in Fig. 4 [127].

5.3 Molecular Dynamics Simulation

MD simulation, the most advanced method, is most thoroughly used to analyse physical and chemical characteristics in the current time of computational nanotoxicology. It can be considered a supportive method to evaluate the 3D structures (atomic motion) that are acquired from experimental facts like X-ray crystallography and nuclear magnetic resonance (NMR). Advanced versions of MD simulations similarly facilitate knowledge of the time-dependent nature of physical activity of molecules and atoms. MD simulation allows the kinetic and thermodynamics characteristics of the nanomaterial systems at the higher level (atomic). MD simulations can be applied to produce prediction models of toxicity that can be utilized in the design and development of NMs. Therefore, computational-based toxicology models are

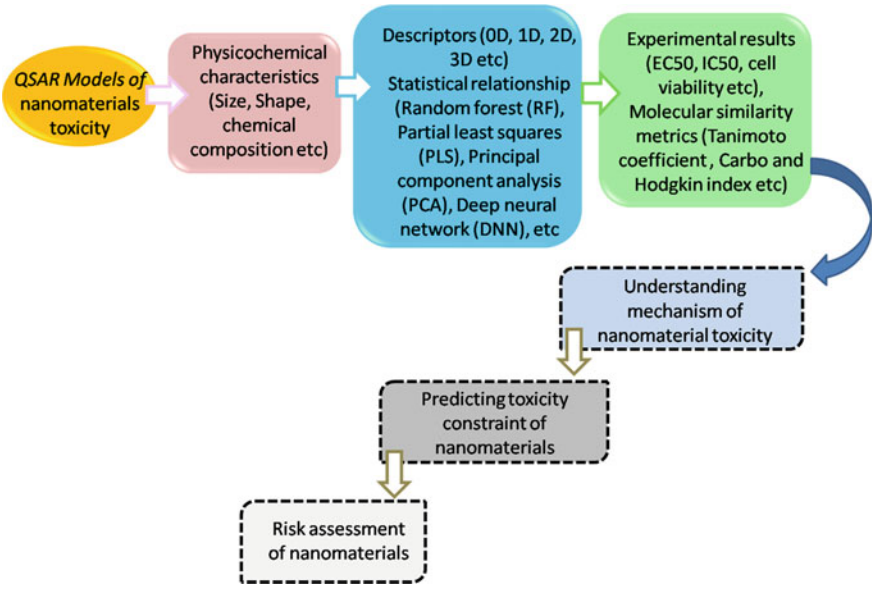

Fig. 4 Schematic showing QSAR model for toxicity assessment of NMs

universally accepted in the field of biomedical sciences to calculate the toxic potentials of numerous biological models. Recently, MD simulations are applied to the analysis of numerous theories of toxicity systems in the subject of computational toxicology and nanotoxicology. To illustrate, agglomeration and aggregation of NMs are associated with induced toxicity at the time of preparation of the polymer matrix [128]. Hence, this can enhance programmed cell death such as apoptosis and produce intracellular ROS [129]. In other studies, agglomeration of NMs of TiO_2 was demonstrated to activate toxic responses in-vivo and in-vitro models. Large agglomerates of NMs of TiO_2 promote severe biological impacts like depletion of glutathione (GSH) content, inflammation, and DNA damage as compared to small aggregates [130]. Hence, studying the aggregation of numerous NMs is a crucial approach to demonstrate their toxic impact.

6 In-Vitro Assessment

In-vitro toxicity assessment of NPs is one of the important methods. The advantages include lower cost, faster, and minimum ethical concerns. Assessment can be subdivided into cell viability and proliferation assay, apoptosis assay, oxidative stress assay and DNA damage assays, etc.

6.1 Trypan Blue Assay

Trypan blue is a widely used assay for the assessment of cytotoxicity in-vitro cell culture. In this assay, cells are treated with NMs or other agents, trypsinized, and later stained with a diazo dye (trypan blue), which is excluded by viable cells and taken up by the non-viable cells. Trypan blue negative cells indicate the total number of live cells collected from a well plate or dish. Trypan blue assay is superior because it brings the real number of live cells and decreases (cytotoxicity) or enhances (cell proliferation) in comparison to control cells. Recently, various studies utilized trypan blue assay to assess the cytotoxicity of various NMs and other cytotoxic compounds such as crocidolite asbestosTiO_2 on a human mesothelial cell line, LP9/TERT-1 (TERT-1 immortalized) [131]. Various other studies using this assay to measure the cellular toxicity of multi-walled carbon nanotubes (MWCNT) and different NPs of metal oxide to the human non-small lung carcinoma cells illustrated that CuO, ZnO and $CuZnFe_2O_4$ and MWCNT, lead to a significant elevation in dead cells at a 20 $\mu g/cm^2$ and 40 $\mu g/cm^2$ concentration of CuO NPs, respectively [132].

6.2 MTT Assay

The 3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide (MTT) assay is the most widely used method to understand the metabolic cell viability of in-vitro cell culture. It is a very reliable and sensitive benchmark of the assessment of cell viability and is favoured over the available assays quantifying termination points such as ATP and Bromodeoxyuridine (BrdU) incorporation assay [133]. This assay depends on the depletion of MTT, a yellow astringent tetrazolium dye, converted mainly by the enzyme mitochondrial dehydrogenases to formazan crystals (purple coloured). The end product is investigated by the colorimetric method at the wavelength of 550 nM after termination in organic solvent such as dimethyl sulphoxide (DMSO) as shown in Fig. 5. The spectra of untreated and treated cells with NPs provide a measurement of cellular toxicity [134]. Recently, advanced variants of tetrazolium salt equilibrated by an intermediate have been described as an excellent alternative for researchers because of their tendency to form water-soluble outcomes, thus preventing the step of solubilization of the conventional assay. NMs interrupting with cell membranes may disturb their depletion by membrane related electron transport. In such conditions, the cellular intake and sequential mitochondrial depletion of the cationic MTT give an excellent analysis of NMs toxicity. However, drug efflux pump or antioxidants suppressors may inhibit MTT assay and therefore NPs loaded with these should be assessed by other techniques to corroborate the outcomes [133]. In the recent past, various other studies also used MTT assay to measure the metabolic cell viability of different NPs such as CaS, on L929 cells and SiO_2 on L-132 cells and THP-1 cells [135, 136].

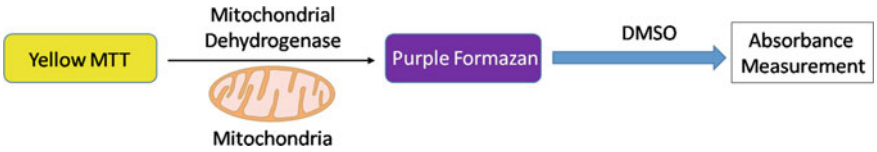

Fig. 5 Schematic representation of MTT assay

6.3 Lactate Dehydrogenase Assay

The lactate dehydrogenase assay (LDH) also known as LDH release assay is an indicator of plasma membrane damage in a cell population. It is immediately discharged into the extracellular medium and damages the membrane resulting from necrosis or apoptosis. LDH assay is a universally approved marker of cell death; this assay is directly an indicator of the integrity of the cell membrane and in specific incidents can be limited when the cell number is not modified remarkably. The actual essay was outlined to estimate the oxidation potential of β-NADH to β-NAD+. At the time, LDH reduced pyruvate to lactate, an event that could be calculated as a reduction at an absorbance (340 nm). Following alteration of this assay concentrated on both buildings the method more accurate, cost-efficient and also enhanced sensitivity through the utilization of fluorometer [137]. The results of optical density (OD) of treated groups are demonstrated as LDH release (in %) relative to LDH values from fully lysed cells. The quantity of LDH release per sample can also be evaluated by creating a linear curve applying standards of LDH [138]. NMs consisting of various groups of metal/metal oxide have recently been investigated by the LDH method for their cytotoxic potential on BRL3A cells (rat liver) [139]. In another study by Jeng et al. [140], NPs carrying ZnO elicited the powerful LDH release in a concentration-dependent way in Neuro-2A cell lines as compared to TiO_2, aluminium oxide (Al_2O_3), iron oxide (Fe_2O_3) and chromate (CrO_4^{2-}).

6.4 BrdU Assay

Another popular assay is the 5-Bromo-2-deoxyuridine (BrdU) assay (Fig. 6), which allows assessment of cell proliferation which is one of the important parameters in the analysis of cytotoxicity of various NMs. Recently, BrdU incorporation has been utilized to prevent the complexity of using hazardous radioactive materials since its existence can be identified by flow cytometry or using distinct antibodies. BrdU also intimates better selectivity for cells undergoing synthesis of DNA materials in comparison to [3H] thymidine, which can be incorporated into newly synthesized DNA during spontaneous DNA synthesis in a generalized manner [138]. A recent study shows that the above assay has been utilized to display the proliferative effects of low dose particulate matter in epithelial cells of pulmonary [141]

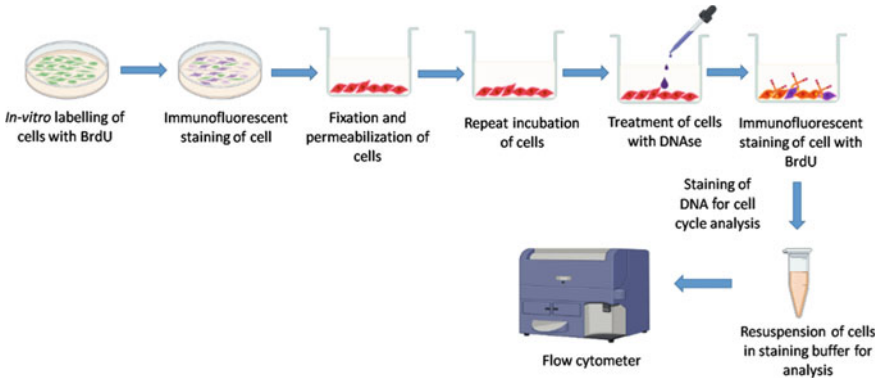

Fig. 6 Schematic representation of BrdU assay

and anti-proliferative effects of NPs (heparin deoxycholic acid) on human umbilical endothelial cells and squamous cell carcinoma cells [142].

6.5 TUNEL Assay

Apoptosis, a programmed cell death pathway, is specified by cytoplasmic and nuclear shrinkage, mitochondrial DNA damage, cell membrane blebbing, chromatin condensation fragmentation into apoptotic bodies and DNA fragmentation. In the recent past, morphological alterations of cells with regard to NPs of hydroxyapatite (HAP) were demonstrated by Liu et al. [143] utilizing a BEL-7402 cell line (human hepatoma). The nuclei of BEL 7402 cells were stained with Hoechst 33,258. When BEL-7402 cells were treated with a 50–200 mg/l concentration of HAP NPs for 48 h, resulting in more fragmented and smaller nuclei and more condensed chromatin in BEL-7402 cells as compared to untreated cells. There are various immune-histochemical methods to detect programmed cell death like apoptosis in-vitro cell culture. The TUNEL method labels the ends of DNA that have been fragmented or broken by endonucleases as an outcome of apoptosis following in biotinylated dUTP at the end of 3' hydroxyl group which can be determined by horseradish peroxidase (HRP)-conjugated streptavidin and a diaminobenzidine chromogen by bright field microscopy. On the other hand, the incorporated nucleotides of dUTP can be tagged with a fluorescent dye and imagined through fluorescent microscopy. TUNEL assay is utilized to demonstrate the increased apoptosis in lung cancer cell lines treated with anticancer drugs paclitaxel post-loading into NPs of PLGA. Paclitaxel can be individually obtained a low apoptotic response but not as much as the PLGA-loaded treatment [144].

6.6 Reactive Oxygen Species Measurement

Reactive oxygen species are chemically unstable molecules that transfer oxygen (O_2), carrying hydroxyl radicals (·OH), reactive superoxide anion radicals (O_2-), and hydrogen peroxide (H_2O_2) [145, 146]. ROS are largely produced most extremely in mitochondria and organelles such as the endoplasmic reticulum [147]. During the time of oxidative phosphorylation, O_2 is utilized for the synthesis of H_2O, by the gain of electrons via the electron transport chain (ETC) of the mitochondria. Few of these electrons are received by oxygen molecules to form O_2-, that can additionally convert into H_2O_2 as well as ·OH [145]. In normal physiology, ROS are generated as a natural reaction to the regular metabolisms of oxygen [148] and performing a crucial role in different signalling pathways in cellular levels [149–151]. The most conventional method for the detection of reactive oxygen species is the 2,7-dichlorodihydrofluorescein (DCFH) probe. This probe is a special indicator of the existence of free radical species (H_2O_2). The diacetate form (containing two acetate groups) of DCFH (DCFH-DA) has been widely utilized to recognize ROS levels in cells due to its potential to penetrate cellular membranes. Acetate groups are hydrolysed by the chemical reactions of intracellular esterase following DCFH-DA carry into cells, and then, the appearance of peroxidases is essential for the oxidation of DCFH by hydrogen peroxide. Few other molecules are suitable for the oxidizing DCFH such as cytochrome c or hematin [152, 153]. That may enhance the fluorescence intensity of the probe without the building of hydrogen peroxide [154, 155]. 2'-7'dichlorofluorescin can also oxidize with hydrogen peroxide (H_2O_2) in the presence of ferrous (Fe^{2+}) ion, but this is more suitable due to the generation of ·OH. However, $O_2·-$ is not able to oxidize the probe of DCFH. In the presence of UV radiation or visible light, a DCF photo-reduction can appear. The product of fluorescence displays fluorescence at 522 nm and excitation at 498 nm. Lots of NMs that enhance the generation of H_2O_2 also enhance the generation of hydrogen peroxide (H_2O_2). In a recent study, cell lines of colorectal cancer were treated with NPs of polystyrene (20 and 40 nm) in combination with two surfactants (carboxylic and amino acid). Post-treatment of cells to NPs of polystyrene, a significant reduction in cell viability was noted, and the activation of apoptosis was decreased by reduced production of H_2O_2 by catalase [156]. Gao et al. 2011 [157] observed a reduction in intracellular concentration of GSH post-treatment of cells to 8 nm NPs of Au. Later, there was increased production of H_2O_2 after the 48 h of incubation with Au NPs. Various other NMs such as ZnO [158], Ag [159], and TiO_2 [160] are also capable of H_2O_2 production.

6.7 Bacterial Reverse Mutation Test

Bacterial reverse mutation test is commonly known as AMES test. This test is a short-term and widely used biological assay to assess the mutagenic potential of chemical

compounds using different strains of bacteria (*S. typhimurium* and *E. coli*) [161]. The AMES test is a short-term assay to assess the carcinogens using mutagenicity in bacteria as most carcinogens are mutagenic and cause cancer somatic mutations [162]. The Ames test is frequently used for screening methods of almost all new pharmaceutical substances and chemicals used in the industry. This test includes different bacterial strains which are sensitive to different types of mutation that inactivate a gene involved in the synthesis of essential amino acid, either histidine amino acid (*S. typhimurium*) or tryptophan (*E. coli*), so they can only grow in the culture medium that is supplemented with that amino acid. This test uses the metabolizing system (S9) to mimic the metabolism of test substances that would occur in mammals. Induction of revertant colonies indicates that some histidine (his-) have been mutated (reverted) to his + which indicates the ability of bacteria to allow restoring of gene function and its ability to synthesize an essential amino acid for growth. This test is limited due to the use of bacterial auxotrophic strains (his- *S. typhimurium* or trp- *E. coli*) to assess the chemical mutagenicity, which is prokaryotic cells and therefore not a perfect test system for eukaryotic mammalian cells. Few studies previously evaluated mutagenicity of NPs by bacterial reverse mutation test. Here, we also briefly illustrate the mutagenicity of metal oxide NPs, in bacterial cells as shown in Fig. 7 [163, 164].

6.8 Single Cell Gel Electrophoresis (Comet Assay)

The Comet assay also called single cell gel electrophoresis (SCGE) is a rapid, simple, and sensitive method for analysing and quantification of DNA strand breaks at the level of an individual eukaryotic cell. The resulting image that is obtained resembles a Comet-like structure with a distinct head (intact DNA) and tail (single-strand or double-strand breaks) or broken pieces of DNA. Comet assay was first developed by Ostling and Johansson in 1984 [165]. Singh et al. later modified this technique with increased applications as alkaline Comet assay in 1988 [166]. The comet assay has wide application in the field of genetic toxicology, either in-vitro or in-vivo and the environment, terrestrial or aquatic. Comet assay is applied widely as experimental models: bacteria, fungi, cell culture, arthropods, fishes, amphibians, reptiles, mammals, and humans [167]. The method involves individual cells embedded in low melting point agarose (LMPA) on a glass slide followed by cell lysing. Therefore, the DNA is allowed to unwind under alkali to denature and electrophoresis which allows the movement of damaged DNA away from the nucleus. After staining with a fluorescent DNA intercalating dye, the sample is visualized under the microscope. The extent of DNA released from the head of the comet is directly proportional to the quantity of DNA damage as shown in Fig. 8. Some in-vitro and in-vivo studies have shown genotoxicity of titanium dioxide (TiO_2) and zinc oxide (ZnO) NPs by measurement of DNA damage by Comet assay [168, 169].

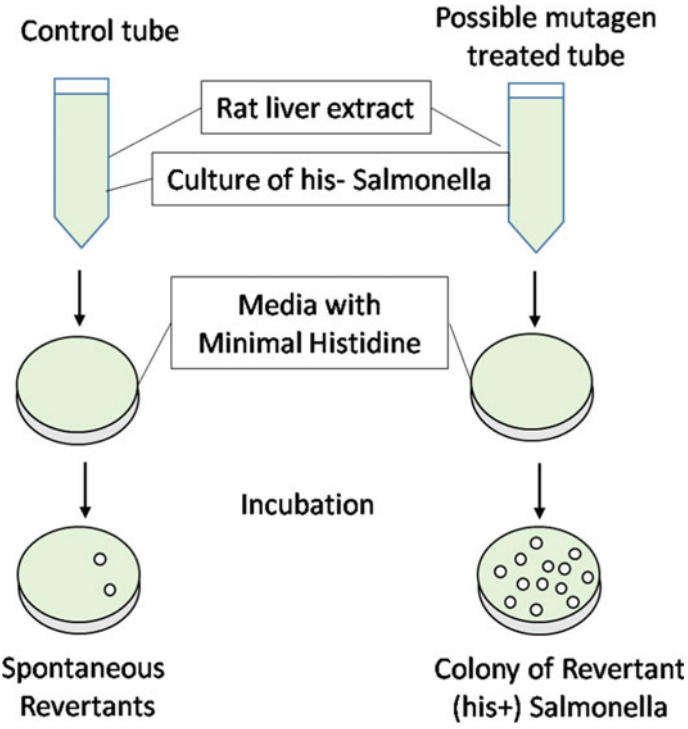

Fig. 7 Schematic representation of bacterial reverse mutation test

7 In-Vivo Assessment

Nanomaterial size, shape, surface chemistry, and degree of aggregation are key factors that influence toxicity. Generally, the in-vivo toxicity studies can provide sufficient data to understand the absorption, distribution, metabolism, and excretion of NMs. The test usually involves the use of isolated tissues and organs or cells. The animal related toxicity tests are mainly conducted for:

- Acute toxicity: Acute toxicity is defined as the hazardous effects of a chemical that occurs as a result of single exposure or multiple exposures for a short duration of time.
- Subacute toxicity: It resembles acute toxicity except that the exposure duration is greater from several days to one month.
- Subchronic toxicity: It is the toxic exposure repeated or spread over an intermediate time range (one to three months).
- Chronic toxicity: It is defined as toxicity elicited because of long-term exposure to chemicals. It is the exposure (either repeated or continuous) over a long period of time (greater than three months).

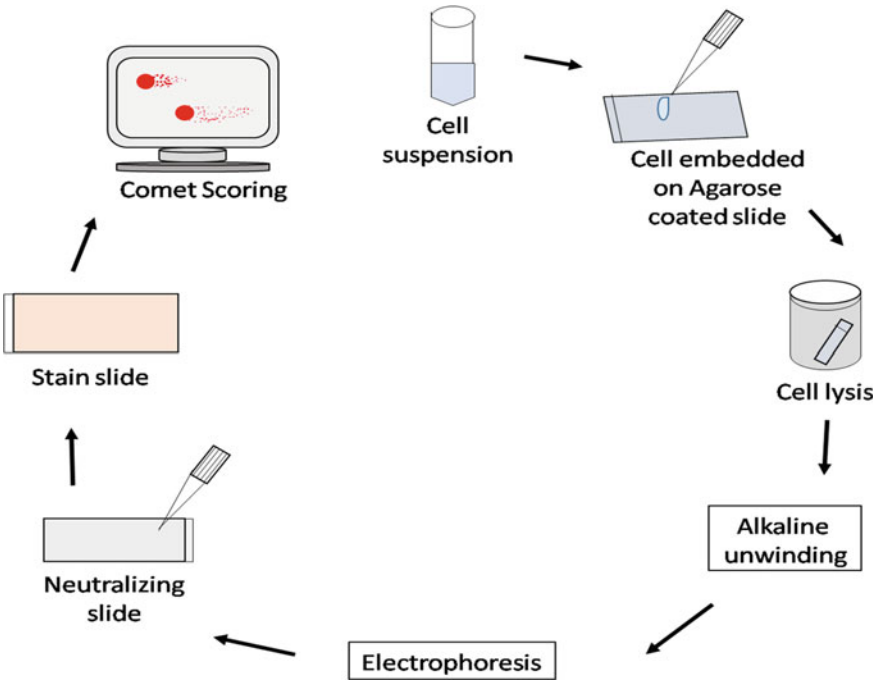

Fig. 8 Schematic representation of alkaline Comet assay

- The mammalian erythrocyte micronucleus test: This test used in toxicological screening for potential genotoxic substances.

7.1 Mammalian Erythrocyte Micronucleus Test

The mammalian erythrocyte micronucleus (MNM) test is widely applied for genotoxicity screening of various classes of chemicals for a long time, i.e. pharmaceutical chemicals, agricultural chemicals and food additives. In this test, micronucleus is the only DNA component in the cell because the main nucleus of the cell is expelled during the erythropoiesis of mammals; for any purposes, the micronucleus test data should be reliable and accurate [170]. This test was performed according to a method described in OECD TG 474, MEM updated in 2016 as shown in Fig. 9 [171]. A standard test battery for genotoxicity testing of pharmaceuticals (ICH S2R1 guidance) has already been announced under the auspices of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals Intended for Human Use [172]. In this assay, commonly healthy young adult animals, i.e. mice or rats should be used. After exposure to the test substance, the femur will be excised, and erythrocyte cells will be harvested and stained cells are then analysed microscopically for the presence of micronuclei. The current revised procedure

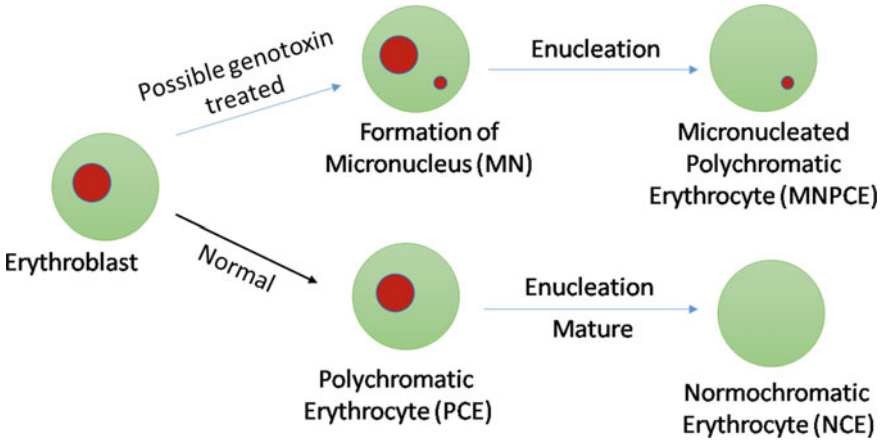

Fig. 9 Schematic for micronucleus test using mammalian erythrocytes

mentioned in OECD TG 474 proposed 4000 young immature erythrocytes should be analysed, which is twice the number of cells stated in the previous guideline. Slide from the entire vehicle should be selected, and scoring should be carefully done by experienced and skilful persons for potential analysis.

8 Challenges and Future Perspectives

In the present chapter, we have critically reviewed the fate, toxicity behaviour, and risk assessment of NMs in human health and the environment. Though most of the research groups have focused only on the toxic effects of NMs, the reasons for the toxicity of NMs are largely unrecognized. There is still a considerable gap in research about the nature of interference of NMs with the human immune systems and tissues and the environmental system. Much more studies are required to assess the risk and stability of various NMs in different test systems to fully understand the potential for human exposure to the NMs of commercially supplied products and the near-future products. Recently to an assessment of toxicity of various NMs using various cell lines and other model systems are gradually being published, but due to the broad range of concentration of NMs, different types of cell lines as and different culture conditions and inadequacy of knowledge of mechanisms, it is very critical to understand whether the observed toxicity of NMs is physiologically consistent. Altogether analytical techniques have required that consent to real-time monitoring (*in-situ*) to improve the production process of NMs. These techniques help in the risk assessment of NMs as well as providing mechanistic information also. Despite the various methods described in this chapter, there are still a lot of challenges within the risk assessment of NMs that remain to be addressed. We are not yet very much aware of which properties of NMs should be estimated like the surface area of concentration

number or a combination of these or something else completely. Once the community accepts NMs as a unique tool for in-vivo imaging for durable scales, we believe that a novel understanding of how cells and organs work, both externally and internally with others, will be acquired.

9 Conclusions

In the last few decades, use of the NMs in human surroundings as well as in various consumer items is rapidly increasing. It is predicted that exposure of various NMs to human being will enhance continuously. Hence, substantial exposure of NMs to human is of serious public concern. Therefore, there is a requirement for more advanced tools to assess the risk of NMs. Present understanding of the impact of exposure of NMs to human is finite or very poor. The knowledge gathered from the present chapter specifies that various NMs present in the human environment may have a potential for cytotoxic impacts. Although, the current studies on adverse effects of NMs are distinct. These studies have utilized various rodent and cell-based test systems, different origins of NMs, different tests for characterization of NMs and numerous experimental settings. Therefore, this knowledge is difficult to analyse. More studies are required on biological interaction, toxicity assessment, characterization of NMs, and effects on human health. The current test methods require to be approved and need to be identified suitable negative and positive control for risk assessment of NMs. Hence, limited information is available for risk assessment of various NMs that exist in different types of consumer items or it may penetrate into the market in near future. In future, validated and standardized test methods are compulsory for risk assessment of various NMs. Therefore, in the deficiency of advanced and standardized methods, any unique regulatory testing requirements for NMs are premature at current situation. In this chapter, we critically have discussed the route of exposure of NMs, physicochemical characteristics, various in-vitro, in-silico, and in-vivo methods for risk assessment of different NMs. We also discussed the fate behaviour and cytotoxicity of numerous NMs in human health.

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Surface-Modified Nanomaterials for Biogenic Applications

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Abstract Due to an increase in the world population, there is a requirement for effective and sustainable technologies to deliver global necessities and diminish the environmental toll. In medicine, nanoscale drug delivery systems endowment has improved therapeutic precision by overcoming biological barricades, which is followed by enhancing drug targeting tactics. A "family tree" is needed to trace the developments in the study of nanomaterials (NMs) more accurately. The utilization of NMs for surface engineerings like metal chalcogenides, metals, metal oxides/hydroxides, polymers, metal-organic frameworks, and hybrid nanostructures in the biological and medical fields is a topic of rapid progress. The implication of NMs in medical through biomedical implants. wound coverings and drug delivery systems trust upon their effective interface between the extracellular matrix, intracellular cells, and components. The cellular and molecular points are mainly determined by the surface characteristics, morphological, and chemical analysis of NMs. An overview of the physical and chemical properties (i.e. superficial charge, surface composition, size, shape, and chemical nature, etc.) of NMs affect the biocompatibility and uptake efficiency of medical platforms which is thoroughly explored in this chapter.

Keywords Surface chemistry · Cellular uptake · NMs · Biocompatibility

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R. S. Mane et al. (eds.), *Nanomaterials for Sustainable Development*,
https://doi.org/10.1007/978-981-99-1635-1_4

1 Introduction

Nanomaterials (NMs) of different organic and inorganic materials are extremely minute in size, (between 10 and 500 nm) [1]. These NMs are surrounded by an interfacial layer that behaves as an entire unit with respect to their transport properties. These NMs display physico-chemical, optical and electrical properties which are expressively different from those of bulk materials and include a huge variability of dissimilar materials ranging from metals to insulators through semiconductors [2]. The size-dependent parameters lead to produce different opto-electrochemical properties. The optics [3], catalysis [4], drug delivery [5], antibacterial activity [6], surface plasmon resonance [7], and superparamagnetism [8], etc., are unique properties of NMs which are reported in several constituents and structures in scientific fields. The recognized applications of NMs include light-emitting devices [9], photodetectors [10], solar cells [11], quantum dots (QDs) nanotechnology [12], liquid crystal displays [13], surface-enhanced Raman scattering (SERS) devices [14], plasmonic photonic crystals [15], battery anodes [16], heterogeneous catalysis [17], and medical platforms [18]. The high surface area-to-volume ratio of NMs offers an incredible driving force for the diminution of Gibbs free energy. This leads to a constant configuration with lower free energy to form a superior functional self-assembly unit. The spatial preparations of NMs formational assemblages can be assembled by molecular interactions, which can externally be directed or indirectly through their environment. Due to the propagation of NM synthesis methods, the design and study of NM assemblies are widely popular. The dipole–dipole, Van der Waals, electrostatic, and depletion interactions are the types of interactions that can induce the formation of NM assemblies [19]. The solvent evaporation method, solvent destabilization method, and gravitational sedimentation method are generally used to prepare NM assemblies in which the modification of interparticle interactions is realized by modifying the type of reaction temperature and solvent, interface with the colloidal solution, and the vapour pressure [20]. The electric field or magnetic field is the application of an external field [21]. The use of structure-directing media is also important for fabricating NMs [22]. The fabrication of NM assemblies containing functional, structural, and stable features is challenging. The 1D, 2D, and 3D NMs avail amorphous and crystalline, or semicrystalline crystal structures [23], etc. These small sized NMs particles of large surface area-to-volume ratio display various physical and chemical features compared to their bulk counterparts. These features have made them attractive for several applications like sensitive sensors, fast-moving consumer goods, electronic devices, pharmaceuticals, and medicinal products [24, 25]. These NMs are widely envisaged in biogenic applications such as biomolecule detection, regenerative medicine, gene and drug delivery, vaccines, tissue engineering, high-accuracy diagnosis, cancer therapy, and theranostics [26]. The inorganic metal oxides, chalcogenides [27–29], and organic NMs such as graphene [30], carbon nanotubes [31, 32], C60 fullerene [33], and carbon quantum dots (CQDs) [34], etc., are used for numerous applications. Owing to the full range of applications in bioscience and biotechnology and also in other biomedical products, it is necessary to understand the

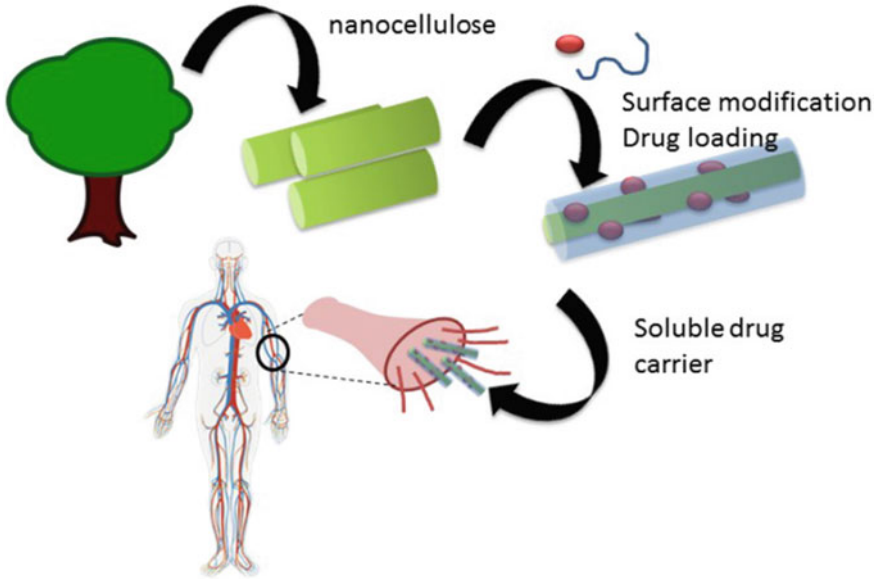

Fig. 1 Schematic presents the interaction of NMs drug with cells and cellular components [36]

interaction between mammalian cells and cellular components of NMs (see Fig. 1) [35].

Many researchers have studied nanotoxicity and reported that nanostructures can produce several adverse effects in biological schemes mostly due to the creation of reactive oxygen species (ROS) that outcomes in oxidative stress [37–40]. In the ROS-independent mechanism, NMs produce toxic effects on cells [41, 42] which is associated with zeta potential, morphology, size, and shape of NMs [43–45]. Therefore, a clear understanding of NMs-cell interaction has the key importance to effectually exploring the potential healthcare applications of these petite particles with minimal adversarial effects. Although, there is sufficient information available in the scientific literature concerning NMs-cellular interactions [46–50], a comprehensive reorganization in a simple understandable form is mandatory. In various biomedical and drug delivery applications, a proper level of interaction between NMs with cells and intracellular organelles is a fundamental issue [51, 52]. To superfine NMs-cell interaction and achieve an appropriate outcome *via* various methods like surface functionalization [53–56], surface modification [57], and monitoring the physical and mechanical properties [58], both theoretical and experimental attempts have no option [59]. Various factors (a net charge, size, shape, hydrodynamic volume, stiffness, etc.) can affect the interaction between NMs and cell membranes [60–63]. A fragile interaction between NMs and cell membrane can result in the Brownian collisions of NMs with the cell membrane without facilitating the adhesion of NMs on it. However, adequate adhesive forces can result in the adhesion of NMs on cell membranes and subsequent internalization by generating provisional pores in the

plasma membrane [64, 65]. The whole internalization of NMs mainly depends on their surface functional groups, size, shape, etc. [66]. Surface chemistry phenomena and stiffness can also substantially influence on the NM-cell interaction [67].

Even with the cytotoxic effects [68], some inorganic NMs are exploited to destroy pathogenic micro-organisms and malignant cells [69, 70]. Inorganic NMs are extensively studied for their potential applications in vaccine delivery and immunotherapy [71]. Thus, it is vibrant to understand both the material characteristics and the doses of NMs to draw a sharp line between the cytotoxic concentration and therapeutic window to use them in clinical settings. These necessitate substantial advancement in understanding the appropriate interactions at NMs-cell interfaces by demanding research [72]. The outcome of interactions between NMs with cellular components, and mammalian cells at various levels, could help to identify the fundamental requirements for their use in the healthcare and fast-moving consumer goods sector. This chapter deals with the multiple properties of NMs that are influenced by their surface modification methods, chemical nature, shape, particle size, rigidity, texture, charge, hydrophilicity/hydrophobicity, and most importantly, the presence of functional groups for knowing the influence cellular uptake and interaction with cellular components. Moreover, these properties are the uptake efficiency of pharmaceutical implants and biomedical products.

2 Surface Modifications *via* Physicochemical Properties

The chemistry of the base materials used for the synthesis of NMs is an important factor that influences their interactions with the cells and cellular components [73]. The NMs synthesized from biopolymers such as chitosan [74] and metals and metal oxide NMs synthesized by biotic routes are generally bioactive [75]. Their advantageous properties are accredited to the occurrence of functional groups such as amino, acetamido carboxyl, and hydroxyl groups [76]. Moreover, non-bioactive NM-based synthetic biopolymers such as polycaprolactone, polyvinyl alcohol, and polylactic acid are companionable with mammalian cells [77].

The cytotoxicity exposed by the NMs is mostly due to the intrinsic toxicity of the elements used for the NMs preparation. Since, noble metals like gold and platinum are slightly companionable with mammalian cells, NMs prepared from noble metals are harmless in spite of their shape, size, surface phenomena, and morphology-associated effects (Fig. 2) [78–84]. However, toxic heavy metals such as cadmium and lead-based NMs are generally toxic to mammalian cells [85]. These NMs can persuade their toxic responses depending upon the interaction with natural or biochemical properties. The cellular responses are dependent on how NMs are produced i.e. by simple molecules or specific chemical molecules, functional groups, and non-specific surface chemical features. Mostly, the systemic toxic effects are dependent on the release of metal ions, elemental chemistry, and the presence of specific biochemical molecules and specific chemical properties of NMs. However, non-specific chemical properties can play a title role in the NMs associated with cell-cell adhesion, cell

proliferation, cell-substrate adhesion, and phenotypic changes in the local cellular responses [86, 87]. The ionization in the solution of metal or metallic-containing NMs plays a title role in the toxicity induced and cellular response by them at the tissue, cellular, molecular, and systemic levels [88]. The ionization in the dissolution of metal or metallic-containing NMs mostly depends upon the chemical behaviour and nature of the NMs in the environment of the biological system [89]. For example, more soluble zinc oxide NMs in aqueous conditions demonstrate comparatively higher cytotoxicity on cells rather than partially soluble titanium oxide NMs [90]. The probable reason for such a pronounced adverse effect is exposed due to the maximum amount of metal ions generated in aqueous conditions of soluble NMs. The silver/copper NMs generate the silver and copper ions in an aqueous solution that could interact with the cell wall components containing oxygen, nitrogen, or sulphur and damages them [91, 92]. A motivating recent study established that even negligible changes in surface coverage of functional groups would significantly affect the cellular interaction and sub-cellular delivery of ultra-small Au NMs [93]. The results of this study showed that subordinate surface coverage results in fast cellular communiqué and sturdy membrane binding but a little cellular uptake. In disparity, high surface coverage induces slow cellular interaction and low membrane binding but higher cellular internalization. Since the integral chemical properties of the materials working for the invention and surface functionalization of NMs can have a direct effect on their interaction with cells and cellular components [94], their bulk and surface chemistry should be sensibly evaluated before recommending them for biological applications [95]. The consequent sections have described detailed information concerning various aspects that influences the interactions between NMs and cells.

2.1 Morphological Strategy

(a) Size

The particle size of NMs acts a dynamic role in the toxicity, drug release kinetics, cellular uptake, bio-distribution, and biological applications [96]. Generally, distinct micro to large particles of NMs cannot be identified as extraneous bodies by the immune system [97, 98]. The particle size of NMs can play an important role in macrophage engulfment, and they recognize only relatively large NMs [99]. Apart from the cellular uptake, the kinetics of cellular uptake and intracellular distribution are influenced by the size and shape of the NMs [100, 101]. NMs should be able to traverse the extracellular matrix (ECM) due to facilitate effective interaction with cells and provide a biological response. The ECM inflexibly controls the movement of NMs across it due to the permeable mesh-like organization, [102]; ECM permits penetration of smaller NMs than its mesh size, and the bigger NMs are restricted [103]. Generally, ECM allows the transport of slightly smaller NMs due to the collagen fibrils of the ECM possessing an interfibrillar spacing of 20–40 nm [104]. While there are

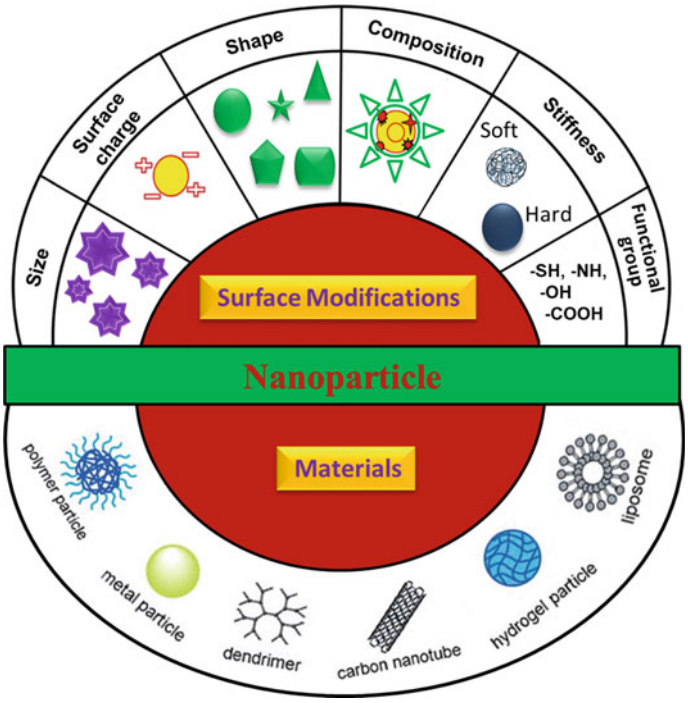

Fig. 2 Physicochemical properties of NMs

many hurdles in the ECM that hamper the diffusion of NMs, there are numerous factors that can significantly enhance NM movement through the ECM, such as the surface charge and hydrodynamic diameter of NMs [105]. Afterwards, NMs successfully pass the ECM barrier, then they should be successful in traversing the cell membrane to enter the cells [97]. The NMs enable their smooth entry into the cells due to the large surface area-to-volume ratio of small [96, 106, 107]. The NM size plays an important role in determining the mechanism of uptake too [108, 109]. Likewise, the size of NMs has an influence on the cell membrane receptor activation and resulting protein expression [110]. A novel study showed that smaller mesoporous silica NMs could obey red blood cells without dislocating the membrane. Moreover, larger mesoporous silica NMs produce subsequent and speculative haemolysis [111]. The variation in cell membrane-NPs interactions can also be observed in metallic NPs, and it is a size-dependent variation [112–116]. In cancer cell studies, the existence of functional groups on the surface of NMs could not change the size-dependent privileged uptake of lesser NMs [117]. The size distribution of structures is one more essential factor to be thoroughly explored as the cellular responses may differ with the size of the NM particles. Furthermore, the accumulation activities of NMs have an influence on interactions and subsequent cellular responses as agglomerative

NMs expose a much bigger size than individual ones [118]. Passive diffusion and active transport through the nuclear pore complex are mainly two different mechanisms in the cell nucleus. NMs should be very less size and passes through the passive nuclear pore complex channel (width 6–9 nm) [119]. The active transport through the nuclear pore membrane complex of NMs is proficient by the support of a cytoplasmic protein [120]. The below ~ 50 nm diameters of NMs can reach the nucleus by active transport through the nuclear pore complex mechanism [121]. The kinetics of NMs to the nucleus is extremely dependent on the size [119]. The ~ 2.4 nm size of functionalized gold NMs can able to enter the nucleus, but slightly greater ones are circulated in the cytoplasm (5.5–8.2 nm) [122]. The GO-QDs (graphene quantum dots) are able to enter the nucleus due to their smaller size to deliver drug cargos and DOX/GO-QD (doxorubicin/graphene quantum dots) conjugates [123, 124]. Even though there are numerous reports about the influence of cell interactions with the size of NMs, the hydrodynamic diameter (HD) is a warning of the apparent size of nanoparticles that can be premeditated from the diffusion properties of the dynamic solvated/hydrated particle. In cell culture systems, hydrodynamic size is the most realistic size of the NMs and an indication of how the particles perform in a fluid. In addition to microscopic imaging techniques like transmission electron microscope (TEM) and atomic force microscopy (AFM), dynamic light scattering (DLS)-based particle size measurement can also provide information on HD. In addition, the particle size measurement techniques such as scanning electron microscopic imaging (SEM), FESEM, TEM, dynamic light scattering (DLS), and atomic force microscopy (AFM), can also provide information on HD. Many researchers reported the protein formed around NMs could significantly vary the size and influence cellular uptake. The self-assembled NMs or size-related effects of such nanostructures on cells need special attention in various biomedical applications [125–131].

(b) Shape

The shapes of nanoparticles are also influenced due to nanomaterial uptake, distribution, interactions with cellular components, and resulting cellular functions [132]. The elongated NMs usually demonstrate higher uptake than sphere-shaped ones due to their sophisticated ability to effectively adhere to cell membranes [133]. Sphere-shaped NMs offer rarer binding sites to comply and interrelate with the cell membrane due to their rounded surface and display comparatively less internalization [134, 135]. Many researchers reported that discoid, rod, triangle sharp-shaped, cylinder, quasi-ellipsoidal nanostructures, squares, circles, etc., are more efficiently internalized by cells equated to spherical particles [132–137]. However, rod-shaped NMs exhibit less effective internalization than disc-shaped ones [138]. Cylindrical shapes have approved higher cellular uptake than spherical nanostructures ones [139]. Additionally, sharp edged NMs can penetrate into the cell membrane and effectively internalize. However, sphere-shaped polymer NMs and their distorted quasi-ellipsoidal counterparts with variable ratios of the feature are investigated where different results are observed [140]. The triangular-shaped morphology of gold NMs have

demonstrated higher uptake than sphere-shaped nanoparticles in HeLa cells [141]. The different morphologies (i.e. triangular rods, stars, etc.) of different functionalized gold NMs have exposed the highest to lowest cellular uptake, respectively [142]. Mathaes et al. completed a detailed examination to understand the dis-similarity of cellular uptake of the sphere or non-sphere-shaped, elongated poly (D, L-lactide-co-glycolide) (PLGA)-based micro and NMs [143]. The carbon-based NMs like fullerenes [144, 145] and CNTs [146, 147] can enter the cells and penetrate the cell membrane by spontaneous penetration/insertion by endocytosis or crosswise the membrane [148–150]. The researchers reported that CNTs may pass the cell membrane by exploiting a lipid-mediated process [151] through multiple steps such as landing, piercing of the membrane, and subsequent internalization [152, 153]. It is also confirmed that tiny uptake of graphene-like materials naturally starts at the uneven sides or corners of these nanostructures [154]. The sharp edges of NMs initiate penetrating the cell membrane and propagate along the rest of it. Such local piercing diminishes the high-energy barricade and helps relatively informal penetration and cellular uptake. Nevertheless, in contrast to the internalization, the exocytosis of big aspect ratio NMs is found to be smaller than that of their sphere-shaped counterparts [155].

(c) Stiffness and topography

The stiffness and topography are influenced by the NMs-cell interaction and subsequent cellular responses [118, 156]. Several studies have revealed that nanoscale surface features can alter cellular response [157], and also influence cell adhesion [158] and cell differentiation [159]. Similarly, the matrix stiffness of the structures can modify the NMs-cell interaction and subsequent cellular response [160]. The polyacrylamide-nanomaterials (PA-NMs) with tuneable stiffness as a role model substratum to validate the association between stiffness and their internalization by mammalian cells are studied by Huang et al. [161]. They have verified that a harder particle could endure bigger internalization per cell basis. Guo et al. reported that the in-vivo tumour penetration and in-vitro cellular internalization of NLGs (nanolipogels) depend on the elasticity. [162]. Guo et al. established that the elasticity of NMs plays a vital role in cellular uptake, and its remnants are a critical strategy parameter to progress the tumour delivery formulations. Moreover, fibrous matrices with sceneries of the natural in-vivo ECM are being commonly used as muscle engineering scaffolds [163, 164]. The electrospinning technique is used then the fibrous scaffolds are realized [165, 166]. The individual fibre diameter of such fibrous membranes frequently comes below the submicron range, which is comparable to the topography of native ECM [167]. Various approaches, such as controlling the solvent ratio [168], polymer concentration [169], incorporation of nanofillers, and inducing breath figure formation [170], have tried to manipulate the fibre diameter and surface topography of fibres.

2.2 Non-covalent Bonding Strategy

The non-covalent strategy is based on a large number of weak interactions (refer. Fig. 4) (hydrogen bonds, ionic, electrostatic, Van der Waals, absorption, and hydrophobic interactions,) and it is especially used with silica and metallic NMs [171–173]. The non-covalent bonds have the advantage of being relatively simple and do not affect the structure of the used molecules and their interaction with biological targets. Contrariwise, non-covalent alterations can also be predisposed by dissimilar variable quantities, such as ionic strength and pH [174].

(a) Surface charge

The surface charge of NMs is influenced due to NMs-cell interaction, cellular uptake, and the resulting outcome. [175]. The zeta potential values of the NMs are usually stated as a net surface charge of NMs [176]. ECM remnants have a net negative (−) charge due to the presence of GAGs (glycosaminoglycans) chains, which are profuse in (−)ly charged functional groups. Away from the size filtering, there is a charge-dependent mechanism for NMs trafficking across ECM, namely interaction filtering [177]. The corona protein creation over the NMs in physio-logical conditions can alter the resulting interaction and the original surface charge of NMs [178]. Generally, NMs with a net positive (+) charge are adopted by cells more energetically than those with a net (−) charge [179]. This privileged internalization can be due to favourable + and − electrostatic interactions, as cell membranes are (−)ly charged [180]. Nevertheless, phagocytic cells are described for the discerning uptake of anionic NMs [181]. In an exhilarating study, the high-affinity binding of citrate-coated superparamagnetic iron-oxide NMs with cell membranes is hindered when GAGs synthesis is blocked [182]. This points out that the communication between GAGs and the (−)ly charged NMs has played a vital role in the cell membrane binding of NMs. A sequence of $NaYF_4$: Yb^{3+}, Er^{3+} up renovation NMs with several morphological structures and surface coverings are synthesized to recognize the effect of surface charge on the scope of cellular uptake. The outcomes of this study have emphasized that the cellular uptake is also bigger when NMs with a bigger surface charge are used. The effect of surface charge on the cellular internalization is protruding in very small-sized NMs, where numerous mechanisms are found to have taken a portion in the cellular internalization such as clathrin-caveolae-mediated endocytosis and physical adhesion-consequent infiltration. However, in the case of relatively larger particles, an energy-dependent endocytosis mechanism played a more protuberant role. Landgraf et al. examined the scope of internalization of neutral, (+)ly charged, or (−)ly charged quantum dots and the Au@MnO particles by CLSM [183]. Huhn et al. reported the impact of the charge on the interactions of NMs with mechanisms of subsequent cellular internalization and biological media [179]. For this, Au NMs with equal physical properties are improved with amphiphilic polymers to make NMs with opposite surface charges (positive/negative) [179]. NMs internalized by mammal cells with a (+) charge demonstrate a more important level than those with a (−) charge

(Fig. 3) [184]. Upon contact with cells, NMs can: (i) basis the distortion of lipid membranes resulting in their internalization [185], (ii) dislocate the phospholipids bilayer [186], and (iii) create "holes" in the cell membranes. NMs with a net (+) charge are much more prospective to generate such membrane falsifications than those with net (−) and neutral charges. Such holes may outcome in the leak of intracellular mechanisms and lead to cell death. Cationic NMs can deliver moderately vigorous interaction with cell membranes with net (−) charge and consequence in their rapid internalization with potential membrane falsifications [187].

In contrast, owing to the analogous net charge with cell membranes, anionic structures are less detrimental. Owed to the net (−) charge, relating to cation NMs are supposed to be electrostatically involved in plasma membranes and afterwards internalized by the cells. Nevertheless, of such theoretical expectations, newly experimental research showed that structures with net (−) charges are also intelligent to pass in the cells by criss-crossing the (−)ly charged cell membrane [188]. In disparity to charged NMs, neutral ones display only low-slung sympathy with cells and thus affect a lesser amount of internalization [96]. There are numerous other aspects such as hydrophobicity which may also play an important role in the uptake of charged NMs,

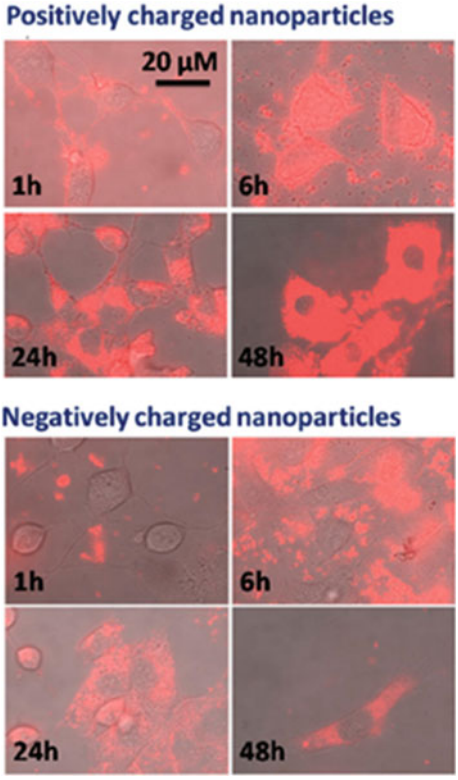

Fig. 3 Microscopic images of charged Au NMs in different culture media [179]

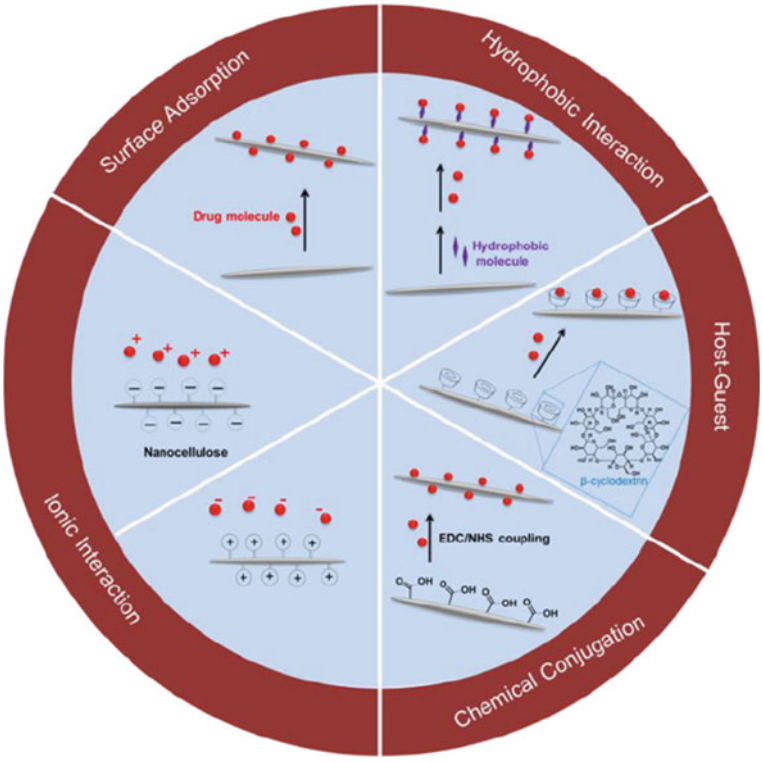

Fig. 4 Drug binding onto cellulose NMs [36]

and this could be one of the reasons for conflicting results concerning the consequence of charge on cellular uptake [181]. NMs also interrelate with cytoskeletal proteins dependent on their surface charge and outcome in the alteration of the possessions of NMs or cytoskeletal proteins [180, 190]. Along with these changes in the properties of NMs, such communications can affect cytoskeletal integrity, as evident from an increase in F-actin expression and the variance in cell polarity [191]. Metallic NMs can every so often result in the loss of cytoskeleton mechanisms such as β-tubulins and F-actins [192]. Artificial cationic macromolecules can interrelate with actin filaments [193] and affect actin polymerization (at 1 $\mu g\ mL^{-1}$). Nevertheless, at higher concentrations ($\geq$ 10 $\mu g\ mL^{-1}$), actin polymerization was augmented. Previous research also showed the reality of numerous mechanisms behind the internalization of cationic liposomes, such as those facilitated by actin links or tubulin-interceded cytoplasmic transportation [194]. NMs with a net charge can also interrelate with intracellular organelles like mitochondria [195]. A few of the charged structures can penetrate cell nuclei and generate genotoxicity [196, 197]. Disdain the probable harmful properties of DNA such as nucleus-targeted NMs are subjugated in cancer therapy [198].

(b) Hydrophobicity/hydrophilicity of the NMs

The development of hydrophobicity/ hydrophilicity NM is highly influenced by the nature of forces between NMs and cells [28, 61, 62, 199]. Fascinatingly, NMs with hydrophilic surface groups are exposed to a prolonged circulation period due to their resistance to phagocytosis [200–202]. Previous research also designated that proliferation and cell adhesion were larger on surfaces with middling hydrophilicity [203]. Among the NMs were functionalized with $–NH_2$–COOH, –OH, or any functional groups. Out of these groups, –OH and $–NH_2$ group functionalized NMs provide larger cytotoxic responses than –COOH functionalized group ones [204]. NMs with hydrophobic/hydrophilic surface functional groups demonstrate probable interaction with an endothelial cell model membrane [205]. The effect of inhibitors on the cellular internalization of carboxyl-modified polystyrene (CPS) and plain polystyrene (PS) NMs by mesenchymal stem cells (MSCs) is also investigated [206]. From the outcomes of the above study, it is highly apparent that dynasore impedes the internalization of CPS-NMs. However, dynasore does not affect the internalization of PS-NMs. The outcomes also established that with the addition of dynasore, the internalization of CPS-NMs was summarized by 30% equated to the controller cells without inhibitor; nevertheless, internalization of PS-NMs persisted the same. These outcomes show that the carboxyl groups currently present in the CPS-NMs resulted in dynamin-dependent endocytosis. The hydrophobic octane thiol surface modification of zwitterionic luminescent glutathione-coated gold NMs (GS-Au NMs) enhanced their interface with the cellular membrane and occasioned higher cellular uptake was studied [207]. The hydrophilic sulphonate ligand bearing NMs, internalized by dendritic cells, provided punctate fluorescence signatures indicating the effective endosomal uptake [208]. The hydrophobic drug transporters are very significant in the delivery of water insoluble therapeutic agents [209, 210]. In the case of vocally managed NMs, effective mucus permeation and epithelial absorption are also challenging except the surface of them is functionalized with specific molecules [211].

Moreover, hydrophobically glycol chitosan nanomaterials (HGC-NMs) are reported for the effective delivery of hydrophobized DNA [212]. The HGC-NMs provide higher transfection efficacies equated to bare DNA and a commercially accessible transfection agent, demonstrating their gene delivery application potential. Thus, the hydrophilicity/hydrophobicity of NMs plays an important title role in defining the NM-cell interactions and influence the consequence of such communications.

(c) Surface adsorption

The informal system is to adsorb drugs on the surface. This is discovered for the distribution of hydroquinone (HDQ) cellulose nanocrystal complex (CNCs) to the skin in order to remedy hyperpigmentation [213]. In this experimentation (refer. Fig. 4), the drug is adsorbed onto the surface by only mixing sulphuric acid-hydrolysed CNCs and drug molecules in condensed water with the accessory of HDQ being confirmed by FTIR peaks [213].

(d) Electrostatic interaction

The charged drugs can be elaborated by electrostatic interactions like cationic drug metformin [214], doxorubicin, and tetracycline [215]. The cellulose NMs are loaded with the drugs by mixing drugs and carriers at set pH values until all drugs are immobilized on the carrier. Jackson et al. reported a comparative study of the binding charged drugs and other neutral drugs as like paclitaxel. Moreover, it is found that only limited adsorption was done from non-charged drugs. [215]. The drug-loaded CNCs were efficiently taken up by KU-7 bladder cancer cells, but no cytotoxicity was measured. In order to deliver (−)ly charged drugs such as methotrexate (MTX), it is essential to functionalize the surface with cationic groups such as tris(2-aminoethyl) amine. After load Fe_2O_3 particles onto CNCs, the drug-loaded carriers are incubated with MCF-7 breast cancer cells. MTX delivered on quaternized CNC is found to be more efficient than free MTX [216]. The resultant particles are solvable in an aquatic solvent, but DLS investigation recommended some accumulation. Fascinatingly, the ultimate structures are sphere-shaped since the preparation method devastated the fibre structure of cellulose NMs.

2.3 Covalent Bonding Strategy

The covalent bond strategy can be achieved by using various alternate methods, dependent on the arrangement of the NMs [217–219]. Furthermore, this approach permits variations at numerous levels *via* consecutive functionalization [220–222]. This method can be demoralized to achieve structures with manifold functions [223, 224], like therapy and diagnosis to implement the theranostic approach [225, 226].

(a) Functional groups

The existence of several functional groups on the surface of NMs can change their interactions with cellular cells. Such functional groups depend on interactions trusted upon the definite interaction of cell ligands with the present functional groups over the surface of NMs. An appropriate surface functionalization permits the NMs to definitely interrelate with the safe cell membrane penetration and cellular uptake [227–229]. The cells reacted with hydrophilic group functionalized NMs left crinkles on the surface of the cell as a trademark of cellular uptake. The functionalization with ligands like small molecules, proteins, nucleic acids, antibodies, and peptides, can work as a vigorous approach to goal NMs to intracellular components or specific cells [230]. The aiming potential of NM is contingent on the chain length of functionalizing representatives too [231]. Functionalization can prevent corona protein creation when it comes to interaction with serum proteins [232, 233]. Owed to the capacity to battle protein adoption, NMs can be ornamented with PEG to minimalize generic membrane interactions. Furthermore, covering with PEG can evade the accumulation of NMs [234]. Functionalizing with exact biomolecules such as antibodies to aim and enable internalization is a perilous approach in the arena

of nanomedicine [235, 236]. A novel study exhibited that biotin integration into pullulan acetate rayon self-assembled NMs can improve the uptake by HepG2 cells [237]. The surface functionalization of NMs with certain agents that have to be distributed to the nucleus is an auspicious approach [238]. This is superficial from the introversions of nuclear cover nearby the internalized structures. Such NMs accompanying differences in nuclear morphology and superior therapeutic efficiency are extremely encouraging for nuclear-targeted cancer therapy [113, 239, 240]. Recent studies have also explored the pertinence of functionalized NMs to minimalize nuclear damage due to nuclease activity [240]. Some studies have considered the cellular internalization of NMs, which are instantaneously functionalized with manifold groups having dissimilar surface charges [241]. The fluorescent silica-based NMs embrace a wide range of zeta potential values. Remarkably, serum proteins adsorbed over these charged NMs neutralize the original surface charges by obstructive the accumulation within them [242]. When serum is non-providing in the medium, NMs with additional (+) zeta potential values can be accrued in cells more than those with (−) zeta potential values. However, in a serum comprehending medium, (−)ly charged FS-NMs demonstrate advanced uptake by the cells, indicative of the reputation of sulphonate-functionalized silica NMs in clinical applications where the presence of serum is predictable. Additionally, the microscopic investigation can be executed to localize FS-NMs in cellular components such as actin cytoskeletons and lysosomal structures [243]. The functionalized and non-functionalized carbon-related NMs are broadly explored in numerous biomedical applications [244]. Cells showing to original graphene directed the incompetence of F-actin arrangement in mammalian cells [245]. In disparity, functionalized graphene did not generate such a consequence on the cytoskeletal proteins. Previously, researchers mentioned that Cl ligands and N ligands edge-functionalized graphene QDs progress the nuclear uptake and histone binding in the nuclei [229]. Aminated graphene QDs have provided higher hollow cleavage and cross-linking of DNA chains in macrophages intervened by π–π stacking and H-bonding [246].

(b) Conjugation of drugs and targeting ligands

Chemical conjugation can frequently be a good means of immobilizing drugs while confirming the leisurely release. The chlorotoxin peptide, which interrelates with MMP-2 confidential cells, is assured to the surface of CNCs by actuating the peptide drug using NHS esters. The (−)ly charged CNCs are occupied by MCF-7 and U87MG. As U87MG has higher MMP-2 concentrations, the carriers are found to be additionally efficient [247]. Cellulose NMs, primarily, oxidized to aldehydes using periodide, followed by the reaction with the amino groups to yield (−)ly charged solvable particles that are internalized by bone-forming cells [248]. Finally, the conjugation of proteins to surfaces is a recognized process to immobilize proteins such as bovine serum albumin (BSA) onto cellulose NMs. In this case, the authors select an amalgamation of physical attachment and chemical conjugation. Deliberate and continued

release of proteins was measured with the free proteins sustaining their structural veracity [249]. These protein-coated CNCs are observed to trigger a higher in-vitro cholesterol effluence accompanying free proteins. The benefit of chemical attachment is the capacity to elect when the drug is unconstrained. The linkage between drugs and cellulose NMs could be approachable to the presence of certain acidic/enzyme atmospheres. Enzymatic cleavage-hollow of the drugs was exhibited using L-leucine linkage. Tang et al. studied the pretreated CNCs with L-leucine linkage to produce responsive amino acid functionalized CNCs. After coupling the drug tosufloxacin tosilate, a drug carrier for colon viruses was formed in which the drug could be unrestricted enzymatically by lysozyme, but not by pepsin [250]. A pH-responsive linkage was generated with a *cis*-aconitylamide linkage. Cellulose NMs were firstly modified with amino groups and reacted to the *cis*-aconitic acid and were subsequently lined with doxorubicin. The conjugation efficacy was satisfactory but small, and it was proposed that the heterogenous reactions play a vital role. In final, the drug is released extra-proficiently at small pH values [251]. The assembly of functional groups on the CNCs surface does not only empower the accessories of dyes, but also that of targeted ligands. This is confirmed by consuming folic acid, which suggestively has improved the cellular connotation of CNCs with the folic acid receptor (+)ve cell lines such as H4, DBTRG-05MG, and C6 cells [252] and KB and MDA-MB-468 [254]. Otherwise, the RGD peptide was conjugated to the surface of CNCs, which also host layers of pDNA and PEI. An improved uptake by integrin over articulating NIH3T3 cells was informed [255]. In all of these cases, it was critical to be able to monitor the uptake of NMs. This was frequently proficient by attributing fluorophores onto the surface [256, 257], but similarly, chemistries are working to conjugate amino-functionalized CQDs to create photoluminescent CNCs, which can be simply imaged throughout the cell uptake studies [258].

(c) Host–guest chemistry

Some drugs are hydrophobic, ionic, and they cannot be conjugated to the surface without trailing movement (Fig. 4). Ntoutoume et al. studied immobilized cationic β-cyclodextrin (β-CD) to the surface of CNCs via electrostatic interaction to host curcumin as a guest. The movement of curcumin against prostatic cancer cell lines and colorectal was prominently improved when transported in this complex [259] and other drugs chalcones [260]. As a substitute for binding cyclodextrin *via* electrostatic interactions, the host can be conjugated to the surface using epichlorohydrin [261] or acrylamidomethyl cyclodextrin [262] by altering the cyclodextrin with citric anhydride, shadowed by the reply with cellulose NMs. The anticancer drugs doxorubicin, paclitaxel, and antibiotic ciprofloxacin (CIP) were used for loading [263].

3 Biocompatibility and Uptake Capacity of NMs

The physical and chemical properties of NMs, such as charge, size, shape of the molecules, and surface chemical groups, impact their toxicity, uptake efficiency, and biocompatibility. Out of these, chemical groups and surface charges are effortlessly altered by surface modification. The surface modification of particles is a prevailing method to fix or diminish issues connected to NMs toxicity, uptake efficiency, and biocompatibility since these phenomena are closely connected to NM's surface conformation. Using dissimilar methods manipulating profitable kits or conventions adapted to the type of investigation, it is probable to assess their aspects.

3.1 Biocompatibility

The functionalization of the NMs surface to improve biocompatibility can be demoralized by using dissimilar molecules; out of these PEG molecules are the best for in-vivo and in-vitro applications. Kostiv et al. reported that the addition of PEG on the surface of iron-oxide and silicon dioxide NMs rises the biocompatibility when PEGylated NMs are used at high concentrations (200 mg/mL) with murine neural stem cells, unlike bare iron-oxide and silicon dioxide NMs that are caused a viability decrease of about 50% previously at a dose of 20 mg/mL [264]. In this study report, the highly appropriate properties of PEG to increase NMs biocompatibility are clearly observed. Moreover, the chromium-doped zinc gallate and diatomite-based NMs improve the hemocompatibility due to the presence of PEG on the NMs surface [265–267]. Dextran is widely used to reduce the toxicity of NMs and modify nanoparticles. Dextran is a branched polysaccharide complex and generally, dextran is exploited to improve iron-oxide NMs surface [268]. Oliveira et al. studied that the addition of dextran to iron-oxide NMs could improve biocompatibility in zebrafish caterpillars; in specific, the action with dextran-coated NMs can not determine any substantial impermanence or changes in the crosshatching rate of the caterpillars. The toxicity of dextran-modified iron-oxide NMs was investigated by Balas et al. [269] on Jurkat cells. The authors studied and observed less toxicity and minor effects on membrane veracity up to 72 h of growth incubation. In the primary cells, improved biocompatibility due to the use of dextran with iron-oxide nanoparticles was reported. The dextran-NMs had no important effects on cell viability and apoptosis in humans, mainly monocyte cells as reported by Wu et al. [270]. The researchers reported that NMs biocompatibility is enhanced through oligosaccharide, i.e. chitosan, [271, 272]. Shukla et al. [271] studied, the toxicity in three different cell lines was decreased when chitosan-NMs equated to iron-oxide NMs. Moreover, the chitosan used to modify silver NMs studied by Peng et al. [272]. The results exhibited that chitosan-coated silver NMs have had a higher biocompatibility when equated with silver NMs without surface modification in human fibroblast cells.

3.2 Uptake

The physical and chemical properties of NMs (such as composition, surface charge, shape, surface size, surface functionalization, and hydrophobicity/hydrophilicity, etc.) surface can be exploited to enhance cellular uptake. They are mainly two types,

(a) Passive uptake

The PEG molecule decreases accumulation and increases NMs stability in biological systems [273, 274]. Moreover, PEGylation of NMs evaluates a reduction of the communication with non-specific proteins resulting in a "stealth" effect which able to enhance PEG-NMs circular time and diminish phagocytosis [275]. This improved stability of PEG-NMs is directly connected to bigger cellular uptake if equated with plain NMs that can be collective in the biological atmosphere. Cu and Saltzman [276] reported that the use of PEG can efficiently modify the behaviour of NMs relative to their transport in tissues. The addition of PEG of dissimilar sizes (2.5, 5, and 10 kDa) on PLGA on the NMs surface can improve particle size. Cruje and Chithrani [277] showed that NMs properties can be affected by the length of PEG molecules and by the surface functionalization density.

To functionalize Au NMs by using longer PEG molecules with a high density, a deduction in the not-specific protein adsorption is observed. Nevertheless, this kind of variation results in a reduction in the uptake of NMs in all cell lines verified. Modifying NMs surfaces include variations in the superficial charge by using other molecules. Generally, they contain R-NH_2 molecules at a pH of about 7.4 and are positively charged. The surface charge of SiO_2 NMs distresses the cellular uptake in the HaCaT cell line and skin explants were studied by Rancan et al. [278]. The (−)ly charged SiO_2 NMs have exhibited lower uptake levels equated to APS, i.e. 3-aminopropyl-trimethoxysiliane altered NMs. Equally, Liu et al. described that the PS-NMs are altered with amino groups on the surface improved toxicity, associated with the high responsiveness of the NH_2 groups [279]. In an intestinal epithelial cell model, the (+)ly charged NMs exhibited higher uptake and toxicity rather than (−)ly charged NMs reported by Bannunah et al. [280]. Moreover, the insincere charge of NMs can be selectively altered to moderate cellular uptake. The Au NMs are improved with (−) charged pyranine which can reduce the NMs uptake. This performance can be inverted through the addition of a (+)ly charged molecular cage that counterbalances the (−) charge of Au NMs and permits cellular uptake [281]. The important role of the surface charge of NMs in cellular uptake efficacy has been elucidated [282], where the surface of f-PLNMs is improved with dissimilar types of functional groups (carboxyl, acetyl, and zwitterionic,) and molecules (polyethylene glycol, guanidinium, and sulphonic acid). These particles are incubated with THP-1 cells and A549 cells. The results disclosed an NMs superficial charge-dependent uptake by both cell lines; in particular, a cumulative trend in incorporation is observed in (+)ly charged modified-NMs, and this relationship is stronger in the THP-1 cells compared to A549 cells. Additionally, the CPPs are widely used to

increase the NMs uptake. These molecules are collected from a specific amino-acidic sequence, usually polycationic or amphipathic structures that enhance NMs uptake capacity [283]. Feiner-Gracia et al. [284] studied the penetrating competence of T at peptide (Tat-NMs) to functionalize PLGA NMs surface. They reported that while basic NMs do not pass in HeLa cells when Tat-NMs are additional, cellular uptake can be perceived. Due to the reputation of pretty the uptake of NMs, research into alternate molecules that predicament on the NMs surface is very dynamic. Yang et al. [285] informed the use of PC, i.e. phosphatidylcholine altered with dissimilar alkyl chain lengths (from C12 to C18), to rapidly grown lipid-PLGA hybrid NMs internalization. If PC had a slight effect on NMs constancy followed physical and chemical properties, then an improved cellular uptake of hybrid particles in A549 cells or HepG2 cells is observed. Moreover, the PC-altered NMs uptake has increased proportionally to the length of the PC alkyl chain.

(b) Active uptake

In the past decades, the surface alteration of NMs was primarily aimed at active targeting and cellular uptake by misusing the specific connections of NMs surface ligands with a wide array of receptors over-expressed in cancer cells [286]. The nanoparticles suitable to perform NMs active uptake include numerous chief types; among them, the maximum used are monoclonal antibodies (mAbs), proteins, small peptides, carbohydrates, aptamers, and small molecules (Fig. 5).

Throughout the coupling process, generally achieved by covalent interactions, these molecules are associated with the NMs surface in order to preserve their ability to predicament the targeted receptors. The mAbs used to achieve active uptake of NMs are expansively studied due to their higher binding ability, specificity, and stability (Fig. 5a). The antibodies are very valuable molecules to improve specific NMs uptake, but they have a higher molecular weight (~ 150 kDa), and this could be an issue in the bioconjugation method, all above with smaller (< 10 nm) NMs. The use of the antibody antigen-binding fragments (Fabs) to achieve NMs active uptake is a viable alternative [287] (Fig. 5b). A viable alternative to the use of antibodies and Fabs to alter NMs surface is denoted by peptides that bind with high affinity to specific

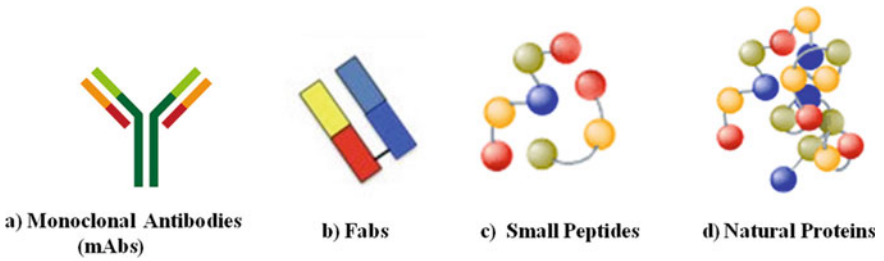

Fig. 5 Design of nanoparticles for active uptake; **a** monoclonal antibodies, **b** fabs, **c** small peptides, and **d** natural proteins

receptors (Fig. 5c). Certainly, precise peptides can be attained by the screening of the phage lending library and by the isolation of binding systems from proteins using 3D structural investigation. The use of ordinary proteins that interrelate with cancer cell receptors has been broadly studied, as described in numerous current studies (Fig. 5d). Scheeren et al. [288] studied and used transferring (Tf) to functionalize the surface of doxorubicin-loaded PLGA NMs. The interaction between transfer in and Tf receptors (Tf-R), highly articulated in cancer cells, is demoralized to improve uptake and drug release system. The authors established that Tf-PLGA@DOX NMs can greatly condense the viability of HeLa cells when compared to eternalized HaCaT keratinocytes with low Tf-R appearance. The other protein used to perform NMs active distribution is human serum albumin (HSA) which interrelates with tumour allied protein SPARC. The modified hybrid MelaSil-Ag-NMs surface using HSA to improve cellular uptake in breast cancer cells was reported by Sanita et al. [289] where the MelaSil-Ag-HSA NMs are frequently internalized by SPARC (+) cell line (HS578T) compared to SPARC (−) cells (MCF10a).

4 Challenges and Future Perspectives

We know that the conclusion of NM-cell interaction is either helpful or harmful to the cells or cellular uptake. It is dependent on many factors as a morphological surface strategy or bonging strategy of functionalization of NMs. Several cellular factors are also inspiration the particle internalization and subsequent interaction with cellular components. Research work related to the potential effects of NMs on several cellular organelles at the biomolecular level in bio-medicinal systems would be of great interest in the future. Communal exertions from all researchers and scientists are essential to understand the plausible interaction between cellular components and NMs to explore outcomes at full capacity. This would be a creative track for upcoming studies.

(a) To improve the solubility of NMs and simplify the access into the target cell resulting in the lessening of the off-target effect.
(b) The drug summarized NMs can be appropriated from the bloodstream by the MPS, which is a link of protected cells located mostly in the lymph nodes, spleen, and liver [290–293].
(c) The NM internalization is commonly problematic when the cells are highly packed [294]. Future studies should attention to the interaction of NMs with cells in a tightly packed state-run both in-vivo and in-vitro.
(d) Numerous reports concerning brain-targeted NMs highlight that much focus should be given to the surface morphological effects and surface functionality-dependent possessions of several NMs on tight junction proteins and other blood–brain barrier (BBB) components. Furthermore, CNS targeted medicines are also vulnerable to this challenge.

(e) The more detailed studies on the interactions of operative crosstalk of ECM protein mechanisms of BBB with NMs are essential to use NMs in brain therapy.
(f) As a more detailed study of the uptake of graphene by subsequent interaction with intracellular components is necessary for commonly used materials in numerous industrial applications.
(g) To develop smart nano-systems with innovative applications in biotechnology and biomedical areas. For example, adjutancy in vaccines, bio-robots, biosensors, etc.

This conversation of current improvement in the field has discovered that the idea of evolution plays a significantly titled role-like an "imperceptible hand". The enlargement of living NMs assures to improve advances in structural and functional and can endure the applications of biological and non-biological systems.

5 Conclusions

This chapter summarizes some developed molecules and experimental works with different combinations of NMs and as well as metallic particles with potential biotechnological applications. Nevertheless, the maximum imperative feature for the optimum performance of these compounds is the choice of the best-tailored functionalization process for individual biological systems. The physical and chemical alteration is a vital step for related applications, leading to chemically stable and well dispersed with the biological atmosphere. The numerous features of NMs such as surface morphological functionalization and chemically structural bonded can influence their interaction with cells or cellular components and other intracellular organelles. These communications will be advantageous to biological systems in the future.

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Nano-antimicrobial Materials: Alternative Antimicrobial Approach

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Abstract The ineffective response of conventional antimicrobial drugs and the rapid spread of drug resistance are major obstructs to the successful management of infectious diseases all over the world. A highly effective antimicrobial approach is urgently needed to replace existing ones. Recent advances in nanobiotechnology and their unique physicochemical properties would be a new hope in the coming years. In this scenario, the excellent antimicrobial efficiency of nanoparticles has received a significant interest across the globe. An improved understanding of nanoparticles following their biological cell linkages would be propitious to develop nano-based antimicrobial services like food sensors, food packaging devices, water purification systems, medical care regimens, etc. The present chapter focuses on the antimicrobial activities of different types of nanomaterials, responsible factors for antimicrobial efficiency, and probable responsible mechanisms. Moreover, this chapter also addresses the major challenges and future perspectives of nanomaterials for their efficient use.

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R. S. Mane et al. (eds.), *Nanomaterials for Sustainable Development*,
https://doi.org/10.1007/978-981-99-1635-1_5

Keywords Nanomaterials · Antibacterial and antifungal activity · Antimicrobial mechanism of nanoparticles · Influencing factors for nano-antimicrobial performance

1 Introduction

Health and diseases of living organisms are the most prevalent medical conditions and a substantial part of life. The emergence and spread of infectious diseases with pandemic incidences such as plague, tuberculosis, cholera, pneumonia, typhoid fever, syphilis, and recently COVID-19 etc., have a long history of adverse impact on the human health [1]. Since ancient times, the discovery of medicine and its development is most likely to evolve over the course of the diseases. Till the discovery of the first antibiotic penicillin, medicinal plant extracts and metals were most preferred medicines for natural treatments [2–4]. This discovery was a breakthrough in the research of antimicrobial agents. Antibiotics have enabled us to fight against several deadly infectious diseases like bubonic plague, cholera, tuberculosis, and pneumonia and could save millions of lives by reducing mortality rate to 95% [4, 5]. This great achievement of medical science is gradually transforming into the healthcare sector. Even now, it is being frequently used in most common medical practices like surgery including ocular, caesarean, organ transplantation, joint replacement, and those treatments in which immunity of the body is drastically reduced, e.g., chemotherapy for cancer and HIV treatment [6, 7]. Despite its outstanding medical applications, it has widely been incorporated into various non-therapeutic applications like water purification systems, textile industry, poultry farms, and food packaging processes etc., [8]. In the golden era of antibiotics, the mortality rate related to infectious diseases has significantly been decreased, assuring shortly infectious disease-related issues would have been completely resolved. In fact, in 1970, the US Surgeon General stated that, "*it's time to close the book on infectious diseases and shift national resources to such chronic problems as cancer and heart disease*" [9]. Even though, infectious diseases are still one of the major health threats of the twenty-first century [10]. Undoubtedly, antibiotics made an incredible contribution to the medical field and society but as we also know that all good things come with a price, unfortunately, antibiotics too. Inappropriate medication management concerning overall antibiotics treatment including over-prescription and over-usage worsens the situation. As a result, various antibiotic drugs compromise their activity against pathogenic micro-organisms [11]. According to the literature, the acquisition of antibiotic resistance usually develops within two to three years after introducing a new antibiotic into clinical practices [12]. Microbial infections related to drug resistance, are not only difficult to treat but also demand prolonged treatment period which ultimately add a burden on healthcare sectors [13]. Much efforts are being made to understand how drug resistance exactly works. It is reported that almost all micro-organisms avail an intrinsic ability to protect themselves by disturbing the antibiotics' function [14]. Biofilm production is regarded as one of the most powerful defence mechanisms

that allow selective permeability to antimicrobial substances for making them 1000 times more resistant than planktonic micro-organisms [15]. Based on the National Institute of Health (NIH) survey, about 80% of infectious diseases are associated with biofilm formation [16]. Most implantable medical devices and immunocompromised individuals are highly vulnerable to biofilm-associated diseases [17]. Similarly, they acquire numerous strategies like decreasing the uptake of antibiotic drugs by producing a certain enzyme to inactivate the antibiotics. They are also capable to alter the cellular structure to block the binding sites of antibiotics. Furthermore, the efflux pump system is an important tactic to pump out antibiotics from their cellular space [18]. A more precise understanding of the structural organization of different microbial groups (like Gram-positive, Gram-negative bacteria, and fungi) provides helpful insight for developing novel antimicrobial agents for effective treatment [19]. To date, several Gram-positive and Gram-negative bacterial pathogens have been reported to cause serious diseases and infections. A list of causative agents for the infectious diseases includes Gram-positive genera *Actinomyces, Bacillus, Clostridium, Corynebacterium, Enterococcus, Listeria, Mycobacterium, Nocardia, Staphylococcus, Streptococcus, Streptomyces* and Gram-negative genera *Acinetobacter, Escherichia, Klebsiella, Neisseria, Pseudomonas, Salmonella, Shigella, and Vibrio* [20]. Among these all bacterial pathogens, Gram-negative bacteria are more challenging than Gram-positive bacteria mainly due to the presence of an outer membrane permeability barrier, multiple efflux pumps, and target-modifying enzymes [21].

Increased infectious pathogenic strains are responsible for ~ 700,000 deaths annually across the globe [22]. A recent report estimated that by 2050, approximately 10 million deaths will be expected every year with the drug resistance trend. This mortality rate will be significantly higher than cancer-causing deaths [23]. Surprisingly, presently being used antibiotics are those antibiotic classes that have already been discovered in a golden age of antibiotics [24]. However, most infection-causing pathogens have demonstrated resistance to at least one group of antibiotics which causes economic and social complications [25]. On the other hand, fungal pathogens are also not an exception to these problems. A wide range of fungal genera including most common filamentous fungi such as *Aspergillus, Fusarium, Cryptococcus, Coccidioides, Mucor, Rhizopus,* and the non-filamentous fungus *Candida* sp. etc., are known to cause severe infections in humans which constituted almost 1.5 million mortality rates each year [26]. Moreover, at present, only a few antibiotics are routinely preferred for antifungal treatment. Most of them exhibited adverse side effects like nephrotoxicity, renal insufficiency, hypokalaemia, hypomagnesemia, polyuria, cardiotoxicity and gastrointestinal disturbances, headache, nausea, and allergic reactions such as skin rashes, itching, mouth swelling, or hand swelling restricting their direct usage [27]. While new antifungal drug development is a bit harder and more complicated as fungi shares similar feature with the host [28]. For instance, antifungal classes mainly azoles and polyenes are ergosterol inhibitors of the fungal cell membrane. However, the function of ergosterol is almost similar to cholesterol in animals [29]. As per the European Centre for Disease Prevention and Control (ECDC), this antibiotic-mediated negative consequence expects

almost 33,000 deaths every year. Thus, their controlled involvements are supposed to be effectively monitored [30]. Apart from the health issue, they amid on several other sectors like food processing, water treatment, and biofouling on surfaces of industrial interest which eventually causes heavy monetary loss [31]. These worrisome situations demand a novel chemical/structural moiety to fight against microbial pathogens [32, 33]. In this regard, researchers have continued their efforts to find innovative antibiotics. However, it is very disappointing that in the past 20 years, only two new classes of antibiotics, i.e., oxazolidinones and lipopeptides are clinically approved (which were already discovered in the late 1900th century but launched in the market very lately). Unfortunately, none of them is efficient against Gram-negative bacteria [34]. In the discovery of antibiotic research, repeatedly rediscovery of already known antibiotic classes is a major challenge not only due to costly efforts but from a time-consuming perspective also [35]. In addition, microbial pathogens are evolving faster than the discovery and development of novel antibiotics [36]. Moreover, the commercial production of antibiotics is a less profitable business as compared to other drugs mainly due to their use should be for a limited duration to avoid resistance. Similarly, the newly approved antibiotic drug is only prescribed in those cases where more established antibiotics failed to treat the infections. As per antibiotic medication guidelines, limited use of antibiotics helps to delay the emergence of the resistance trend of pathogenic strains. However, this is a major reason for lowering the returns on investment which makes it an unattractive business [9].

In the last quarter of the twentieth century, the origin of many technological advances particularly genomic techniques paves a new hope to discover novel antibiotic classes [37]. In this approach, repositories of the sequenced and annotated genome of microbial pathogens are used to find conserved genes encoding targets that are mainly missing in mammalian cells. Thereafter, a high-throughput screening assay is carried out to identify 'druggable' molecules (which are bound to these targets) from existing chemical libraries [38]. Although, the target-based screening approach is not pragmatic because these druggable molecules mostly fail to reach the target sites, due to the low permeability of bacterial membranes or the action of efflux pumps [39]. Also, single gene targets are more often to lead single point mutations which cause drug resistance and thus there is a high probability to select resistant mutants. This case is more evident through the beta-lactamases resistance which is mainly conferred by point mutation [40]. According to the reports, a single nucleotide substitution in beta-lactamase leads to introduce a new beta-lactamase-resistant penicillins, cephalosporins, carbapenems, and monobactams [41]. In this regard, the World Health Organization suggested that limited exposure to antibiotics is the only way to avoid the evolution and spread of resistance [37]. From these perspectives, exploring non-antibiotic approaches may find a special interest.

2 Nanotechnology: Pursuit of Progressive Science

Nanoscience is a highly interdisciplinary field that includes physics, chemistry, mathematics, pharmacy, biology, engineering, and materials science which stimulates innovations at the nanoscale level by reflecting the intersection of ideas [42]. As per the International Organization for Standardization (ISO), nanoscience can be described as the science of nanoscale objects, while nanoparticles are defined as ultrafine substances of a diameter within the range of 100 nm with at least one dimension [43]. The novel 1D, 2D and 3D nanomaterials should be fabricated through more investigation towards the broad range of nano-oriented services in various industries including biomedical, pharmaceutical, cosmetics, environmental, agricultural, and many more [44]. This outstanding progress of nanotechnology has been strikingly apparent to society/public *via* the wide adoption of in-market products, which are most regularly consumed on daily basis like toothpaste, cosmetics, sunscreen lotions, paints, water purifiers, etc. [45]. A recent report from the Institute for Health and Consumer Protection (IHPC) envisages that the vast expansion of the nano-based market will significantly intensify up to $30 billion by year 2025 [46]. While looking at the success graph of the nanotechnology, the most usual question is expected, "why these nanoparticles are so interesting?" Its answer is concealed in the unique properties of nano-scaled particles which are completely different from their bulk counterparts. In short, it's all about the matter of size [47]. As the size of bulk material decreases, the surface area and surface-to-volume ratio exponentially increase [48]. This size variation leads to alteration in the electronic structure from continuous bands to discrete electronic levels as result it exhibits amazing properties including mechanical, electronic, optical, and chemical ones [49]. This projects them as a topic of intensive research in various sectors such as sensor devices, photo and electro-catalysts, electronics, photoluminescence, magnetic data storage, superconductors, dilute magnetic semiconductors hydrogen production, solar cells and battery components, fuel cells and supercapacitor [50].

3 Nanoparticles: A Promising Alternative

In modern medical sciences, nanotechnology is emerged as a new fascinating field to develop promising nanomaterials, for possible clinical utility, at a lower cost [51]. The less toxic behaviour of nanomaterials against the human cells and unconventional antimicrobial mechanisms has demonstrated a great advantage over antibiotics [52]. In recent years, metal nanoparticles (NPs) have adduced a huge potential for their use as antimicrobial agents, such as in medical implants, waste-water treatment, food packaging, and dentistry [53]. However, the medicinal properties of metals like silver and copper are known and documented throughout history [54]. In ancient history, silver and copper were widely utilized in the form of jewellery and utensils to prevent microbial infections [55]. Because ancient people were already aware of

the ‘contact killing’ phenomenon in which micro-organisms are get rapidly killed on metallic surfaces [56]. Similarly, aqueous silver nitrate was most preferred to prevent the transmission of *Neisseria gonorrhoeae* from infected mothers to their new born babies [57]. In 1891, surgeon B.C. Crede was the very first person who used colloidal silver to sterilize wounds [58], whereas Robert Koch was the first to explore gold’s biocidal potential [59]. Moreover, magnesium, arsenic oxides, copper, and mercury salts are also known to treat diseases such as leprosy, tuberculosis, gonorrhoeae, and syphilis [55, 60]. Therapeutic practices of these metals have gained more popularity from 1900 to the 1940s and are still under use. Nowadays, medical-grade forms of silver such as silver nitrate, silver sulfadiazine, and colloidal silver are extensively being utilized in several clinical practices such as dental amalgam fillings, wound dressing, personal care products, domestic household products, etc. [61, 62]. Although, their use as medicine is known for ancient Indian medicinal systems i.e. in Ayurveda [63]. The concept of ‘reduction in metals particle size’ is more evident in the document ‘Indian Charaka Samhita’ [64]. In Ayurveda, Bhasma is regarded as a traditional form of medicine and claimed to be biogenic nanoparticles. For instance, Swarna Bhasma (gold powder) has been used in different formulations for the treatment of rheumatoid arthritis which has also been used for rejuvenation and tuberculosis treatment. In addition to Swarna Bhasma, Rajat Bhasma (silver ash), Tamra Bhasma (cupric oxide), Jasada Bhasma (zinc oxide), and Loha Bhasma (iron oxide) are reported to prescribe for their beneficial medicinal properties [65]. Similarly, around 2600 years ago, Indian surgeon Sushruta mentioned the biomedical uses of naturally occurring magnetite (a type of ferrite NPs which is also known as lodestone) [66]. This ancient knowledge and recently advanced understanding of nanofabrication have opened up unique opportunities in the diverse field of medical sciences and unlocked dreams which would never have had previously.

In the last few years, the antimicrobial activity of metal and metal oxide NPs has been extensively explored against various types of pathogenic bacteria including *Staphylococcus aureus, Escherichia coli, Streptococcus mutans*, *Bacillus subtilis, E. coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa*, which are mainly responsible for the outbreak of several diseases [67]. However, the antifungal activity of NPs has relatively been less explored as compared to antibacterial activity [68]. During the past decade, many studies on the antimicrobial of metal-based NPs include silver (Ag), copper (Cu), gold (Au), titanium (Ti), platinum (Pt), zinc (Zn), magnesium (Mg), and selenium (Se) NPs, and metal oxide NPs like titanium dioxide (TiO_2), zinc oxide (ZnO), copper oxide (CuO), iron oxide (Fe_2O_3), and selenium oxide (SeO) etc., are reported (see Table 1) [69]. Most of these studies have suggested that metal and metal oxide-based NPs are potent antimicrobials. Moreover, nanomaterials of metal sulphide (MS) and metal–organic framework (MOFs) have also been represented as promising antimicrobial materials in different biological fields [69, 70].

Table 1 Various nanomaterials and their antimicrobial applications

Nanomaterials	Antimicrobial applications	References
Ag NPs	Intrinsic antibacterial and antifungal agents	[62, 71]
	Food packaging, preservation of fruits and vegetables	
	Dental care	
	Antibacterial coating on an implantable device	
Au NPs	Healthcare products (ointment, face cream)	[72–74]
	Mixed with bone cement for dental applications	
	Nano-carriers for antibiotics to reach target site	
Pt NPs	Antimicrobial applications	[69]
	Therapeutic evaluation	
Cu NPs	Intrinsic antibacterial agent	[75–77]
	Antimicrobial water disinfectants	
Se NPs	Antibacterial, antifungal	[69, 78]
	Antibiotic drug delivery	
	Food processing and packaging industry	
Mg NPs	Antibacterial applications	[69, 79–81]
	Antibiotic drug delivery	
CuO NPs	Antibacterial applications	[69, 77]
	Antibacterial coating on an implantable device	
	Antimicrobial water disinfectants	
ZnO NPs	Antibacterial and wound-healing properties	[82, 83]
	Skin protectant	
	Food packaging	
	Photothermal-mediated antibacterial activity	
TiO_2 NPs	Antimicrobial	[76, 84, 85]
	Food industrial applications	
	Water disinfectants	
	Antibacterial coating on orthopaedic implantable device	
Fe_2O_3 NPs	Antimicrobial	[86–89]
	Hyperthermia treatment	
	Wastewater treatment	
MOFs	Antibacterial and antifungal properties	[70, 90–94]
	Nano-carriers for antibiotics to reach target site	
	Antimicrobial filter mask	
Graphene oxides	Antimicrobial, antibiofilm properties	[69, 95]
	Water decontamination applications	
Ferrites	Antibacterial, anticandidal, anti-adhesion, antibiofilm	[28, 96–98]
	Hyperthermia treatment	

4 Antimicrobial Activity: Governing Parameters

The physicochemical properties and different morphologies of nanomaterials are essentially important and are directly connected with antimicrobial efficiency [99]. Morones et al., found that antimicrobial activity is closely linked with the size of the Ag NPs [100]. The smaller sized NPs exhibit a strong antibacterial activities than the larger ones [101]. This size-dependent antimicrobial performance initiates curiosity about their influencing behaviour which basically raised several questions like, is this size-dependent antimicrobial phenomenon applicable to other nanomaterials too? And do different physicochemical parameters of nanomaterials account for extraordinary antimicrobial activity? Many studies were conducted to demonstrate the impact of NPs properties on micro-organisms. The main conclusion highlighted by these studies could be that size, shape, concentration, colloidal state, zeta potential, surface morphology, and crystal structure of NPs are the decisive fate of microbial survival (Fig. 1) [100–102]. Excluding physicochemical properties, a few more factors such as environmental conditions like pH, bacterial strain, and exposure time play a vital role in antimicrobial performance [103].

4.1 Size

Particle size is a very crucial property of NPs to determine antimicrobial efficacy. Numerous studies have extensively been discussed that small-sized NPs demonstrate higher specific surface area-to-volume ratio which is responsible for higher antimicrobial action [104]. In general, particle size within a range of 50 nm can offer greater antimicrobial efficiency [105] as smaller size enables them to penetrate the

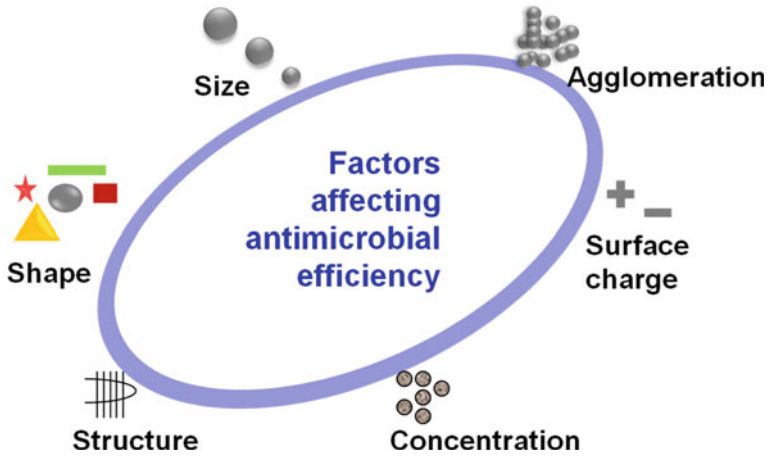

Fig. 1 Factors influencing antimicrobial efficiency

cell membrane barrier more easily and also can disturb the biofilm integrity greatly [106]. For ages, Ag NPs have been a first choice for exploring antimicrobial applications owing to their inherent antimicrobial potency [107]. Wani et al., evaluated higher antifungal efficiency for Au NPs of 25 nm than 30 nm as smaller NPs reveal a higher surface area (1795 m^2g) than larger ones (1505 m^2g) [108]. Similarly, selenium-based NPs have demonstrated broad-spectrum antimicrobial activity [109]. Shakeable et al. identified that the Se NPs carry a powerful bactericidal effect against clinical isolates as compared to the SeO_2 NPs, wherein toxicity of the NPs mainly relies on their oxidation states [110]. Copper-based NPs are also well-known for antimicrobial action [111]. However, a very few studies are reported on size-dependent antimicrobial activity. For example, the size-dependent antibacterial activity of the CuO NPs was investigated against *S. aureus, B. subtilis*, *P. aeruginosa,* and *E. coli* [111, 112]. The CuO NPs of 14.62–22.80 nm sizes exhibited a major inhibitory effect on *Candida albicans* [27]. The antibacterial activity of the Cu NPs was explored against several bacterial and fungal pathogens including *M. luteus, S. aureus, E. coli, K. pneumoniae, P. aeruginosa*, *A. flavus, A. niger, and C. albicans.* Results of this study showed that bacteria are highly susceptible to Cu NPs than fungi [113]. Another study revealed that the CuO NPs have considerable bactericidal effects against different Gram-positive and Gram-negative bacterial strains excluding *K. pneumoniae* [114]. On an account of these studies, it is well-established fact that smaller NPs endow a greater antimicrobial potency. However, it was not the case with $Mg(OH)_2$ NPs. A study analysed that the smallest $Mg(OH)_2$ NPs reveal the weakest antibacterial effect [79]. In another study, it is reported that the larger and non-spherical Au NPs are more toxic to fungi [115]. A similar finding was also observed in the biofilm inhibitory study. In this study, three different-sized Ag NPs of 5, 10, and 60 nm dimensions exerted biofilm efficiency against *C. albicans* which is basically not size-dependent [116]. These contradictory results have drawn a huge attention of the research community. Extensive research activities have revealed that particle size is a very important factor, but it cannot solely be credited to antimicrobial activity [117]. For instance, some studies have assessed the excellent bactericidal effect of MOFs ranging from a few sub-nanometres to a few hundred micrometres including Materials of Institute Lavoisier frameworks (MILs), MIL-100 (120 ± 40 nm), MIL-101-NH2 (100 ± 18 nm), MIL-88B (100 ± 20 nm) [90]; BioMIL-5, (9.83 ± 6.12 Mm) [91]; Ag-MOF, (3.0–10.0 Mm) [92]. These studies have suggested that bacterial cells are get affected, similarly to other nanomaterials [93].

4.2 Shape

Several studies have reported that the well-defined geometries of NPs can also vary the antimicrobial results [118]. For instance, Pal et al., demonstrated the antimicrobial activity of the Ag NPs having three different shapes i.e. truncated triangular, spherical, and rod-type, where, the truncated triangular-shaped Ag NPs have adduced stronger antimicrobial activity over rod-shaped NPs [119]. Similarly, cube-shaped

Ag NPs have confirmed higher antimicrobial competency than sphere-shaped and wire-shaped Ag NPs. These studies suggested that shape-dependent antimicrobial activity is mainly attributed to the specific surface area and facet reactivity of the Ag NPs [120]. Moreover, Cheon et al., endowed that sphere-shaped Ag NPs exhibit stronger antimicrobial activity as compared to triangular plate and disk-shaped Ag NPs. Antimicrobial activities of the Ag NPs strongly depend on releasing rate of the Ag ions from the different surface areas of the Ag NPs which is greatly differed from one surface area of NPs to another [121]. Recently, many metals and metal oxide NPs such as Au NPs, ZnO NPs, and CuO NPs are very well documented to confirm a shape-dependent antimicrobial activity [72, 73, 122]. More recently, Au NPs of various shapes like spheres, stars, and flowers have also been studied for shape-dependent antimicrobial activity. In this attempt, flower-shaped Au NPs have elucidated more promising antimicrobial results than others [72]. Similar observations are also made by Wani et al. who demonstrated that the disc-shaped Au NPs offer significantly higher fungicidal activity against *Candida* sp. than polyhedral-shaped Au NPs [108]. In another study, nanospheres (10 nm) and nanorods (41 nm) exerted more toxicity than the stars (240 nm), flowers (370 nm), and prisms (160 nm)-shaped Au NPs [122]. The antibiofilm potential of Au NPs has also been studied with diverse shapes like spheres, rods, cubes, stars and flowers, and peanuts. Among them, peanut and rod-shaped Au NPs have approved an excellent inhibitory effect on biofilm formation [73]. Different morphologies of the ZnO NPs with broad-spectrum antimicrobial activities were reported in the past [123]. As compared to rod or sphere-shaped ZnO NPs, flower-shaped ZnO NPs have documented enhanced photocatalytic inactivation of *E. coli* and *S. aureus* bacterial pathogens [124]. Whereas, Ramani et al., observed that the spherical-shaped ZnO NPs approve greater antibacterial propensity than the flower-like ZnO NPs, suggesting involvement of sufficient defects in the form of oxygen vacancies that can be the main reason for distinct antimicrobial effects [125]. Another study confirmed that the mulberry-like ZnO NPs are more toxic to *fungi C. albicans* than sheet-like and flower-like ZnO NPs [126]. Interestingly, Cha et al., examined the shape-specific nanomaterials inactivate the bacterial growth of methicillin-resistant *S. aureus* (MRSA) *via* inhibition of β galactosidase (GAL) enzymes. In this study, pyramid, plate, and sphere-shaped ZnO NPs were used to inhibit the GAL enzymes. The result of this study revealed that MRSA bacterial cells get highly damaged by pyramid-shaped ZnO NPs mainly due to the complete inhibition of GAL enzyme whereas, plates-shaped ZnO NPs showed a dose-dependent inhibition and sphere-shaped ZnO NPs do not exhibit any inhibition [127]. In recent years, TiO_2 NPs in three different crystalline forms including anatase, rutile, and brookite are used as potential antimicrobial agents [128]. These crystalline structures with specialized shapes have generated high interest in their antimicrobial properties. Regarding the crystal structures, anatase has exhibited promising antimicrobial results as compared to others [129, 130]. Moreover, diverse shapes like spherical, rod-shaped, hollow nanotubes of the TiO_2 NPs were also found to be excellent antimicrobial agents [131, 132]. In particular, quasi-spherical shaped TiO_2 NPs with a smaller size (15–19 nm) identified stronger antibacterial effects against several bacterial and fungal pathogens including *S. aureus, E. coli, B. subtilis, P. aeruginosa,*

C. albicans, and *A. niger*. This study reveals higher antimicrobial efficiency against Gram-positive bacteria [133]. Similarly, the TiO_2 NPs with a size ranging from 25 to 87 nm exhibit superior antibacterial activity against *E. coli, B. subtilis, S. typhi*, and *K. pneumoniae* [134]. In a study developed by Haghighi et al., the authors reported that the TiO_2 NPs significantly inhibit the biofilm formation of *C. albicans* where growth of the biofilm in medical implants is restricted [135].

4.3 Concentration

Regarding antimicrobial activity, metallic and non-metallic NPs are being extensively studied with size, shape, and the surface-to-volume ratio [136]. Apart from these, the concentration of nanomaterials is an influential parameter for antimicrobial activity [137]. Several studies have stated that the change in concentration range is directly affecting the antimicrobial response [138]. A higher concentration of nanomaterials is more effective against microbial pathogens than a lower concentration [139]. To date, studies on aforementioned metal and metal oxide NPs are reported that the antimicrobial activity increases with increasing concentration of nanomaterials [140]. Dong et al., performed antimicrobial activity of Ag NPs with different sizes and concentrations [141] where the smaller particle size (10 nm) completely inhibits bacterial growth at a lower concentration (1 μg/ml) while the larger particle size (90 nm) inhibits bacterial growth at a higher concentration only (11.5 μg/ml) [141]. Another study reported that smaller NPs exhibit greater antimicrobial activity than larger NPs at the same concentration (6 mM) [142]. These studies indicate that the antimicrobial propensity is comprehensive action of concentration along with the particle size. However, some studies demonstrated that the different microbial species can respond differently at particular concentrations [143]. For instance, Elkady et al., revealed that the complete inhibition of different bacterial strains can be achieved at different concentrations of the ZnO NPs [54]. Minimum inhibitory concentration (MIC) values were found to be 0.0585 mg/mL, 0.234 mg/mL, 0.234 mg/mL, 0.938 mg/mL for *E. coli, S. aureus, P. aeruginosa,* and *B. Subtilis,* respectively [143]. Kim et al., demonstrated that the antibacterial activity of the Ag NPs is less susceptible to *S. aureus,* while *E. coli* is completely inhibited at lower concentrations. The same study also observed that the Ag NPs were more effective against Gram-negative bacteria than Gram-positive bacteria though both types of bacteria show complete inhibition at higher concentrations (> 75 μg/mL) [144]. In another study, Se NPs with 10 μg concentration exhibited a higher antimicrobial activity towards Gram-positive bacteria, whereas Gram-negative bacteria and fungi *C. albicans* were not inhibited at this concentration [145]. Lkhagvajav et al., reported that the 2–4 μg/ml of Ag NPs could be more effective against several bacterial strains including *E. coli, S. aureus, B. subtilis, Salmonella typhimurium, P. aeruginosa, K. pneumoniae* as well as fungal strain *C. albicans* [146]. Over the past few years, iron oxide-based NPs (Fe_2O_3 NPs) are widely investigated as a potential antimicrobial agent against

both Gram-positive and Gram-negative bacteria [147]. The range of the bacteriostatic concentrations of Fe_2O_3 NPs was relatively higher i.e. 25–2000 μg/mL. This excess concentration of the Fe_2O_3 NPs could be toxic to bacterial pathogens, but it did not show any toxic effect on human cells because iron acts as one of the major trace elements for the human body [86]. Overall studies suggest that antimicrobial activity is also depending on metal type used.

Furthermore, it is also explained that the microbial ability to respond to any nanomaterial mainly depends on various characteristics of the microbial cell surface [87]. Generally, either Gram-positive or Gram-negative bacteria are the most sensitive toward different nanomaterials [148]. These differences are largely attributed to the cell wall structure and metabolism of Gram-positive and Gram-negative bacteria [96]. From this perspective, researchers have developed a nanomaterial stabilizing strategy that provides better interaction with biological molecules like polysaccharides and proteins, and increased their antimicrobial performance [97]. More recently, a study was carried out with both IONPs and surface-modified IONPs with chitosan where higher antimicrobial efficiency of chitosan-coated Fe_2O_3 NPs was noticed [149].

4.4 Surface Charge and Surface Coating

The surface charge of nanomaterials is represented as one of the most important physicochemical parameters that can significantly affect on antimicrobial activity [88]. Several studies have revealed that the surface charge of NPs regulates the interaction of NPs with the biological environment, making substantial differences in antimicrobial action [150]. This property is characterized by the zeta potential by calculating the electrophoretic mobility of the NPs in an electric field [151]. Zeta potential measurement gives a better insight into the long-term stability of NPs as well as predicts the microbial sensitivity towards NPs [152]. Generally, it is considered that the NPs with a zeta potential between − 10 mV and + 10 mV are almost neutral, whereas, if this value is greater than + 30 mV or less than − 30 mV NPs are denoted as strongly cationic and strongly anionic, respectively [153]. This zeta potential can influence the membrane penetration ability of NPs [154, 155]. To date, various positively and negatively charged nanomaterials have been explored for antimicrobial activity [156]. Abbaszadegan et al., evaluated the antimicrobial activity of three different Ag NPs of three different electrical surface charges i.e. positive, neutral, and negative. This study was performed against Gram-positive (i.e. *S. aureus, S. mutans, and Streptococcus pyogenes*) and Gram-negative (i.e. *E. coli and Proteus vulgaris*) bacteria. Results of this study demonstrated that the positively-charged Ag NPs exhibit the highest antibacterial activity against all micro-organisms, while negatively-charged Ag NPs reveal the least and the neutral NPs avail intermediate antibacterial activity [157]. Another study investigated the antibacterial response of a model bacterium *E. coli* towards three fluorescent carbon dots (C-dots) with the positive, negative and uncharged electrical surfaces where

both positively charged and uncharged C-dots have a stronger antimicrobial efficiency than negatively charged C-dots [158]. Recently, it has been shown that the surface modulation or surface coating of the NPs can be a good strategy to alter the surface charge of nanomaterials for obtaining desired bactericidal efficiency [97, 159]. Several materials are explored as efficient coating agents including organic molecules, polymers, biomolecules, or coating with an inorganic layer [159]. Interestingly, Se NPs were synthesized and modulated their surface with three different polymers i.e. polyvinylpyrrolidone (PVP-Se NPs), poly-L-lysine (PLL-Se NPs), and polyacrylic acid (PAA-Se NPs) to obtain neutral, positive, and negative charged Se NPs, respectively then determined their antimicrobial activity. Results of this study confirmed considerable activity against Gram-positive *S. aureus,* but these NPs were not effective against Gram-negative *E. coli* and *S. cerevisiae* [78]. Similarly, a study was carried out with both negatively charged (n- Fe_2O_3 NPs) and positively charged (p- Fe_2O_3 NPs). In this study, n-Fe_2O_3 NPs were synthesized whose surface was altered with chitosan polymer to obtain p-Fe_2O_3 NPs then explored for antimicrobial efficiency measurement where p-Fe_2O_3 NP has a relatively higher zeta potential magnitude (+ 36.3 mV) than n-Fe_2O_3 NP (− 32.2 mV) [160]. Arakha et al., synthesized two types of ZnO NPs that have opposite potentials (+ 12.9 mV and − 12.9 mV) and tested them against Gram-positive *S. aureus, B. subtilis, Bacillus thuringiensis,* and Gram-negative *E. coli, P. vulgaris, and Shigella flexneri* bacteria with varying surface potentials, ranging from − 14.7 to − 23.6 mV. The as-obtained results demonstrated that the surface potential of nanomaterials plays an important role in the interaction between bacteria and NPs. Positively charged ZnO NPs exhibit superior results than negatively charged ZnO NPs [89].

Recently, biogenically synthesized NPs have gained more popularity as an economical and environmentally friendly alternative approach to chemical and physical synthesis methods. This approach is fascinated by the use of biological entities as natural reducing and stabilizing agents which mainly include bacteria, fungi, actinomycetes and yeast, algae, and plant materials [161, 162]. Mostly, micro-organisms have the inherent metal-tolerant ability, and they can survive under extreme environmental conditions by tolerating metal and converting them into metal ions. While, plant extract contains phytochemicals mainly phenolic compounds, terpenoids, and flavonoids which can help in the reduction of metal ions and form a stable complex with metallic NPs [163]. These biological reducing agents can influence the size, shape, and surface charge of NPs. As result, they display varying levels of bactericidal activity [164]. Recently, Kumar et al., performed a comparative study on biogenically and chemically synthesized Ag NPs, where a stronger bactericidal effect than chemically synthesized Ag NPs is noticed [165]. These biogenic NPs are highly stable for clinical treatments due to their antimicrobial activity [166]. For instance, *Syzygium aromaticum* (clove)-mediated Ag NPs have zeta potential in the range of − 15.7 to − 16 mV which shows acceptable stability of the Ag NPs and demonstrated strong antimicrobial activity against several oral micro-organisms including Gram-positive (*S. aureus, S. mutans, E. faecalis*) and Gram-negative microorganisms (*E. coli*) and yeast (*C. albicans*) [167]. Similarly, extracellular biosynthesized

CdTe quantum dots from the fungus *Fusarium oxysporum* have also shown excellent antibacterial activity [168]. Similarly, in another study, sulphur (S) NPs were synthesized from different plant extracts with strong negative zeta potential in the range of − 7.12 to − 34.1 mV. These values have confirmed the stabilization of NPs. The highest negative zeta potential of sulphur NPs has demonstrated a strong stability with bactericidal efficacy against common pathogenic bacteria *E. coli* and *S. aureus* [169]. In another study, Ag NPs were synthesized using natural plant polymers of Indian origin: gum ghatti (GT) (*Anogeissus latifolia*) and gum olibanum (OB) (*Boswellia serrata*). These Ag NP-GT (5.7 nm) and Ag NP-OB (7.5 nm) were having zeta potential values of − 22.4 ± 8.7 mV and – 14.9 ± 6.6 mV, respectively. In this study, Ag NP-GT revealed higher antimicrobial potential than Ag NP-OB [170].

5 Antimicrobial Mechanism

The adventitious properties of NPs have made them fascinating tools to treat microbial infections. Several studies have confirmed their broad spectrum of antibacterial potential against both Gram-positive and Gram-negative bacteria. As well as they can fight against fungal infections [97, 171]. However, their exact antibacterial mechanisms are not clearly understood. Emerging evidences suggest that the generation of oxidative stress, metal ion release, and non-oxidative mechanisms can significantly contribute to the toxicity of the NPs against microbial pathogens (Fig. 2). Previously reported studies revealed that the disruption of cell wall and cell membrane, ROS production, enzyme inhibition, photocatalysis, and interference in DNA and RNA are the most common processes mainly involved in the antimicrobial activity of the NPs [172, 173].

5.1 Cell Wall and Membrane Damage

The cell wall and cell membrane of micro-organisms play a vital role in maintaining bacterial cell integrity that take part in various cellular processes like homeostasis, nutrient supply, and also provide the first line of defence against environmental threats or stress conditions [174]. Thereby, targeting the bacterial cell wall is the primary strategy of NPs for the successful eradication of microbial pathogens [175]. The cell wall damage caused by NPs can occur through different adsorption pathways as different micro-organisms have different cell wall compositions [176]. Many studies have demonstrated that NPs exert higher antimicrobial activity against Gram-positive bacteria as compared to Gram-negative bacteria [177]. The cell wall of Gram-negative bacteria is composed of lipoproteins, lipopolysaccharides, and phospholipids, which allow the penetration of only macro-molecules. Whereas, the cell wall of Gram-positive bacteria contains a thick layer (20–50 nm) of peptidoglycan and teichoic acid with numerous pores that allows easy penetration of

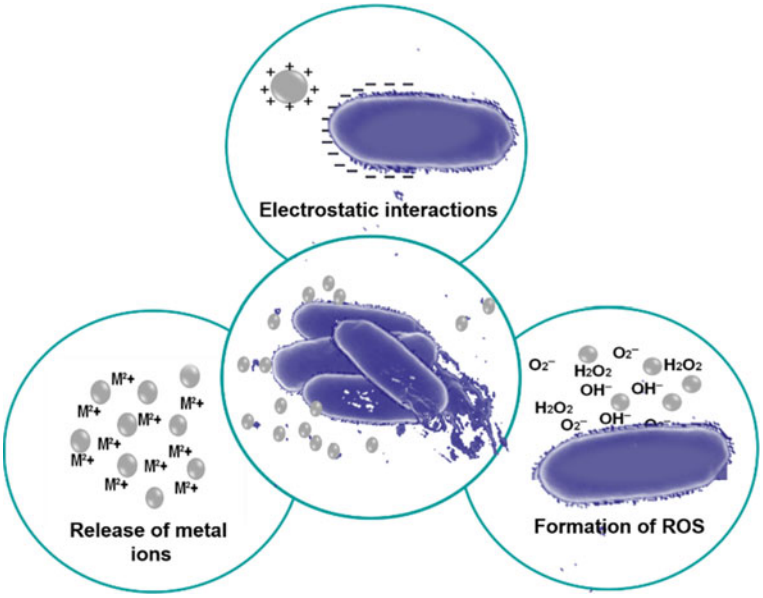

Fig. 2 Antimicrobial mechanism of nanomaterials

foreign molecules, which leads to membrane disruption, and ultimately causes cell death [178]. Furthermore, the cell wall possesses a negative charge on both Gram-positive and Gram-negative bacteria. However, several studies have confirmed that Gram-negative bacteria adduce a slightly higher negative charge than Gram-positive bacteria mainly due to the presence of lipopolysaccharide in their cell wall [179]. This can influence the interaction of NPs with microbes. The metal and metal oxide NPs including Ag Au, ZnO, and TiO_2 NPs can be attracted to the cell wall by electrostatic attraction, Van der Waals forces, and hydrophobic interactions, which make changes in the cell morphology, disturb the cellular function and permeability of the cells [180]. The accumulation of the Ag NPs on the surface of the cell wall causes numerous pits that alter the membrane permeability which leads to membrane leakage [181]. The biogenic Se NPs creates pits and holes on the surface of Gram-negative bacteria. While the membrane of Gram-positive bacteria could be wrinkled and flattened, resulting in intracellular leakage [182]. In recent years, the strong antimicrobial potential of graphene nanomaterials has been well documented, and their antimicrobial effect is mainly associated with the physical damage to the bacterial membrane by the sharp edges of graphene sheets [95]. The positive chitosan-based NPs can be electrostatically attracted to negative bacterial cell walls to rupture of the cell wall by forming a strong bond with the cell membrane [97]. Similarly, positively charged SiO_2 NPs lead to increase interaction with the negatively charged bacterial cell, causing prominent antimicrobial activity [183]. Interestingly, few studies evaluated the higher bactericidal effect for Gram-negative bacteria than Gram-positive bacteria, while other studies observe no such discrepancy among bacterial species [97, 184].

In this context, some researchers believed that bacterial species can largely affect the antimicrobial efficiency of NPs [173, 185]. For instance, Cu NPs demonstrate excellent bactericidal activity to *B. subtilis* mainly due to the surface of *B. subtilis* having a higher number of amines and carboxyl groups which facilitate high affinity to Cu NPs [186].

5.2 Intracellular Penetration and Damage

Many studies revealed that the intracellular penetration of the NPs through the membrane greatly affects the metabolic functions of microbial cells [187]. This action is mainly based on the release of metal ions, a probable mechanism for the antimicrobial action of NPs [188]. Several studies reported that ions released by metal and metal oxide NPs directly penetrate through cell walls and inactivate the enzymes, proteins, and interrupt the metabolic action [80]. The release of Ag^+ ions from Ag NPs is known to be the key contributor to antimicrobial action. Ag^+ ions have a higher affinity towards the thiol group of the cell membrane which can adhere to the cell wall more easily. The adhered ions can increase the permeability of the cell membrane. After the uptake of Ag^+ ions, the cellular respiration process is interrupted after inhibiting the enzyme by disturbing adenosine triphosphate production process [189]. The Ag^+ ions can also affect the DNA replication process by interacting with sulphur and phosphorous components of DNA and cause DNA damage and cell reproduction of bacteria [190]. Similarly, Zn^{2+} ions released by ZnO NPs also have a high affinity to the thiol group of proteins which are mainly responsible for cellular dysfunction and causes cell death [191]. However, Fe^{2+} ions released by Fe_2O_3 NPs reveal antimicrobial activities at higher concentrations. Because less concentration of Fe^{2+} ions can act as a nutrient source for bacterial growth, and also take part in various cellular processes which promote tolerance in various micro-organisms [192]. In the past few decades, different research groups have reported that metal and metal oxide NPs such as Ag, Zn, Cu, Ti, Mg, Cd, and Au etc., release metal ions to kill microbial pathogens [80, 81]. Metal-based MOF NPs such as Ag, Cu, Ni, Zn, etc., have widely been researched for antimicrobial applications [193]. Studies reported that the leaching of metal ions from the MOF can contribute excellent antimicrobial activity [93, 193].

5.3 Oxidative Stress

Oxidative stress is the cellular process that maintains the healthy redox process within cells, and also plays a crucial role in the defence response and programmed cell death [98]. The NPs exposure can induce excessive production of reactive oxygen species (ROS) which may interrupt the bacterial antioxidant defence responses [98, 194]. This increasing ROS level causes excessive oxidative stress which is responsible

for irreversible damage to cell metabolism and affects cell viability by changing the cell membrane permeability [173]. The ROS is regarded as a contributing factor to the antimicrobial activity of several metal and metal oxide NPs [98]. A study was conducted to investigate the ROS generation mechanism for several metal NPs including Ag, Au, Ni, and Si NPs in aqueous suspension under UV irradiation. The as-obtained results revealed that the Ag NPs produce superoxide and hydroxyl radicals, while Au, Ni, and Si NPs produce only singlet oxygen which is responsible for antimicrobial action [195]. Similarly, Cu NPs produce singlet oxygen, superoxide, hydroxyl radicals, and hydrogen peroxide [75], whereas ZnO NPs can generate hydroxyl radicals and hydrogen peroxide [196]. This leads to creating stress reactions on cell membrane which eventually cause cell death [96]. The iron-based NPs including ferrite NPs catalyze the formation of ROS *via* Fenton reactions, Haber–Weiss, and heterogeneous redox reactions [28]. Moreover, the semiconductor nature of the ZnO NPs and TiO_2 NPs is the main cause of antimicrobial activity [197]. The presence of holes in valence band and electrons in conduction band of the ZnO NPs and TiO_2 NPs, produces a large number of electron–hole pairs system by generating free radicals through a series of reactions, is responsible for redox reactions. Holes react with water to produce a hydroxyl radical, while the lone electron in the conduction band reacts with dissolved oxygen molecules to form a superoxide anion. It causes oxidative stress on bacteria and ruptures the cell membrane, resulting in cell death [198]. A similar mechanism is attributed to explaining the antimicrobial activity of ferrite NPs [28, 97].

6 Applications of Nanomaterials as Antimicrobial Agents

The remarkable properties of NPs have made them an efficient solution for several human health problems particularly to microbial-associated health problems. In recent years, the antimicrobial activity of NPs serves many applications, and their huge commercialization in market products has widely been noticed (Fig. 3).

6.1 Food Packaging

Since few decades, food-borne diseases become a global public health issue [199]. Extensive research has been carried out to meet practical expectations for safe, healthy, and fresh food [200]. In recent years, nanotechnological involvement has increasingly been explored in food products and food packaging materials and processes [201]. The nanomaterial-based food packaging systems are mainly useful to protect food from microbial pathogens and chemical contaminants [76]. It also increases the shelf life, food quality, and safety of products with better cost benefits. Antimicrobial food packaging systems are useful to minimize microbial growth and spoilage [202]. Many metallic NPs such as Ag, Cu, and metal oxide NPs like ZnO and

Fig. 3 Antimicrobial applications of nanomaterials

TiO_2 have been widely reported in food industrial applications [76]. Nano-polymer-based edible capsules are found to be suitable for providing micronutrients in daily foods [203]. However, a sole polymer fails to meet the expectations of effective food packaging. Thereby, incorporating metal NPs with polymer gaining interest can fulfil the desired applications [204]. The Ag NPs and Ag-based polymer nanocomposites have proven to be excellent materials for antibacterial packaging [205]. For instance, nanocomposite based on PVP polymer with Ag NPs can successfully prevent food from microbial spoilage for almost 25 days [206]. More recently, nano-based food storage bags, containers, and milk bottles are available on the market that protects food from microbial deterioration [207]. Despite food packaging, Ag NPs and their composites have widely used for food preservation purposes. Biogenic Ag NPs with sodium alginate can be used to preserve fruits and vegetables [71]. Similarly, polyethylene-based Ag nanocomposites have successfully used to preserve fresh orange juice [208]. Chitosan NPs can be incorporated in starch and hydroxypropyl methylcellulose to get biodegradable food packaging [209]. SiO_2 NPs and TiO_2 NPs are the most commonly used food nanomaterials to maintain colour and flavour in

food products [76, 84]. Nano-biosensor-based food packaging systems are gaining significant attention in the food industry. It not only detects the presence of microbial pathogens, and toxins in food products, but also gives an alert about the existing status of food quality like freshness, smell, etc. [210].

6.2 Water Purification

Water has always been the most precious key resource for humans, and its purity poses an important health concern regarding hygiene. The present scarcity of drinkable and clean freshwater, as well as increasing anthropogenic and industrial activities demands effective wastewater treatment practices [211]. Biological contaminants including bacteria, fungi, and viruses can have serious health concerns. Consumption of biologically contaminated water can face a high risk of waterborne diseases which are mainly carried by pathogenic micro-organisms [212]. Moreover, waterborne diseases are the leading cause of human morbidity and mortality throughout the world, particularly in developing countries due to the lack of capital resources. Therefore, it is necessary to manage water quality risks by using inexpensive and effective techniques to ensure safety [213]. According to the World Health Organization, the most common waterborne diseases are diarrhoea, cholera, and typhoid causing about 350 million illnesses, whereas the mortality rate associated with these diseases is about 190,000 per annum [214]. Moreover, outbreaks of these diseases are mainly associated with the most reported pathogens like *E. coli, Shigella, Salmonella, Klebsiella,* and *Campylobacter* [215]. All these pathogens are widely reported with a higher incidence of diarrhoeal disease, which is mostly affecting children's health [216]. Since the past century, chlorine has been widely applied as a water disinfectant, due to its efficiency to inactivate pathogens, economical, and ease to use. However, it produces disinfection by-products (DBPs), which pose a potential health risk and limits its service [217]. Apart from that various alternative water disinfection techniques to chlorine are also available and are well reported. This includes UV radiation, ultrasonic treatment, membrane technology, silver electrochemistry, bromine, titanium dioxide, potassium permanganate, etc. Unfortunately, less efficiency and high costs mar their utility. In addition, a few of them are also frequently producing toxic DBPs, causing serious health concerns [218]. Thereby, safe drinking water becomes a major challenge in the twenty-first century across the globe, and there is high demand for novel alternative approaches to overcome the limitations of conventional methods [219].

Exceptional properties of nanomaterials have forced researchers to look after these problems. Most recently, their introduction as water disinfectants seems to be a promising way. Many nanomaterials like Ag, Cu, and Zn NPs etc., have extensively been incorporated as antimicrobial water disinfectants [77]. Similarly, nanosorbents, nano-catalysts, nanostructured catalytic membranes, and nanoparticle-enhanced filtrations have received much interest in the water purification system

[220]. TiO_2 is the second most used nanomaterial (next to silver) to inactivate microbial pathogens. The photocatalytic activity of the TiO_2 NPs supports solar disinfection [221] as in presence of UV light, Ag-TiO_2 nanocomposites can completely eradicate *E. coli* [222]. The usage of nanomaterials as water purifiers may cause potential risks to the aquatic ecosystem [223]. The main reason is the difficulty in separating of NPs from water solution after treatment. Therefore, due to easily separation ability from waste effluent by applying an external magnetic field, magnetic NPs have taken considerable attention [224]. Organized research can help greatly to minimize the adverse effects of water purification.

6.3 Wound Dressings

Skin is the body's primary protective barrier that helps prevent the entry of foreign materials or microbial pathogens into the body [225]. Any type of structural damage to skin tissue results in a skin wound [226]. The wound healing process consists of several stages which is more susceptible to microbial infection and makes it highly challenging for quick recovery [227]. Multidrug-resistant bacteria such as *Acinetobacter baumannii*, *P. aeruginosa*, extended-spectrum β-lactamase-producing *Klebsiella* species, *E. coli*, and methicillin-resistant *Staphylococcus* strains are most frequently reported pathogens that interfere in the wound healing process [228]. Presently, available antibiotics-based wound healing therapies are not so useful due to the increasing resistance of pathogens [229]. Similarly, the commercially available wound dressing is also not much effective in 44–70% of patients, especially with chronic wounds. Therefore, the development of alternative wound dressing materials is urgently required [230]. Nanomaterial-based approaches are gaining more attention mainly due to their excellent physicochemical, antimicrobial properties and their efficiency in drug delivery, penetration ability, and cellular responses [231]. In this context, metal or metal oxide NPs including Ag, Au, and ZnO NPs are most reported materials as they have potential wound-healing properties [82]. Since ancient times, Ag NPs are being applied in wound dressing process [232]. Over the past few years, Ag NPs-based treatment therapy has widely been used in various medical applications. Recently, Ag NPs-based wound-dressing products including Aquacel Ag®, DynaGinate™ AG Silver Calcium Alginate Dressing, CuraFoam™ AG Silver Foam Dressing, DynaFoam™ AG Bordered Silver Foam Dressing, Biatain® Alginate Ag, and SilverIon® are commercially available [62]. Moreover, the Ag NPs with different biopolymers like collagen, gelatin, silk, keratin, chitosan, starch, cellulose, and hyaluronic acid are extensively used for wound dressing [233]. Similarly, the outstanding antimicrobial and antioxidant properties of the Au NPs have made them efficient for wound-healing process [234]. Their functionalization with collagen, gelatin, and chitosan polymers has confirmed better results in wound repair [235]. The wound-healing ability of ZnO NPs is widely reported, but some studies also presented that intrinsic toxicity can limit its applications [83].

6.4 Antibacterial Coating of Implantable Devices

In the modern healthcare system, implantable devices play an important role to improve the quality of a patient's life [236]. These can be either fully implantable devices such as heart valves and dental implants, or partially implantable devices like catheters, intravenous catheters, or neurosurgical catheters [237]. Most implantable devices are more susceptible to bacterial, fungal, and mixed infections [238]. Many microbial pathogens such as *S. mutans*, *S. epidermis*, *E. coli*, and *Candida spp.* etc., are frequently reported to colonize on implantable devices [239]. Moreover, implantable devices are often reported with a high risk of biofilm-associated infections which cause both implant failure and reoperation and even may lead to patient death [240]. The antimicrobial coating reduces microbial adhesion and its growth and prevents inflammation around the implants [241]. Nowadays, metals, alloys, ceramics, polymers, and nano-composites are most widely used as implant materials [242]. Biocompatibility, mechanical strength, and corrosion resistance make them suitable as implant materials [243]. However, microbial infection is one of the main reasons for implant failure which increases patient's recovery time followed treatment cost [244]. Nano-coating on implants is a promising approach to improve implant applications [245]. Owing to the excellent physicochemical and antimicrobial properties NPs like TiO_2 and Ag NPs are widely used in dental and orthopaedic implants [85]. Moreover, bimetal nanocomposites and polymer-based nanocomposites are extensively used in implant coating [246]. Ag-TiO_2 film coatings have demonstrated a high bactericidal effect against *S. aureus* and *E. coli* [247]. A study reported that TiO_2-film-coated silicone catheters revealed better antibacterial activity as compared to conventional catheters [248]. Similarly, Ag-polytetrafluoroethylene (Ag-PTFE) coating for catheters has reduced bacterial adhesion by up to 60.3%, while biofilm formation decreased by up to 97.4% [249].

6.5 Other Antimicrobial Applications

Bone cement is commonly used for implant fixation in various surgeries including knee or hip replacement surgery, by filling the gap between the implant and bone, etc. [250]. Several studies have demonstrated that bone cement loaded with antibiotics is not much effective to reduce infection rate [251]. Bone cement mixed with Ag and Au NPs significantly minimizes biofilm formation [74, 252]. Nano-based antimicrobial has been widely explored in dental applications [253]. As compared to other metal NPs, Ag NPs have the first choice in the dental field [254]. A study demonstrated that root-canal surfaces treated with ZnO and chitosan NPs significantly reduced adherence of *E. faecalis* to dentine [255]. Similarly, Si NPs are used to polish the human tooth surface to protect it from bacterial damage [256]. Furthermore, Si NPs incorporated onto polystyrene surfaces could decrease the *C. albicans* growth in the

oral cavity [257]. Over the years, nano-sized hydroxyapatite has been developed as oral healthcare products, including dentifrices, and mouth rinses [258].

MOFilter mask incorporated with ZIF-8 was developed to study the bactericidal properties under actual protective conditions. After spraying artificial pathogenic aerosols for 5 min and being exposed to the simulated sunlight irradiation for 30 min, almost no *E. coli* survived on three layers of the MOFilter mask, which was better than the commercial mask (N95) [94]. This work opens a door to the air disinfection and basic protection applications of MOF-based nanoplatforms with photocatalytic antibacterial effects.

7 Challenges and Future Perspectives

It is known that power comes with more responsibility; this belief is equally applicable to nanotechnology. Nanotechnology is a new frontier that deals with diverse aspects of human life and improved quality of life. The outstanding properties of nanomaterials have made them useful in innumerable commercial products. However, safety issues associated with nanomaterials cannot be neglected. As every nanomaterial has its individual beneficial properties and toxicity that can be vary from material to material. Therefore, comprehensive studies should be required to analyse every aspect of nanomaterials. Accordingly, some safety regulatory standards for commercial products must be developed to ensure safety. In medical science, nanomaterials are widely envisaged for diagnosis and therapeutic applications. Though, the cytotoxicity, restricted cell targeting, and drug release efficacy of nanomaterials are still not completely explored. Therefore, these challenges must be addressed before using NPs as practical therapeutic agents. On the other hand, an extensive usage of nano-products and their inappropriate discarding in the environment can introduce serious toxicity problems. From this perspective, a more detailed investigation is necessary to emphasize the risk assessment of the environment.

The nanofabrication technique is a crucial aspect to decide the fate of nanoparticles, which has drawn attention to focus more on commercially reliable, cost-effective, and environmentally acceptable synthesis approaches. Biogenic nanomaterials are gaining considerable popularity mainly due to their stability, smaller size, and biocompatibility. Numerous biogenic techniques are being developed to synthesize nanomaterials with various structures, morphologies and optoelectrochemical properties. However, the inability to large-scale production of biogenic nanomaterials is a major limitation. More research should be conducted to resolve this problem in coming years.

8 Conclusions

This chapter summarizes the opportunities that nanomaterials offer in various antimicrobial-based applications like food packaging, water purification, wound healing, medical implant coating, dental, and personal care to minimize microbial infections. Known antimicrobial mechanisms of diverse types of nanomaterials are shaded in brief. Moreover, the physicochemical relationship between the size, shape, concentration, and surface modification of NPs is also discussed as an important aspect to elevate the antimicrobial efficiency. However, challenges related to the cytotoxicity of NPs towards human and the environment needs to be studied more deeply and addressed systematically.

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Antiparasitic Activity of Nanomaterials

A. Najitha Banu, Natasha Kudesia, Neha Rana, Durdana Sadaf, and A. M. Raut

Abstract Parasites continue to cause substantial illness and mortality all over the globe to date. Malaria, Chagas disease, Ascariasis, Leishmaniasis, etc., are the major parasitic infection that carries a tremendous burden of diseases, particularly in tropical and subtropical regions. Antiparasitic drugs are widely used for the control of parasitic diseases, but drawbacks such as low efficacy and short shelf-life limit their utilization. The incompetence of the antiparasitic drugs and the absence of a functional vaccine has prompted the development of a new strategy for the treatment of these diseases. With the continuous development of nanotechnology, nanoparticles have attracted a lot of attention because of their great potential in medical applications. Different nanomaterials function as antiparasitic drug carriers to overcome the difficulties faced during drug delivery. Nanomaterial-based drug delivery system effectively targets the loaded drugs into the sites of infection as well as increases the efficacy of the drugs. While nanoparticles are efficient in the treatment of parasitic diseases, they also demonstrate promising applications in controlling parasite vectors. Currently, research is also being carried out for developing nanovaccines that are suitable candidates to prevent and fight against parasites. This chapter focuses on different nanocarriers developed for antiparasitic drug delivery. The role of nanoparticles in keeping a check on vectors harboring parasitic organisms has also been discussed. In the final section, major challenges and further research on the use of nanoparticles in making potent vaccines are recommended.

Keywords Parasitic infections · Nanotechnology · Drug delivery · Vector control · Nanoparticles · Nanovaccines

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R. S. Mane et al. (eds.), *Nanomaterials for Sustainable Development*,
https://doi.org/10.1007/978-981-99-1635-1_6

1 Introduction

Since antiquity, human beings and their ancestors are suffered from various diseases which are either caused by infectious pathogens (bacteria, viruses, parasites) or by the process of aging. Parasitic diseases are found throughout the world, but they are mostly endemic in tropical areas leading to morbidity, mortality, and socioeconomic backwardness in these areas [1]. The climate is the primary reason for the high prevalence of parasitic infections in the tropics; high temperatures and humidity are optimal for parasite growth. The infected populations are mostly living in tropical, subtropical, and remote areas where they are far behind the development, as these diseases are closely linked to many socioeconomic factors such as poor sanitation, lack of personal hygiene and health as well as poverty, development in drug resistance, and increase in global tourism [2].

Human parasite infections have a wide range of impacts, ranging from acute symptoms like severe diarrhea or anemia to more long-term issues like growth retardation, chronic limb, and organ enlargement, or blindness. Despite medical advancements, parasitic diseases continue to pose a significant threat to human health and life [3]. Moreover, parasitic infections are not restricted to human beings but are an equal threat to wild and domestic animals wreaking havoc on already poor countries [4]. A parasitic disease is an infectious disease that is caused or transmitted by a parasite, also referred to as parasitosis. A parasite (Greek pará: besides, on; sítos: food) is an organism that lives in or on another organism and derives nourishment at the expense of its host health [5]. Parasites are a wide and multifaceted group of organisms that can be broadly classified into three main categories: protozoa, helminths, and ectoparasites. Protozoa are microscopic, unicellular, heterotrophic organisms that multiply by binary division in people and lead to serious infections from a single cell. Protozoans that thrive in blood or tissue are transmitted with the help of an arthropod vector, whereas intestinal-inhabited protozoans are transmitted by the fecal-oral route. The protozoans are further classified on the mode of locomotion (Fig. 1). Helminths are large (1 mm–1 m long), invertebrate multicellular worms characterized by elongated round (nematodes) or flat bodies (cestode and trematode). Mortality by helminthic diseases is not high, but they have a negative impact on the host's nutritional and immune condition, resulting in low resistance to subsequent infections [6]. Ectoparasites thrive either on the surface of the skin or burrow into it from which they derive their sustenance including lice, ticks, mites, and fleas. Ectoparasites are potential vectors for interspecific and intraspecific disease transmissions.

Several strategies have been undertaken in previous years to combat parasitic diseases. Antiparasitic drugs are used for the control of these diseases. However, the drawbacks of antiparasitic drugs such as toxicity and negative impact on human life could not be ignored. Likewise, as the drugs used in the treatment are so expensive, their use is mostly limited in undeveloped and developing countries [7, 8]. However, there is a major obstacle before the treatment efficiency of various diseases, which is the delivery of therapeutic agents to the target area. The application of conventional therapeutic agents has limitations such as non-selectivity, undesirable side effects,

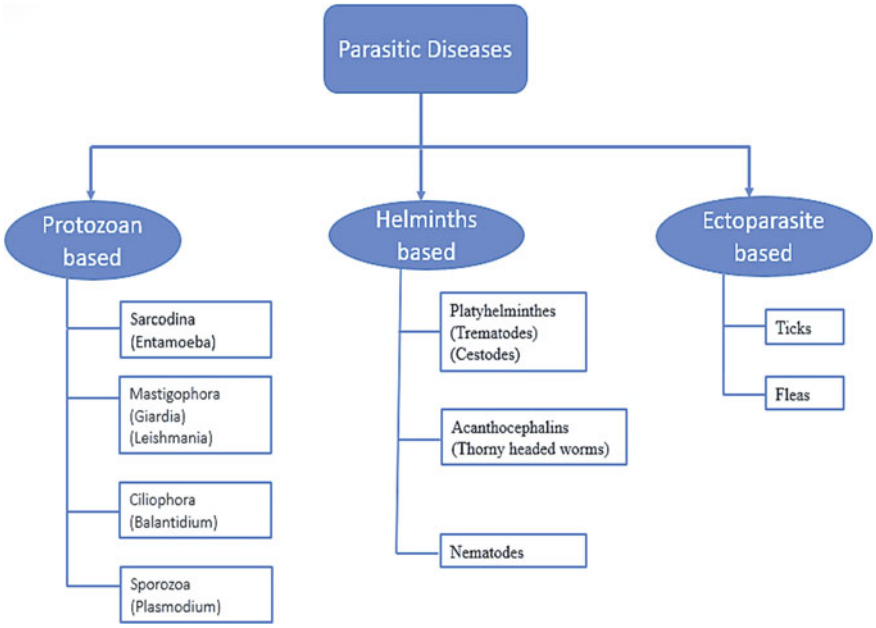

Fig. 1 Flowchart presenting types of parasites

low efficiency, and poor biodistribution [9]. Malaria is on the increase because of the development of drug resistance on the part of the parasites and insecticide resistance on the part of the mosquito vectors. Sleeping sickness is also on the increase, but there are no cheap and effective drugs or simple control measures to combat it. Despite a vast amount of effort, there are no vaccines against any human parasitic diseases [10]. Controlling the population of vector organisms, harboring these parasites has been considered to be a major approach to limiting the spread of parasitic diseases. The application of insecticide had proved to be highly successful, but due to the prolonged usage, resistance was developed by the vector against the insecticide. Similarly, a wide species of *Aedes, Culex,* and *Anopheles* have developed resistance against a wide variety of insecticides such as carbamates, pyrethroids, and organophosphates [11–13]. In the past few years, microbial agents like *Bacillus sphaericus* and *Bacillus thuringiensis* have received gained a lot of popularity in combating the vector population. These bacterial insecticides act as effective and eco-friendly mosquito larvicidal agents. They act as an ultimate substitute for chemical insecticides. However, presently a high level of resistance is observed in the vector population against them [14, 15]. Similarly, disease-causing fungi referred to as entomopathogenic are highly destructive pathogens that can help in keeping a check on the vector population. However, entomopathogenic fungi also have limitations such as difficulty in their mass production and the need for highly humid conditions makes entomopathogenic fungi slow killers [16].

These drawbacks have prompted the development of a novel strategy to control parasitic diseases. In this scenario, nanotechnology has been regarded as a boon. The use of nanotechnology and nanomaterials in medical research is growing rapidly. Nanotechnology makes use of materials and systems at atomic scales (1–100 nm). The size of nanoparticles (NPs) is alike to that of most biological structures and molecules; therefore, nanomaterials can be helpful for both in vivo and in vitro parasitical studies and applications [17]. Formation of stable interactions with ligands, variability in size and shape, high carrier capacity, and convenience of binding of both hydrophilic and hydrophobic substances makes NPs favorable platforms for the target-specific and controlled delivery of micro- and macromolecules in parasitic disease therapy [9]. Likewise, there has been an increase in the plant-based and microbial-based metal NPs in vector control, owing to their pupicidal and larvicidal activity. The underlying mechanism may be related to the ability of NPs to penetrate the exoskeleton and bind to the proteins and DNA. This leads to the denaturation of the cells and organelles [18–20]. Nowadays, nanovaccines are also gaining a lot of prominence as NPs can be utilized as adjuvants for generating long-lasting immunity through oral, intravenous, and transdermal administration [21, 22]. Therefore, the main focus of this chapter is to emphasize the growing importance of nanotechnology in controlling parasitic diseases. The chapter also throws light upon different kinds of parasitic diseases along with their vector species. Different strategies undertaken to date along with their drawbacks have also been discussed. Finally, the role of nanotechnology in controlling parasitic diseases through drug delivery as well as putting a check on vector populations has been explained. In the final section, the importance of designing nanovaccines for developing long-lasting immunity has been done for future prospects.

2 Nanotechnology-based Solutions (Targeted Drug Delivery) for the Treatment of Parasitic Diseases

Parasitic infections are one of the leading causes of death in tropical and subtropical locations across the world. Malaria, produced by the single-celled apicomplex *Plasmodium* protozoan, is still a major parasitic illness. *Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium malariae*, and *Plasmodium ovale* are four significant species of this protozoan that may infect humans [23]. In 2013, 198 million malaria cases were recorded globally, according to the World Health Malaria Report 2015. Malaria claimed the lives of 584,000 people worldwide (90% of the deaths were in Sub-Saharan Africa), with 78% of those under the age of five. The bulk of malaria cases in Africa is caused by the renowned *P. falciparum*, and the most common vector in transmitting malaria is *Anopheles gambiae*, one of the most efficient and difficult-to-manage vectors. In 2014, malaria was still being transmitted in 97 countries, putting 3.2 billion people at risk of illness, with 1.2 billion at high risk [24, 25]. Despite scientific progress, infectious diseases such as malaria continue

to be a global problem. The development of resistance to many of the currently available antimalarial medications is the fundamental reason why this illness still poses a threat in many areas throughout the world [26]. Enhanced solubility and bioavailability of hydrophobic pharmaceuticals, greater drug payload, extended drug half-life, improved therapeutic index, and controlled release of bioactive along with reduced immunogenicity and toxicity are all advantages of nanotechnology-based drug delivery systems [27–29].

NPs, especially liposomes, have gained considerable prominence in the field of drug delivery for the treatment of human diseases, particularly cancer; they provide several advantages, including controlled drug release, protection of the drug against degradation, improved pharmacokinetics, long circulation, and passive targeting to tumors and inflammatory sites due to the enhanced permeability and retention effect. The functionalization of liposomes with monoclonal antibodies or antibody fragments to generate immune liposomes has emerged as a promising strategy for targeted delivery to and uptake by cells overexpressing the antigens to these antibodies, with a consequent reduction in side effects [30].

2.1 Recent Advances in Treating Leishmaniasis: Impact of Nanotechnology

Leishmaniasis is one of the fatal infectious diseases caused by an intracellular protozoan. There are three main types of leishmaniasis, viz., Visceral (VL), often known as kala-azar, cutaneous (CL), and mucocutaneous leishmaniasis [31]. According to Kalepu and Nekkanti et al., 40% of the novel compounds licensed for therapeutic development, including those for the treatment of leishmaniasis, have limited water solubility, and this proportion rises to 90% when medicines in the discovery pipeline are included [32]. Several studies have revealed the use of nanosystems for treating leishmaniasis in the recent decade, including metallic, polymeric, and lipid NPs, as well as liposomes and nanocrystals [33]. According to Nanomedicine and drug delivery Symposium (NanoDDS 2019), the efficacy of anti-leishmaniasis drugs can be increased by releasing the drugs in macrophage-rich organs like the liver, spleen, and bone marrow because in leishmaniasis infection macrophages are the main phagocytic cells involved (Fig. 2) [34]. The macrophage cells have receptors that can internalize and engulf drug-loaded nanoparticles in the range of 50–500 nm [35].

2.2 Techniques for Targeted Drug Delivery

Active and passive techniques are the two basic ways for targeted administration of drugs.

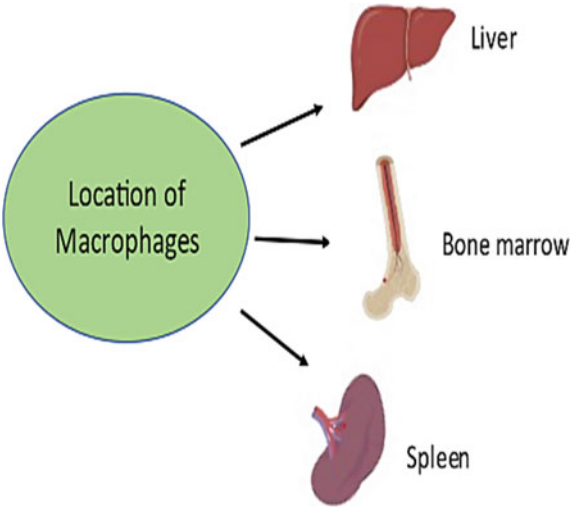

Fig. 2 Macrophage-rich organs targeted for Leishmania treatment

(a) Active targeting

Urban et al. [36] described an immunoliposomal nanovector capable of delivering its contents to *P. falciparum*-infected red blood cells (pRBCs). The scientists found that delivering chloroquine within pRBCs-specific monoclonal antibody BM1234-functionalized immunoliposomes increased the efficiency of the antimalarial medication. The antibody revealed a preference for pRBCs with parasites in the late stages of maturation. In cell culture, surface-functionalized liposomes with an average of five antibody molecules per liposome performed significantly better than non-functionalized liposomes. The results show that encapsulating chloroquine and fosmidomycin in immunoliposomes increased treatment efficacy ten-fold [36]. Using peptides and long-circulating liposomes, targeted therapy using liposomes has also been researched for malaria treatment. A 19-amino acid sequence from the N-terminal region of a protein synthesized by *P. berghei* circumsporozoite was used to surface functionalize PEGylated liposomes. Bioavailability studies of such a system revealed that surface-functionalized liposomes were 100-fold more selectively targeted to hepatocytes and non-parenchyma liver cells, and organs of the body revealed that 80% of the injected dose was found in the liver within fifteen minutes and that the uptake of peptide-bearing PEGylated liposomes by hepatocytes was over 600-fold higher than that of cardiac cells and over 200-fold higher than that in lungs or kidney cells. These findings imply that by employing peptide-targeted liposomes, antimalarial medications might be tailored to eliminate parasites from hepatocytes [37].

(b) Passive targeting

In malaria, passive targeting is neglected. When nanocarriers are administered intravenously, the mononuclear phagocyte system quickly absorbs them. As a result of the nanocarriers carrying medications inside macrophages, the

phagocyte uptake pathways are blocked, resulting in a two-fold increase in macrophage capacity. While this may delay the antimalarial drug's immediate action, it may also result in a depot-type release of medicines into the blood. This depot-type method might be useful for treating *P. vivax* infections in which the hypnozoites are latent within the hepatocytes. Because these hepatocytes reside in close proximity to the Kupffer cells, a depot release may be more therapeutically effective. Surface modification of the nanodrug delivery carrier with hydrophilic polymers such as poly (ethylene glycol) might potentially be used to accomplish passive targeting. Passive targeting is known to delay phagocytosis, resulting in a change in the drug's pharmacokinetic profile by lengthening the drug's plasma half-life. Malaria, which was once thought to be a problem only in impoverished countries, is now found in both industrialized and developing nations. The development of quick drug resistance, widespread presence, and limited private sector participation due to a lack of economic advantages are all important challenges in the fight against malaria. Furthermore, bringing a novel drug to market takes a long time and demands a significant expenditure [38]. To address this issue, it is critical to maximize the effectiveness of already available medications and improve their therapeutic efficiency. Combination therapy is preferred over monotherapy for the treatment of malaria, and artemisinin-based combination therapy is the most popular among the several options [39]. Despite the fact that artemether and lumefantrine are widely used as a combination therapy for uncomplicated malaria, the currently available formulation has various flaws, including drug breakdown in the gastrointestinal system, unpredictable absorption, and so on. Because of its nontoxicity, cost-effectiveness, and high success rate, the artemisinin combination therapy of artemether and lumefantrine is the first-line treatment for uncomplicated malaria [40]. The combination of artemether and lumefantrine is currently accessible as oral tablets. Even though this combination has a high success rate, the oral dosage form has several drawbacks, including; (a) the need to take these drugs with fat-fortified food to avoid low and/or erratic absorption, (b) the need to administer the drugs twice a day, and (c) drug degradation in acidic conditions [41]. These circumstances require the application of novel drug delivery approaches that have been previously successful in overcoming pharmacokinetic mismatches such as bioavailability, controlled release, and stability, in comparison to other drug molecules that are used to treat similar parasitic infections in general and malaria in particular [42–44]. As a result, the goal of this study is to develop an injectable (intraperitoneal; i.p.) co-loaded (artemether) nanolipid drug delivery system with the following advantages:

1. Method of administration: Fabricating injectable formulations avoids drug degradation in the gastrointestinal system, bioavailability dependence on fat intake, low patient compliance, and variable assimilation, among other issues [45].
2. Drug delivery systems: Due to the lipophilicity of the core materials (artemether and lumefantrine) and previous successes in using these lipids as

carrier materials in developing injectable delivery systems, lipid nanoparticles were chosen over other carrier materials in the current formulation [46].

Due to these issues, an injectable formulation of artemether and lumefantrine is required, which is currently unavailable. Recently, curcuminoids, a type of phytochemical, have been found to exhibit promising antimalarial activity. Curcuminoids are polyphenols obtained from the root of *Curcuma longa* Linn. Curcumin, desmethoxycurcumin, and bisdemethoxycurcumin are the three main active components; among them, curcuminoids are being researched for use in the treatment of inflammation, oxidative stress, hepatic diseases, diabetes, and cancer [47–50]. In vitro (chloroquine resistance and sensitive *P. falciparum* strains) and in vivo (*P. berghei*), curcuminoids have shown considerable antimalarial efficacy [39, 51]. These delivery systems have the advantages of being biodegradable and biocompatible, as well as allowing for regulated medication release. Drugs encapsulated within liposomes can also be protected from chemical degradation and have increased solubility. According to the researcher Owais, chloroquine was encapsulated into MAb F10-bearing liposomes and its efficiency was assessed in mice infected with chloroquine-susceptible or chloroquine-resistant *P. berghei* [52]. The chloroquine-loaded MAb F10-liposomes were able to remove both chloroquine-susceptible and chloroquine-resistant *P. berghei* infections. On days 4 and 6, chloroquine-resistant *P. berghei* was completely cured after intravenous injection of chloroquine-loaded MAb F10-liposomes at a dose of 5 mg/kg of body weight each day. This was attributable to the MAb F10-fragment's strong selectivity for *Plasmodium*-infected erythrocytes. For the past decade, a renewed attempt to identify next-generation antimalarials has been ongoing since resistance to all existing antimalarials has been reported [52].

In recent decades, the use of nanomaterials in medicine for the diagnosis and treatment of parasitic disorders has acquired a lot of interest. Nanomaterials have shown diagnostic potential against malaria, toxoplasmosis, cryptosporidiosis, amebiasis, and leishmaniasis [53–56]. NPs have shown efficacy in targeting infected macrophages for the treatment of visceral leishmaniasis (VL) when used as a therapy option for parasitic infections [57]. Silver, alone or in conjunction with chitosan NPs, had anti-toxoplasma actions by increasing serum and decreasing parasite burden. Spiramycin-loaded chitosan NPs have been found to cure toxoplasmosis efficiently. Combination nanotherapy with silver, chitosan, and curcumin NPs has been demonstrated to successfully eliminate parasites from the intestine without causing any side effects in giardiasis.

NPs' biodegradability and non-immunogenic qualities make them ideal delivery vehicles for medicines and vaccines. Pfs25H, a nanoformulation of recombinant *P. falciparum* protein, was used as malaria transmission-stopping vaccine, preventing the parasite from infecting mosquitos. Similarly, antigen-specific immune responses against *P. vivax* were elicited by polymer poly (lactide-co-glycoside) acid (PLGA) NPs containing the malaria antigen VMP001 and immunostimulatory monophosphoryl A (MPL-A). Furthermore, macrophages and DCs successfully absorbed iron oxide nanoparticles coupled with recombinant merozoite surface protein 1

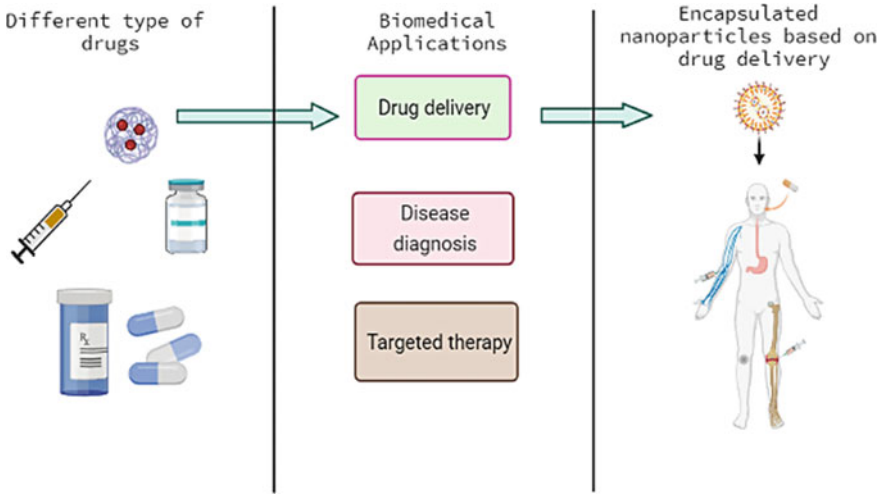

Fig. 3 Different types of drugs in the drug delivery system

(rMSP1), triggering pro-inflammatory responses. In the treatment of VL, quercetin–gold (Au) NP conjugation, doxorubicin–chitosan conjugation, amphotericin B as chitosan nanocapsule, and mannose–chitosan-based nanoformulation of rifampicin have functioned as effective delivery systems. Figure 3 depicts the different types of drugs used in the drug delivery process.

Drug developers are embracing a molecular medicine strategy that promises to deal with parasite diseases and improves the chances of successful therapy in a world where the expense of creating medicine for parasitic illnesses remains the greatest hurdle. Molecular medicine has changed drug discovery and development, yet there are enormous barriers to overcome before the promise can be realized. With the use of molecular platforms, better bioinformatics services, and better pharmacogenomics studies, the scientific community and stakeholders have considerably facilitated the scientific community and stakeholders to work together on a shared platform to battle parasitic illnesses.

3 Nano-based Strategies to Prevent the Transmission of Parasitic Diseases (Vector Control)

3.1 Different Parasitic Diseases and Their Vectors

Parasites and pathogens causing diseases are transmitted by arthropods such as mosquitoes, bugs, blackflies, tsetse flies, sand flies, lice, and ticks. These arthropods belonging to different orders Phthiraptera, Siphonaptera, Heteroptera, and Diptera

act as a vector for transmitting pathogens causing infectious diseases in humans [58, 59]. It has been estimated that vectors harbor parasites that cause approximately 17% of infectious diseases and about 700,000 deaths. The burden of these diseases is highest in the tropical and subtropical regions which affect the poorest population. In such areas, insects act as a predominant vector for parasites causing malaria, filariasis, chagas diseases, leishmaniasis, etc. [60]. Malaria is caused due to the infection of a protozoan parasite belonging to the genus *Plasmodium.* The parasite is vectored by the female *Anopheles* mosquito. *Anopheles* mosquitoes that pose a great threat are abundant and dwell in the proximity of people. They also have a long life and commonly feed on humans [61]. Likewise, lymphatic filariasis is a parasitic disease that is transmitted through *Culex* mosquitoes. *Brugia malayi*, *Brugia timori,* and *Wuchereria bancrofti* are mosquito-vectored filarial parasites causing human lymphatic filariasis. *Culex* species of mosquitoes are globally distributed due to which the probability of an outbreak of such diseases tends to increase. It has been stated that in the year 2018, approximately 893 million people were affected by this ailment [62–64].

Likewise, leishmaniases are also a vector-borne parasitic disease that infects approximately 1.4 million people every year worldwide. The vector responsible for the transmission of leishmaniases is the sandfly. It has been estimated that there are about thirty different species of sandfly that have been recognized as disease vectors. The protozoan parasite *Leishmania* is vectored predominantly by sandflies belonging to the genera *Phlebotomus* and *Lutzomyia.* These vectors are principally found in tropical and subtropical regions. They are highly prominent near human habitation and breed in organic wastes such as feces, manure, leaf litter, and in dark corners in the crevices of the walls having high humidity and temperature [65, 66]. Chagas disease, or American trypanosomiasis, is the result of infection by the parasite *Trypanosoma cruzi.* The parasite is transmitted by the blood-sucking triatomine vector also known as the kissing bug. It has been estimated that approximately six million people are found to be infected by this disease worldwide. The vector transmitting Chagas disease mainly occurs in poor rural areas. They nest mainly in the holes and cracks in walls and on roofs made of bamboo and sugarcane. They forage at night. Similarly, African trypanosomiasis or sleeping sickness is a dangerous, life-threatening, tropical parasitic disease triggered by trypanosomes belonging to protozoans. *Trypanosoma brucei gambiense* and *Trypanosoma brucei rhodesiense* are two species of trypanosomes that are responsible for the development of the disease in people. The vectors transmitting the parasites containing approximately 20 species of tsetse flies (*Glossina*) have inhabited tropical and subtropical Africa. Tsetse flies commonly inhabit fields and rural areas. It has been estimated that sleeping sickness has been detected in 36 different countries of Central and South America [67, 68]. Likewise, Babesiosis is a parasitic enzootic disease triggered by the protozoan *Babesia* parasitizing erythrocytes of vertebrates, including humans. The parasite is vectored by Ixodid ticks. *Ixodes ricinus* has been identified as the primary vector for the parasite in Europe. According to surveillance conducted in the USA, there has been an increase in cases of Babesiosis by 11% in the year 2018 [69, 70]. Figure 4

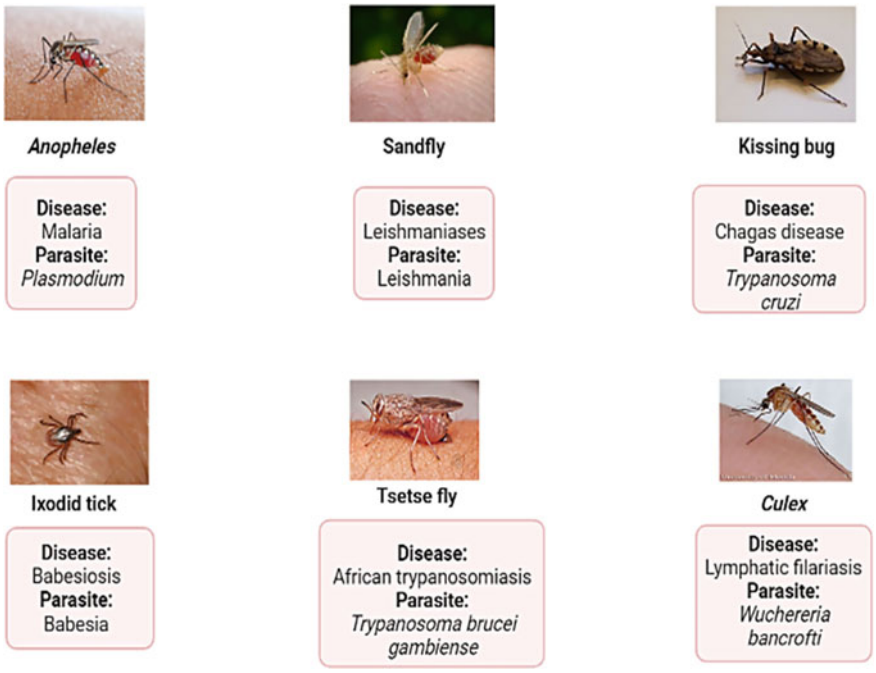

Fig. 4 Different vector species harboring a variety of parasites responsible for severing parasitic diseases

illustrates different kinds of insect vector that carry deadly parasites which causes deadly diseases.

The above-described parasitic diseases have rooted themselves throughout the globe, especially in Asia, Africa, and South America. They are continuously spreading at a fast pace due to a lack of awareness, education, and hygiene. People migrating to the natural environments of parasite occurrence also increase the likelihood of spreading infection. Destruction of the natural environment of vectors transmitting parasites also results in vectors moving to new areas to spread diseases. These insects occur in huge numbers, reproduce rapidly, and move quietly. They can very quickly and efficiently transmit a parasite to us, often painlessly and often during our sleep. Therefore, it becomes highly essential to combat the insect vector so that the chances of the disease spreading are minimized [67].

3.2 *Strategies Undertaken to Control Vector-Borne Parasitic Diseases*

The principal method for the control of parasitic diseases is through vector control strategy. Since the eighteenth century, vector control programs have been highly effective in the eradication of vector-borne parasitic diseases. Vector control aims to limit the transmission of parasites and pathogens by reducing or eliminating human contact with the vector. Various chemical and non-chemical-based methods that target the immature and adult stages of the vector have been undertaken to date [59]. Chemical insecticides like dichloro-diphenyl-trichloroethane (DDT) gained a lot of prominence during the nineteenth century. The DDT spray operation significantly reduced the mosquito and sandfly populations. However, in the later years, vector population developed resistance against DDT [12, 71]. Likewise, other chemical insecticides such as pyrethroids have been used for a long period to control the Triatomine vector, despite that pyrethroid resistance has been developed by the vector population. Control of tick vectors using acaricides had been highly effective in controlling the tick population, although recently resistance has also been developed by these vector species against the acaricides. Along with that, toxicity posed by the acaricides toward the environment also limits their utilization. Furthermore, the development of new acaricides is a long and expensive process, which reinforces the need for alternative approaches to control tick infestations [72–74].

In the past few years, microbial agents such as *B. sphaericus*, and *B. thuringiensis* have gained a lot of popularity in combating the mosquito vector population. They act as an ultimate substitute for chemical insecticides. However, presently, a high level of resistance has been observed in the vector population against them [15]. Likewise, entomopathogenic fungi have also been utilized for the eradication of the mosquito vector population. Although apart from being highly effective, entomopathogenic fungi [16]. Natural enemies of the vector such as tadpoles and larvivorous fishes act as potential predators of mosquito larvae. However, the introduction of larvivorous fishes belonging to the genus *Gambusia* and *Poecilia* is a threat to the native species. Along with this, though tadpoles and salamanders are efficient in putting a check on the mosquito larvae population, still they cannot be used alone as an independent intervention. More detailed knowledge is required to use them effectively. Other disadvantages such as the low survival rate of tadpoles and caution needed at the time of introduction of invasive species limit their applications [18, 75, 76].

Nowadays, nanobiotechnology is gaining a lot of prominence in vector control. Several nanopesticides and nanoformulations serve as important strategies for vector control. The specific utilization of nanoscience and polymer science that specifically affects vector physiology has been regarded as an efficient approach to vector eradication [77, 78]. Over the past decade, NPs have also been used as an alternative to minimize vector populations. NPs synthesized from microbes and plant parts have contributed to the area of public health in combating the vectors such as mosquitoes. Therefore, it can be stated that nanotechnology is the most promising

branch of the twenty-first century which facilitates vector control and reduces the rate of transmission of infection [79–81].

3.3 Nanotechnology in Vector Control

(a) Nanoemulsion

The emulsion system which comprises droplet size on the nanometer scale (20–200 nm) is often termed miniemulsions and nanoemulsions [82, 83]. As the nanoemulsion has an appropriate size, they appear transparent or translucent to the naked eye and therefore attains stability against sedimentation or creaming [84]. Due to these properties, this system is being practically applied in various fields such as pharmaceuticals and cosmetics. Currently, few studies have described possible applications of these nanoemulsions in the field of insect vector control strategies [77]. Nanoemulsion of essential oils is highly effective against insects. The underlying mechanism behind the toxicity is the deregulation of the growth hormone that ultimately stops insect shedding which finally leads to death. Recent studies have also reported the biological activity of nanoemulsified essential oils on etiological agents of parasitic origin. This potentially increases the diversification of the use of these nanoemulsions in the control of infectious/parasitic diseases [85]. Table 1 describes a variety of plant species utilized for the synthesis of nanoemulsion which has shown good efficacy against vector species. Eucalyptus oil nanoemulsion formulated using water, tween 80, and eucalyptus oil has been found to have mosquito larvicidal activity. Eucalyptus oil acts as a natural pesticide due to its allelopathic property. After exposing the larvae to nanoemulsion, it was concluded that at a concentration of 250 ppm, nanoemulsion caused 98% mortality of *Culex* larvae. Along with this, the histopathological studies reveal that the midgut of the larvae was completely damaged which led to death [93]. Tarragon essential oil has also been found to be highly effective against malarial vector *An. stephensi*. It was stated that the decrease in the droplet size of the nanoemulsion caused an increase in larvicidal activity. It was concluded in the study that the nanoemulsion can be suggested as a low-cost, environment-friendly mosquito larvicide [94]. *Pelargonium roseum* essential oil has been a potent larvicidal agent as it caused more than 90% mortality above 40 ppm in the Anopheles vector. The major components such as citronellol, L-menthone, linalool, and geraniol present in *P. roseum* essential oil were responsible for the mosquitocidal property. Therefore, essential oil-based nanoformulation has been considered a potent candidate for mosquito larvae control [95].

(b) Nanoparticles

NPs have been considered the most eligible candidate for the control of insect vectors. The insects have a hydrophobic and porous external surface. This waxy cuticular surface has orifices ranging from 0.5 to 2 μm, which is larger than the nanometer size scale. This allows the NPs to penetrate through

Table 1 Different kinds of plant species engaged in the synthesis of nanoemulsion which is found to be highly effective against vectors

Plant species	Vector species	Droplet size (nm)	Effective LC_{50} concentration	References
Neem *(Azadirachta indica)* oil	*Culex quinquefasciatus*	31.03–251.43	11.75 mg L^{-1}	[86]
Anethum graveolens	*Anopheles stephensi*	10.7–1880.0	_	[87]
Ocimum basilicum	*Culex quinquefasciatus*	200	36.53–38.89 ppm	[88]
Ocimum basilicum	*Culex quinquefasciatus*	28	3 mg/L^{-1}	[89]
Ricinus communis	*Anopheles culicifacies*	114	3.4 ppm	[90]
Mentha spicata	*Culex pipiens*	97.8	43.57 μg/mL	[91]
Schinus terebinthifolius	*Culex pipiens*	41.3	6.8–40.6 μl L^{-1}	[92]

the exoskeleton and bind to the proteins and DNA. This leads to the denaturation of the cells and organelles, which leads to death [18, 96]. Currently, several NPs include aluminium oxide (Al_2O_3), titanium dioxide (TiO_2), zinc oxide (ZnO), gold (Au), and silver (Ag) have been widely studied for the evaluation of their insecticidal and acaricidal properties [97–99]. Nanosilica is considered to be ideal for the control of *Anopheles* and *Culex* mosquitoes. Larvicidal bioassay reveals that 50% mortality was observed when *Anopheles* and *Culex* were exposed to hydrophobic nanosilica at the concentration of 32.3 and 128.9 ppm. Along with this, hydrophobic nanosilica has also pupicidal and ovideterrence activity against both species of mosquitoes [100]. Nowadays, biosynthesized NPs are gaining popularity. Plants' metabolites and microbial cultures are being extensively used for the synthesis of NPs. The advantages of this green synthesis include cost-effectiveness, single-step process, and eco-friendly. Although bio-fabricated metal NPs are found to be highly effective against a wide variety of insects, to date majority of the studies are being carried out on mosquitoes [12, 98].

Vinca rosea leaf extract-based Ag NPs are suitable for controlling malarial vector *An. stephensi. V. rosea* leaf extract when mixed with silver nitrate ($AgNO_3$) produces brownish-colored nanosilver particles. The synthesized particles were tested against *An. stephensi* larvae for a period of 24, 48, and 72 h. It was observed that more than 90% mortality was seen at the concentration of 68.62 mg/mL after 72 h, thereby making phytofabricated nanosilver a potent candidate for malarial vector control [101]. Likewise, Au NPs synthesized using flower extract of *Couroupita guianensis* were highly effective in controlling pesticide-resistant *Anopheles* vectors. The Au NPs synthesized were oval, spherical, and triangular in shapes of 29.2–43.8 nm

dimensions. A field study conducted concludes that a single treatment with *C. guianensis* flower extract-fabricated Au NP had led to complete larval mortality after 72 h [97]. Entomopathogenic fungi like *Fusarium oxysporum* have also been involved in the synthesis of NPs. Fungus-based Ag NPs exhibit mosquito larvicidal properties. The characterization of the fungi-mediated nanosilver reveals the presence of functional groups present in the fungal extract that assisted in the formation of Ag NPs. This myco-synthesized nanosilver tested for larvicidal activity against *A. stephensi* has shown strong mortality at the concentration range of 69.985–401.639 lg/ml. Thereby, the study confirmed that *F. oxysporum* cultures filtrate-mediated synthesized Ag NPs as a very effective green pesticide for the control of mosquitoes. *B. marisflavi* has also been considered suitable for the synthesis of NPs [102]. Ag NPs synthesized using *B. marisflavi* culture was elucidated to evaluate their efficacy against the immature stages of *An. stephensi.* The study illustrates that the LC_{90} value for the ovicidal and pupicidal activity was attained at 65.84 ppm and 58.41 ppm concentrations of *B. marisflavi*-mediated Ag NPs. The larvicidal activity was also possessed by the nanosilver, which led to more than 90% mortality at the concentration of 55.90 ppm. Therefore, it was concluded that the marine *Bacillus* proves to be appropriate for NPs' synthesis which can control malarial vectors [103].

Soil fungi such as *Chrysosporium keratinophilum* and *Verticillium lecanii* have been considered ideal for Au and Ag NPs formation. NPs based on soil fungus were studied to evaluate their larvicidal efficacy against *Culex quinquefasciatus.* After conducting the larvicidal bioassay according to the guidelines of the WHO, the results were analyzed. It was observed that the larvae of *Cx. quinquefasciatus* were found highly susceptible to the synthesized Ag NPs than the Au NPs [104]. Likewise, Ag NPs synthesized using the aqueous extract of the seaweed *Sargassum muticum* was studied to investigate their field efficacy against *Cx. quinquefasciatus.* The biosynthesized Ag NPs are mostly spherical in shape, crystalline in nature, with face-centered cubic geometry, and with a mean size of 43–79 nm. In the field, a single treatment of Ag NP in water storage reservoirs was effective against the *Culex* vector, allowing the complete elimination of larval populations after 72 h. In ovicidal experiments, egg hatchability was reduced by 100% after treatment with 30 ppm of Ag NP. Ovideterrence assays highlighted that 10 ppm of Ag NP reduced the oviposition rate by more than 70% [105]. Similarly, Ag NP synthesized using *Cassia fistula* (fruit pulp), *B. amyloliquefaciens,* and *B. subtilis* has also been studied for their larvicidal and pupicidal property against *Cx. pipiens.* It has been concluded that the exposure of larvae to the biosynthesized Ag NP led to a decrease in protein content. Along with this, there was an alteration in the activity of different biochemical constituents that affected the nervous system of the larvae ultimately leading to death [106, 107]. Marine sponge *Spongia officinalis*-synthesized ZnO-NPs were found to be an excellent insecticidal agent against *Cx. pipens* larvae. The synthesized NPs were subjected to characterization techniques such as FT-IR which confirmed the presence of different chemical functional groups such as polysaccharides, hydrocarbons, phenols, amines, amides, and carboxylates that helped in the formation of ZnO NPs. ZnO NPs of very small size of 11.5 nm were obtained that were exposed to the mosquito larvae. It was observed that the tested ZnO-NPs severely induced

larvicidal activity with LC_{50} and LC_{90} of 31.823 and 80.09 ppm for *Cx. pipiens*. The study thus concluded the possibility of using *S. officinalis*-mediated ZnO-NPs for vector control [108].

NPs are highly effective in controlling tick vectors. Studies are being carried out to prove that NPs synthesized through chemical and green fabricated routes have high acaricidal properties. Most of the studies assessed the toxicity of Ag NPs against ticks, followed by TiO_2 NPs, and to a minor extent by ZnO, nickel (Ni) NPs, and copper (Cu) NPs. However, most of these studies have been carried out on the effect of NPs in controlling economically important ticks that parasite a variety of livestock species [99]. A study was undertaken by Avinash et al. [109] to investigate the acaricidal property of neem-coated Ag NPs on the deltamethrin-resistant strain of *Rhipicephalus (Boophilus) microplus*. It was observed in the study that after 24 h of exposure, maximum mortality of 93.3% was seen at the concentration of 50 ppm of neem-coated nanosilver [109]. According to a very recent study, the acaricidal activity of green-synthesized nickel oxide (NiO) NPs using an aqueous extract of *Melia azedarach* ripened fruits was investigated against different developmental stages of the camel tick *Hyalomma dromedarii*. The synthesized NPs were exposed to the egg, nymph, larvae, and adult stages of the tick. NiO NPs of size ranging from 21 to 35 nm were able to cause more than 50% mortality at the concentrations of 5.00, 7.15, and 1.90 mg/mL in embryonated eggs, larvae, and engorged nymphs, respectively, whereas the egg productive index (EPI), egg number, and hatchability (%) were lower in females treated with the NiO NPs [110]. Table 2 summarizes the efficacy of biologically synthesized NPs against different developmental stages of the vector.

It can be concluded that nanotechnology is a science that is being widely employed for controlling a wide variety of pest and vector species such as mosquitoes and ticks [120–122]. In spite of that to date, maximum studies and research work have been done to control mosquito adults, pupae, and larvae [116, 123–125]. Several works have also been carried out to investigate the efficacy of NPs in controlling tick vector species causing parasitic diseases in livestock. However, the field application of NPs is still a major research gap in this field. In addition to this, further challenges for future research should be focused on broadening the number of studied tick species as this field is completely unexplored [17, 99, 111]. These NPs have also played an important role in controlling parasitic diseases such as Chagas disease, Leishmanial diseases, and African trypanosomiasis through various nanoformulations and via nanoparticulate drug delivery. No such study for controlling these vector populations through NPs has been performed to date. Therefore, it becomes highly essential to carry out further research work so that steps can be undertaken to put a check on vectors causing deadly parasitic diseases [126]. Figure 5 shows the diagrammatic representation of nanoemulsions and metal NPs fabricated through plants and microbes such as bacteria, algae, and fungi. The synthesized nano-based particles and emulsions have been considered eligible candidates for controlling the vector population.

Likewise, essential oils obtained from plants assist in nanoemulsion formation which also helps in the vector control strategy.

Table 2 Plant extract and microbial culture used for the synthesis of NPs which are found to cause more than 50% mortality in different vector species

Plant/microbial extract	Metal nanoparticle	Vector species	Stage	LC50	References
Mimosa pudica	Ag	*Rhipicephalus microplus*	Larvae	8.98 mg/l	[111]
Euphorbia hirta (plant leaf extract)	Ag	*Anopheles stephensi*	Pupa Larvae	34.52 ppm 10.14–27.89 ppm	[112]
Vinca rosea leaf extract	Ag	*Anopheles stephensi Liston* *Culex quinquefasciatus*	Larvae	16.84 mg/mL (after 72 h) 43.80 mg/mL (after 72 h)	[101]
Calotropis gigantea	TiO_2	*Rhipicephalus microplus*	Larva	24.63 mg/l	[113]
Solanum trilobatum	TiO_2	*Hyalomma anatolicum*	Larva	25.85 mg/l	[114]
Bacillus megaterium	Ag	*Culex quinquefasciatus*	Larvae	0.567–8.269 ppm	[115]
Caulerpa scalpelliformis (frond extract)	Ag	*Culex quinquefasciatus*	Pupa Larvae	7.33 ppm 3.08–586 ppm	[116]
Lobelia leschenaultiana	ZnO	*Rhipicephalus microplus*	Adult	1.7 mg/ml	[18]
Citrus limon leaf extract	Pd (Palladium nanoparticles)	*Anopheles stephensi*	Larvae	7.215%	[117]
Sargassum myriocystum	Ag	*Culex quinquefasciatus*	Larvae	5.59 mg/L	[118]
Penicillium corylophilum	Se (Selenium)	*Anopheles stephensi*	Larvae	25 ppm	[119]
Penicillium chrysogenum	MgO	*Anopheles stephensi*	Larvae	12.5–15.5 ppm	[20]

4 Recent Advancements in the Development of Nanovaccines

Control of parasitic diseases necessitates a complex combination of public health, education, political will, and medical science efforts. As the key components vary widely, the nature of the interplay differs for each parasitic disease [127]. The following key points explain the limitations of drugs and vaccines that prompted the development of nanotechnology in controlling parasitic diseases.

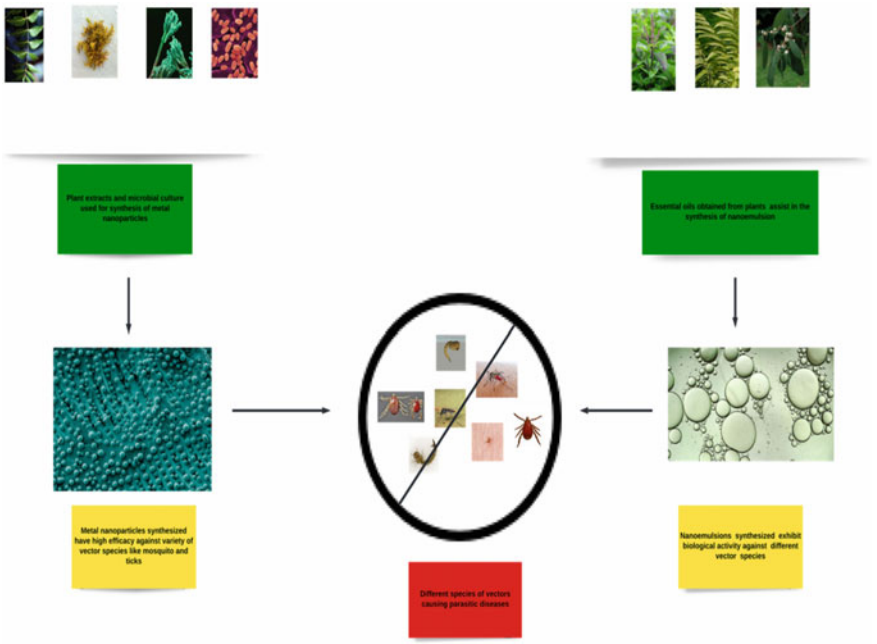

Fig. 5 Plants' extract and microbial culture have been used for the synthesis of metal NPs which have the potential for controlling mosquito larvae, pupae, and tick population

4.1 Available Drug-Related Problems

Antiparasitic drugs are still the best option for managing parasitic infections. Most of the available antiparasitic drugs by their insolubility are poorly absorbed and excreted out of the body. Additionally, the low gastrointestinal absorption profile and variable bioavailability of poorly soluble medicines pose a considerable challenge in developing appropriate dose forms [128]. Antiparasitic drug resistance as a result of widespread and irrational use is one of the major threats around the globe and is responsible for the mortality of millions per year [129]. Satisfactory effects often necessitate high and multiple doses, which are prone to drug resistance, low efficacy, reinfection, and hazardous side effects. Several ways to develop nano-sized medication delivery devices have been researched in recent years. Particularly, in the case of novel antiprotozoal, the lack of effective vaccinations, safe and affordable medications, increased drug resistance, and lack of novel drugs for the prevention and treatment of human protozoan infections have amplified the disease's impact manifold [130].

4.2 Drug Resistance and Lack of Vaccines

Resistance to various antiparasitic drugs remains a major threat to global efforts to control and eliminate parasitic diseases. Vaccination has long been considered the most long-term approach for parasite disease control in humans and animals. The parasites share complex biology by the virtue of which their life cycle proceeds through various developmental stages in different hosts and the harvesting of vaccines from these animal hosts is a daunting task in terms of cost, quality control, standardization, and shelf life [131]. A substantial impediment in vaccine development is the absence of in vitro methods required to culture different stages of parasites. The capacity of many parasites to modify host immune responses in order to postpone or prevent parasite clearance complicates vaccine development even more. Additionally, the maintenance of parasite populations necessitates passage through or formation of persistent infections in their specific animal host.

4.3 Lack of Novel Drugs

Increasing drug resistance among animal parasites along with the high cost of drugs, limited availability, and food safety concerns over drug resistance are the few notable limitations that have facilitated the need for the development and implementation of alternative management techniques [132]. Antigenic variation, sequestration, and immunosuppression are examples of adaptive strategies used by protozoan and metazoan parasites to evade immunity. Many parasites use these strategies to extend their survival in the mammalian host to compensate for their low transmissibility to the arthropod vector on which their cyclical development depends. Parasites can delay sterilizing immunity which leads to their chronicity in the host cell. Many parasites have the ability to modify host immune responses in order to postpone or prevent parasite clearance.

4.4 Nanotechnology as a Solution

NPs are at the forefront of the rapidly developing field of nanotechnology with several potential applications. NPs with exceptional biodegradability and biocompatibility are regarded as the most effective vehicle for delivering drug compounds in the biomedical field. Nano-based drug delivery systems improve the bioavailability and therapeutic efficiency of drugs while lowering the side effect profile [133]. Reduction in particle size leads to higher dissolution rates due to increased surface area, which is one of the most effective strategies to solve these issues [134]. NPs, as an innovative novel drug carrier, offer a promising technique to treat parasitic infections effectively by addressing the constraints of limited bioavailability, poor cellular permeability,

nonspecific distribution, and quick removal of antiparasitic medications from the body [135].

4.5 Availability of Different Nano-based Delivery Systems

Over the years, nanomaterials have emerged as potable drug carriers. Nanotechnology-based drug delivery systems have included biodegradable nanoparticles, dendrimers, polymeric micelles, liposomes, microcapsules, solid lipid nanoparticles, and solid core–shell nanoparticles.

(a) Nanocapsules

Nanocapsules consist of one or more active materials (core) and a protective matrix (shell) in which the therapeutic composition can be encapsulated (Fig. 6) [136]. The protective layer of nanocapsules is normally pyrophoric (liable to ignite spontaneously on exposure to air) and easily oxidized [137]. Nanocapsules are a class of polymer-based nanoparticles other than nanospheres that can penetrate the basal membranes due to their small size, making them suitable carriers for drug delivery. Their shape has a low aspect ratio, making them easier to penetrate cells than capsules with a high aspect ratio, such as rods. Antibodies and cell-surface receptors can be added to their surfaces to detect biomolecules for targeted administration. Nanocapsules are of biological relevance because they can be utilized for controlled drug release and targeting while protecting enzymes, proteins, and foreign cells, among other cellular components [138, 139]. Sustained release, improved drug selectivity and effectiveness, enhanced therapeutic bioavailability, and reduced drug toxicity are some of the key advantages of nanocapsules. Polymer-based NPs are being investigated as a means of delivering chloroquine and artemisinin against intracellular Plasmodium and amphotericin B against Leishmania [140–142].

(b) Nanosphere

Nanospheres of inorganic materials are used as lubricants with the help of nano-sized "ball bearings." By virtue of particle size, nanospheres are ideal to be administered orally, locally, and systematically. Nanospheres have small particle sizes; thus, they are suitable to be administered orally, locally, and systemically. Usually, most nanospheres are prepared using polymers that are biodegradable and biocompatible. They are used as a delivery system in order to enhance the entrapment and release of the drug (Fig. 7).

(c) Solid lipid nanoparticles

Solid lipid nanoparticles (SLN) have emerged as a versatile alternative to polymer-based nanoparticles as the paucity of safe polymers with regulatory approval, as well as their exorbitant cost, have restricted the use of polymer-based NPs in clinical practice. SLN contains aqueous surfactant dispersions with a matrix composed of solid lipids which is biodegradable [143, 144]. Generally, the lipids that are well metabolized by the body can be employed. Large-scale

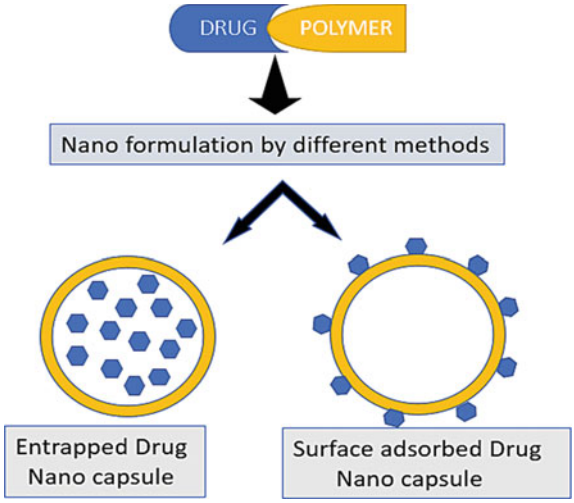

Fig. 6 Drug association with nanocapsules

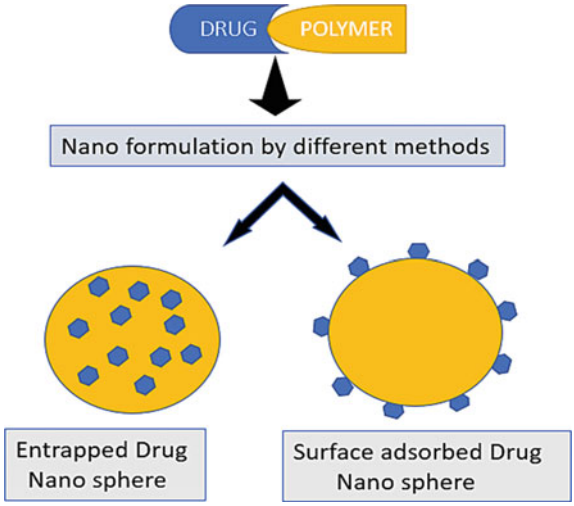

Fig. 7 Drug association with nanosphere

production can be performed in a cost-effective and relatively simple way using high-pressure homogenization leading to SLN (Fig. 8) [145].

(d) Liposomes

Liposomes are a well-known formulation technique for enhancing drug delivery and boosting therapeutic results in a variety of medications, and vaccines. Liposomes are structurally related to the lipid membrane of viable cells. Liposomes are tiny artificial aqueous vesicles encircled by phospholipid bilayers that encapsulate hydrophilic, hydrophobic, and amphiphilic compounds [146]. Liposomes are biocompatible, shielding the encapsulated drugs from metabolic processes, enabling them for a bigger pharmacological payload per

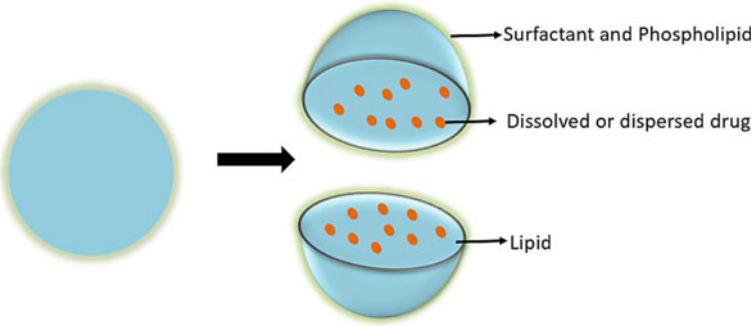

Fig. 8 Solid liquid nanoparticles loaded with drug

particle as well as increasing chemical biodistribution to the targeted regions in vivo [147].

(e) Dendrimers

The presence of a well-defined nanoscale polymeric framework with a low polydispersity index and high functionality is evolving dendrimers as viable drug delivery vehicles [148]. 'The term dendrimer' is derived from the Greek word 'dendron,' which means 'tree/branch,' due to its similarity to a tree, and meros, which means portion. A dendrimer consists of a symmetrical core, multiple branches emanating from the core referred to as generations (first generation, second generation, and third generation subsequently), and the periphery functional groups [149]. Dendrimers are nano-sized polymers of a regular structure and a high density of end groups that are heavily branched fractal-like macromolecules with well-defined three-dimensional structures, shapes, and topology [150]. Recently, dendrimers have been employed for the management of malaria, leishmaniasis, toxoplasmosis, and acanthamebiasis (Fig. 9) [151].

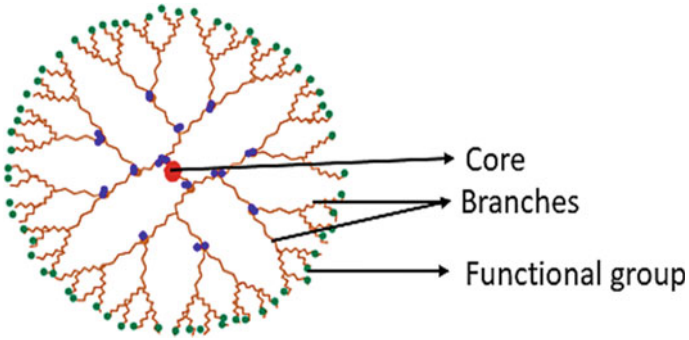

Fig. 9 Structure of dendrimer showing the core, branches, and periphery groups

4.6 Brief Introduction of the History and Evolution of Vaccines

Vaccination is the most effective and realistic strategy for eradicating infections since Edward Jenner's pioneering work 200 years ago. Vaccination has made a huge difference in terms of human and animal health by eradicating two major infections, smallpox and rinderpest [152]. Polio has nearly been eradicated, and the success in combating measles makes it another possible eradication target. The disciple of vaccination is emerging rapidly and many new vaccines, including those for non-infectious disorders, are likely to be produced in the next decade. Presently, seventy different types of vaccines are approved against thirty infectious diseases around the globe [153]. In recent times, SARS-CoV-2 vaccines are the most promising approach for curtailing the pandemic, and they have been an extraordinary success. Vaccines have got an upper hand when compared to conventional drugs because the enhanced drug resistance along with low efficacy, low shelf life, surging toxic effects, and drug incompetence to latch on to the site of infection are a few of the undesirable effects of traditional conventional drugs [126]. To design an optimal vaccine, there are some key facets to be kept under consideration like safety, stability, cost-effectiveness, and the property to show adequate and lasting immunity with the least number of doses [154, 155]. With the advent of science and technology, there was a breakthrough in the types of vaccines to boost the immune response and prevent life-threatening diseases. Currently, four types of vaccines including live attenuated vaccines, inactivated or dead vaccines, subunit vaccines [protein vaccines, polysaccharide vaccines, nucleic acid-based vaccines], and toxoid vaccines are widely known [156]. There are obvious challenges associated with vaccines in terms of safety with live attenuated vaccines, the inefficiency of dead vaccines to evoke an immune response, the need for prime-boost vaccination regimens as well as cold storage for preservation [157, 158]. These shortcomings demand an alternative that can prevent these challenges.

4.7 Need for Nanovaccines

Nanotechnology advancements and their applications in medicine and pharmaceutical fields have transformed the twentieth century [159]. In the realm of vaccination, nanotechnology can aid in the improvement of existing vaccines [160]. Nanovaccines contain nanoparticles that specifically target the site where the infection arises, as opposed to conventional medicines that impact the entire body [161]. Caused by small tailored effects, nanotechnology is gaining prominence in biology [162, 163]. Nanoparticles have the properties like unique particle shape, size as well as hydrophobicity to manifest self-adjuvant effects, hydrophobicity and release kinetics [164]. The administration of particles from 20–100 nm in size can directly enter the lymphatic system while the larger particles need to be internalized by antigen-presenting cells prior to reaching the lymphatic system which signifies the

relevance of size in the biodistribution of nanoparticles efficiently [165]. The rod-shaped nanoparticles are found to be circulating more efficiently in the blood and gastrointestinal tract when compared to their spherical counterparts. As opposed to hydrophilic formulations, particles synthesized from hydrophobic polymers are more efficiently phagocytosed [166]. Nanovaccines are new-generation vaccines in which NPs are utilized as carriers and/or adjuvants and can elicit cellular and humoral immunity which is both immediate and long-lasting [21, 161, 167]. Nanovaccines can be designed to mimic the size and shape of pathogens to promote easy uptake by immune cells [168]. Materials at the nanoscale level can incorporate into membrane-bound endosomes, hence never getting access to the cytosol and cell machinery in contrast to other synthetic drugs which disrupt the integrity of biological barriers. Nanotechnology-based vaccines can also be delivered via a variety of routes, including intranasal, intravenous, transdermal, and oral administration, and can be functionalized to breach the blood-brain barrier [22, 169].

5 Challenges and Future Perspectives

Based on the elaborated literature explained in this chapter, it can be concluded that nanotechnology can play an important role in controlling parasites causing deadly diseases along with their respective vector species. Nanotechnology provides unlimited opportunities for improving the efficacy of the currently used antiparasitic drugs by overcoming the drawbacks such as short half-life and low bioavailability of the medicines. NPs loaded with drugs can be applied either orally or could be directly injected for drug delivery. Despite all these, still research carried out on this is in its infancy and requires further studies. Likewise, controlling the vector population through nanotechnology is another strategy undertaken for the eradication of parasitic diseases. Nowadays, NPs synthesized using plants and microbes are gaining a lot of importance due to their insecticidal and acaricidal property against different vector species. To date, maximum research has been done to evaluate the mosquitocidal and acaricidal effect of metal NPs on different vectors. However, apart from these, there are other vectors such as bugs and sandflies that cause deadly parasitic diseases. Until now, no such study has been done to control these vectors using nanotechnology. Recently, NPs-based vaccine platforms (nanovaccines) have emerged as promising alternatives to more traditional vaccine platforms. Nanovaccines offer several benefits over traditional adjuvants by offering stability outside the cold chain, strengthening immunogenicity, activating humoral and cellular immune responses, and facilitating long-lived responses without the need for booster doses. However, further studies investigating the use of nanovaccines for disease prevention or therapies are urgently needed, so that the large-scale manufacturing of nanovaccines could be practiced.

6 Conclusions

Through the reformulation of conventional medications into site-specific targeted administration of drugs, nanomaterials-based drug delivery systems provide an upgraded and effective alternative therapy. The combination of nanotechnology and pharmaceutical sciences research is promising and has increased fast in recent years. They are frequently nanoscaled in size because nanoengineering-enabled drug delivery materials are intended at the atomic or molecular level. As a result, unlike larger materials or traditional medications, they can freely circulate throughout the human body. The development of novel medications for the control and treatment of neglected tropical diseases (NTDs) is a big problem that will require significant funding. Despite the fast proliferation of parasite infections throughout the world, novel therapeutic options are urgently needed to combat them. According to the findings, the nanoparticulate-mediated drug delivery method improves efficacy by allowing for site-specific administration, improved targeting efficiency, and greater drug bioavailability at the illness site. Disease causing parasites are vectored by arthropods, out of which mosquitoes, sandflies, and bugs are highly prominent. Putting a check over these vector populations has also been one of the most important strategies for controlling parasitic diseases. Several methods have been undertaken in the past to eradicate vectors, but the drawbacks of these traditional methods prompted the development of a novel approach. In such a scenario, nanotechnology can be considered an effective way to eliminate parasitic infection. Metal NPs are highly efficient in suppressing the insect vector population. Nanotechnology-enabled vaccinations are also a novel technique for successfully eliminating NTDs; there are currently no vaccines against NTDs, but research is underway to develop effective nanovaccines. Several reported outcomes in this research revealed that reformulation of conventional medications using nanoparticles can improve drug quality, efficacy, and minimize toxicity. Nano-based vaccinations, on the other hand, are required to enhance investigations and research to generate effective, safe, and low-cost medications to combat NTDs.

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Cancer Diagnosis and Treatment with Nano-Approaches

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Abstract Since several decades, scientists are actively engaged in finding out effective diagnoses and treatment methods for cancer therapy. Early accurate detection is a key factor for effective treatment. However, conventional cancer diagnostic methods have several intrinsic limitations. The advent of nanotechnology boosts cancer research. So far, nanoparticles, hybrid nanosystems, and nanoplatforms have been proposed under the umbrella of nanomedicine for the same. These nanoplatforms are highly sensitive and specific for the detection of cancer cells, extracellular cancer biomarkers, and also for vivo imaging. Nanomedicine has the potential to effectively treat cancer by reducing the limitations of existing traditional cancer treatments. This chapter gives a detailed account of nanoparticle-based methods for the early detection and treatment of cancer.

Keywords Nanomaterials · Nano-diagnostic approach · Nano-biomarker for cancer · Nano-based cancer treatment

1 Introduction

Complex pathophysiology characterized by uncontrolled, random cell division and invasiveness is associated with cancer, and due to this, it becomes a leading cause of death worldwide. About four major risk factors for cancer are found to be associated

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R. S. Mane et al. (eds.), *Nanomaterials for Sustainable Development*,
https://doi.org/10.1007/978-981-99-1635-1_7

with cancer: (a) specific environmental factors such as prolonged exposure to radiation and pollution; (b) an unhealthy lifestyle like tobacco consumption, smoking, poorly balanced diet, stress, and lack of physical activity [1, 2]; (c) inherited genetics due to the mutations of proto-oncogenes, tumor suppressor genes expression patterns, and those genes involved in DNA repair [3]; and (d) advancing age for cancer and many individual cancer types. It is very difficult to diagnose the cancer tissue due to the heterogeneous nature of cancerous tumors accurately. Inaccurate diagnosis often results in inappropriate treatments followed by the development of complications in the cancer patient. Interpatient tumor heterogeneity arises due to a variety of cancer sub-types, unique genetics, and epigenetics and dynamic factors such as age, medical history environment, and lifestyle [4]. Early detection and effective treatment of cancer re crucial for saving lives. Traditional cancer therapies include chemotherapy, radiation therapy, and immunotherapy, but acute side effects and a high risk of recurrences always question the effectiveness of these therapies. Chemotherapy and radiation therapy possess cytostatic and cytotoxicity abilities, such as suppression of bone marrow, gastrointestinal, neuropathies, skin disorders, hair loss, and fatigue. Few drugs like anthracyclines and bleomycin demonstrate drug-specific side effects such as cardiotoxicity and pulmonary toxicity [5, 6]. Immunotherapeutic agents have generated very good results by not only treating primary cancer but also preventing distant metastasis with minimal risk of recurrence [7]. However, immunotherapy is ineffective against solid tumors due to the unusual extracellular matrix (ECM) which is difficult for immune cells to infiltrate and autoimmune diseases limit the use of immunotherapy [7, 8]. Chemotherapy and radiotherapy do not consider the patient-specific heterogeneous nature of cancer tissue, so it is not that effective in combating cancer. Such an individualized platform includes the delivery of chemotherapeutic drugs to the patient under specific clinical situations.

Efforts are being made to address the limitations of traditional therapeutic approaches using nanoparticles (NPs). The new era of cancer diagnosis and treatment has begun with the application of nanotechnology principles to cancer therapy. NP-based drug delivery systems have reflected benefits in cancer treatment and management by demonstrating good pharmacokinetics, precise targeting, and drug resistance to lower side effects [9, 10]. These advantages enable NP-based drugs to be broadly applied to chemotherapy, targeted therapy, radiotherapy, hyperthermia, and gene therapy. Several types of NPs, including organic and inorganic NPs, have already widely been used in the clinical treatment of several cancer types. The use of nanotechnology in cancer medicine has a leading impact on the diagnosis and treatment of tumors. One goal of nanomedicine is to develop therapeutic or diagnostic platforms using specially designed chemotherapeutic drug-conjugated nanocarriers to address cancer theranostics (therapy + diagnostics) [11–14]. Nanocarriers can be monitored through highly complex physiological networks and thus maximize the delivery of chemotherapeutics to the tumor. Present chapter provides detailed information on various diagnostic and therapeutic approaches employed using NPs.

2 Nanotechnology in Cancer Diagnosis

2.1 Cancer Cells Versus Normal Cells

Cancer cells are distinct from normal cells. Some of the changes have been identified, while others are unprecedented. Cancer cells influence various parts of the body. It arises due to the accumulation of mutations in genes that control the cell cycle. The unlimited and independent development of cells is responsible for the development of different cancer cells which are immortal. Cancer cells are continuously growing, while normal cells stop increasing or reproducing when there are sufficient cells. Cancer cells have irregular blood vessels as compared to normal cells [15]. Normal cells stay where they belong in the body and are tightly bound to neighboring cells. Carcinoma cells liberate themselves and migrate to other regions by getting rid of underlying basement membranes and then attacking neighboring stromal segments which is nothing but metastasis [16].

2.2 Tumor Physiology

In the 1860s, Rudolph Virchow revealed the fundamental structure of a solid cancer tumor, including its blood supply and some other important structure-related characteristics [17]. Angiogenesis is the development of new blood vessels from existing vessel networks, and it occurs through the development, relocation, and variation of endothelial cells of the existing wall of blood vessels. Certain chemical signal in our body plays an important role in the angiogenesis process [18]. Several parameters need to be explored that affect the transportation and circulation of therapeutics to the tumor site including blood flow percentage, movement across the vascular wall, and migration within the interstitial medium [19].

2.3 Importance of Cancer Diagnosis

Accurate analysis plays an important role in all stages of cancer. An early cancer diagnosis helps to recognize and trace cancers and subsequent best treatment strategies. Several complications are associated with progressing cancer due to which treatment plan becomes more complicated, increasing the chances of failure of treatment. So, an early cancer diagnosis is almost important. An early cancer diagnosis is associated with a greater than 90% survival rate. Early-stage diagnosis of cancer is currently a dynamic research area [20]. Currently, imaging techniques and morphological analysis such as histopathology or cytology are used for the diagnosis of cancer. The most commonly used imaging techniques include X-ray, computed tomography (CT), magnetic resonance imaging (MRI), endoscopy, and ultrasound which are effective

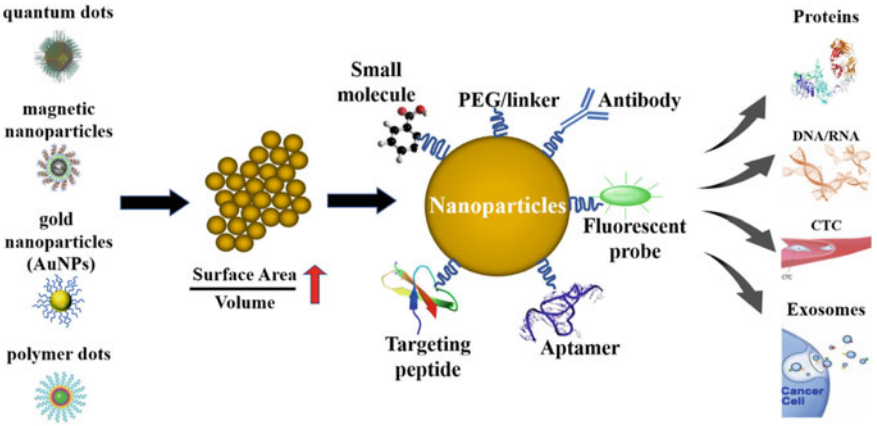

Fig. 1 Strategies used for the detection of cancer by nanotechnology [28]

only when there is a visible change in the tissue [21]. By that time, many cancer cells may have proliferated or metastasized. In addition, these imaging methods cannot distinguish benign lesions from malignant lesions [22]. Moreover, cytology and histopathology cannot be successfully and autonomously applied to detect cancer at an early stage [23]. Detection of abnormalities at the macroscopic level, such as detection of cancer-associated molecules and molecular changes even in a minor proportion of cells, has the potential to offer quick, sensitive, and early detection of cancer [24]. Therefore, the development of the method for diagnosis of cancer at an early stage, before metastasis, is a major challenge.

NPs-based diagnostic methods are being developed as promising tools for real-time, convenient, and cost-effective cancer diagnosis and detection [25]. For cancer diagnosis, NPs are being applied to capture cancer biomarkers, such as cancer-associated proteins, circulating tumor cells, circulating tumor DNA, and exosomes [26]. A large surface area-to-volume ratio of NPs can be densely covered with antibodies, small molecules, peptides, aptamers, and other moieties. By presenting various binding ligands to cancer cells, multivalent effects can be achieved that can improve the specificity and sensitivity of an assay as shown in Fig. 1 [27].

2.4 Detection of Cancer Biomarkers

Cancer biomarkers are biomolecules that are secreted or present on cancer cells and are found in blood and other tissues or body fluids, such as saliva and urine [29, 30]. The presence of biomarkers in these body fluids indicates the existence of cancer in the body. Cancer biomarkers are proteins [31], carbohydrates [32], or nucleic acids (circulating tumor DNA, miRNA, etc.) [33] that are secreted by the body or cancer cells when cancer is present [34, 35]. The measurement of these cancer biomarkers

enables early detection of cancer or tumor recurrence and helps to monitor the efficacy of the therapy. The concentration of biomarkers in body fluids is extremely low and heterogeneity in the abundance and timing of biomarkers within patients, so it needs an efficient system for the detection of these cancer biomarkers [36]. NPs offer high selectivity and sensitivity and the ability to conduct simultaneous measurements of multiple targets. The performance of biosensors can be improved with NPs to provide efficient detection [37]. NPs provide an increased surface-to-volume ratio for making biosensors more sensitive in fulfilling the demands of specific biomolecular diagnostics [38]. Polymer dots (PDs), quantum dots (QDs), and gold (Au) NPs are three common NP probes used in diagnosing cancer [39, 40].

(a) Protein detection

FDA has approved various protein molecules such as prostate-specific antigen (PSA), cancer antigen 125 (CA-125), carcinoembryonic antigen (CEA), and alpha fetoprotein (AFP) for the detection of prostate cancer, ovarian cancer, colorectal cancer, and liver cancer respectively. A sandwich-type assay is most commonly used for finding protein biomarkers. It consists of many components such as a biomarker, a capture antibody, a second capture antibody, and a secondary antibody that binds to the capture antibody [23]. The secondary antibody is converted into a quantifiable signal that can visualize through various methods, such as staining and fluorescence [41]. QD-based biosensors are used for detecting protein-based cancer biomarkers. Unique properties of QDs such as high quantum yield, wide absorption with narrow, high-efficiency Stokes shift, and high resistance to photobleaching and degradation make them more suitable for detection [42, 43]. A zinc oxide (ZnO) QD-based sandwich immunoassay was developed using ZnO nanowire and two conjugated antibodies against neuron-specific enolase (NSE) and CEA. CEA, the most popular cancer biomarker, is useful for monitoring anticancer treatment as well as for predicting tumor recurrence after surgical resection in late-stage cancer patients. NSE is an enzyme that catalyzes the conversion of 2-phosphoglycerate to phosphoenolpyruvate, which shows a relationship with carcinoids, small-cell lung carcinoma, and islet cell tumors. This biosensor can detect two cancer biomarkers at very small concentrations in body fluid such as 15 ng/mL, and the limit of detection (LOD) of each reached 1.0 ng/mL [44]. Another immunosensor-based detection is done for pancreatic ductal adenocarcinoma. In this immunosensor, ZnO QDs are coated with antibodies against carbohydrate antigen 19–9 (CA 19–9, specific protein for pancreatic ductal adenocarcinoma). The immunological reaction of biosensor and CA19-9 gives amplified signals presented by square-wave stripping voltammetry (SWV) as well as the inherent photoluminescence (PL) exhibited by the labeled QDs. The dynamic range of the electrochemical assay was 0.1–180 U/ml, and the LOD reached 0.04 U/ml, while the dynamic range exhibited by the optical spectral detection was 1–180 U/ml, and the LOD reached 0.25 U/ml [45]. A10 RNA aptamer-conjugated polymeric NPs incorporating Cy5 can bind to prostate-specific membrane antigen (PSMA). Cy5-PLA/aptamer NPs could only bind

to LNCaP cells and canine prostate adenocarcinoma cells, which have PSMA. Cy5-PLA NPs have been applied in *balb/c* mice that displayed strong signals with low background fluorescence [46].

(b) Circulating tumor DNA

Circulating tumor DNA (ctDNA) is released from primary tumors or circulating tumor cells (CTCs). It is approximately 100–200 base pairs long and present in the bloodstream, allowing the detection of cancer through cancer-specific genetic aberrations [47]. Hybridization with nucleic acid probes of complementary sequences can be employed to detect cancer-associated genetic aberrations [48]. A DNA silver nanocluster (NC) fluorescent probe was fabricated for finding a single exon in the *BRCA1* gene in breast cancer [49]). Large deletion mutations in *BRCA1* gene were identified through nanocluster fluorescence after hybridization. Under optimized conditions, this probe has increased the LOD to 6.4×10^{-11} M [49].

(c) MicroRNA detection

MicroRNAs (miR) are small RNA molecules present in serum samples of the cancer patient. miR-141 is a biomarker for prostate cancer. Jou AF et al. described a two-step sensing platform for the sensitive detection of miR-141. For the first step, the sensing platform uses CdSe/ZnS QDs modified with FRET quencher-functionalized with nucleic acid, containing telomerase primer sequence and recognition sequence for the miR-141. The FRET quencher has shown covalent binding with nucleic acid-functionalized CdSe/ZnS QDs. Hybridization of miR-141 from serum sample with probe results in the formation of a duplex, which is then cleaved by duplex-specific nuclease (DSN), thus releasing the quencher unit and is activated the fluorescence of the QDs. This cleavage results in exposure of the telomerase primer sequence. In the second step, primer unit elongation is initiated by telomerase/dNTPs, incorporation of hemin, and chemiluminescence is generated with the help of luminol/H_2O_2. This method helps to detect miR-141 in a serum sample [50].

(d) DNA methylation detection

The genome methylation landscape (Methylscape) was recently reported as a common characteristic as a cancer biomarker of most types of cancers. The differences between cancer genomes and normal GenomeScan are detected on the basis of DNA-gold affinity and DNA solvation. Based upon this study, a simple, quick, selective, and sensitive electrochemicalor colorimetric one-step assay to detect cancer was developed [51].

(e) Extracellular vesicle detection

Circulating vesicles (30 nm^{-1} μm) and extracellular vehicles (EVs) bundle molecular information, such as miRNA, DNA, protein, and mRNA from mother cells. Study of these EVs allows the detection of the molecular state of tumor cells that are difficult to access. A magnetic nanopore capture technique was developed to isolate certain subsets of EVs from plasma for a mouse model of pancreatic ductal adenocarcinoma. Capturing of EVs and subsequent machine learning and RNA-sequencing help in the identification of eleven EV miRNAs cancer biomarkers [52]. Another biosensor has been fabricated using Au NPs

and an aptamer panel. Here, 13-nm Au NPs were noncovalently conjugated with a panel of five aptamers that profile proteins on the surface of exosomes. The aptamers complexed with Au NPs have prevented NP aggregation in a solution of high salt concentration. Exosomes help in breaking non-specific and weak interactions between the Au NPs and aptamers, while strong and specific binding between aptamers and exosome surface proteins separates aptamers from the Au NP surface, thus facilitating Au NP aggregation. Due to aggregation, the color of the Au NPs is changed from red to blue, which is indicative of aptamers that could bind to exosomal proteins. The intensity presented by the Au NP aggregation (A650/A520) is suggestive of the relative abundance shown by target proteins on the surface of exosomes [53].

2.5 Detection of Cancer Cells

(a) Detection of circulating tumor cells

Early detection of metastatic cancer cells in the bloodstream is recognized as circulating tumor cells (CTCs). Metastasis is the property of cancer cells in which cancer disseminates from the primary tumor and invades the surrounding tissue and enters the micro-vasculature of the blood (intravasation) and lymph systems. These CTCs survive in the bloodstream and translocate toward the micro-vessels in distant tissues, subsequent exit from the bloodstream (extravasation), and survival in the microenvironment of distant tissues. In this way, CTC will form secondary tumors at distant tissues [16]. Approximately, 90% of deaths from solid tumors are attributed to metastasis [54]. The CTCs display relatively low abundance and heterogeneity, presenting technical challenges for CTC isolation and characterization. NPs of large surface-to-volume ratio enable the adsorption of high-efficiency targeting ligands that recognize specific molecules on cancer cells; therefore, CTC isolation shows high specificity and recovery due to which the detection sensitivity is enhanced. Researchers have reported different types of nanomaterials, such as magnetic nanoparticles (MNPs), QDs, Au NPs, nanowires, nanopillars, silicon nanopillars, carbon nanotubes, dendrimers, graphene oxide, and polymers, for CTC detection (Table 1) [55].

MNPs are mature nanomaterials, which can effectively bind to cells and in vitro separation with the help of an external magnetic field [56]. Antibody-functionalized MNPs, namely, immunomagnetic NPs, are frequently applied in the biomedical field. For CTC detection, anti-EpCAM functionalized MNPs are used that specifically bind with EpCAM expressing CTCs. Powell et al. used MagSweeper, which has the ability to isolate tumor cells from unfractionated blood. MagSweeper works on the principle of a magnetic cell sorting system that uses magnetic rods covered by a sheath to sweep across capture wells and attract target cells labeled with magnetic NPs [57, 58]. It can be used to obtain high-purity CTCs from patient blood, while retaining their capacity to initiate tumors

Table 1 Nanomaterials used in the detection of the cancer cells

Nanomaterial	Type of affinity probe on NPs	Specificity ligand on cancer cells	Cancer type	Reference
Quantum dots	Aptamer	PTK7	Leukemia	[60]
Magnetic NPs	Antibody	EpCAM	Colon/liver /lung/breast	[64]
Polymer dots	Antibody	EpCAM	Breast	[65]
Gold NPs	Aptamer	Her2	Breast	[66]
	Antibody	Cd2/cd3	Leukemia	[67]
Upconversion NPs	Antibody	Her2	Breast	[62]
Nanorod arrays	DNA aptamer	EpCAM	Breast	[68]
Nanofibers	Antibody	EpCAM	Breast	[69]
Nanoparticle-coated silicon beads	Antibody	EpCAM/CD146	Breast Colorectal	[70]

and metastasize, facilitating strong analysis of single CTCs. This method has successfully been applied to patients with primary and metastatic breast cancer and performed direct measurement of the gene expression in individual CTCs. High quantum yield and special optical properties enhance the usefulness of QDs in the detection of materials with low abundance [59]. A new photocatalyzed renewable self-powered cytosensing device is presented on the basis of ZnO NDs@g-C_3N_4 QDs [60]. It conjugates with membrane PTK7-specific aptamer Sgc8c, and the device has been used to identify CCRF-CEM cells (human acute lymphoblastic leukemia cells), which express PTK7. The device offers better performance in terms of detection range, detection limit, reproducibility, and selectivity as it captures only CCRF-CEM cells (500 cell/mL) and no other cell types, such as K562, HL-60, and HeLa cells.

Semiconducting polymer dots (PDs) functionalized with streptavidin and immunoglobulin G (IgG) have been synthesized and utilized for the effective and specific labelling of cellular targets. The fluorescence exhibited by PD-labeled MCF-7 cells is 25 times higher than that of QD labeled cells and 18 times higher than that of Alexa Fluor-labeled cells, according to flow cytometry analysis. Therefore, PD is ideal for CTC detection. Upconversion nanoparticles (UCNPs) are usually selected for fluorescent labeling by considering the capacity to excite UCNPs with near-infrared (NIR) light to infrared (IR) light for the generation of fluorescence emission in the visible spectrum, leading to minimize background noise. Furthermore, applying NIR light as the excitation source can prevent damage to normal tissue and allows deep tissue penetration [61]. Multifunctional nanoparticles (MFNPs) with the core–shell structure of UCNP@-Fe_3O_4@Au coated with anti-HER2 antibody and polyethylene glycol (PEG) and exhibited an outstanding dispersity in different aqueous solutions and a high signal-to-noise ratio. These MFNPs have exhibited the specific detection

of breast cancer BT474 cells (biomarker HER2 positive) with a high signal-to-noise ratio [62]. Magnetic targeting multifunctional nano-bioprobes (MBMNs) were applied to detect and separate a small subset of malignant cells from normal cells. $CoFe_2O_4@BaTiO_3$ magnetoelectric NPs distinguished different cancer cells from each other and from their normal counterparts through a magnetoelectric effect [63].

(b) Detection through cell surface protein recognition

Detection of cancer cells depends on binding of conjugated NP probes with moieties (protein, antibodies, short peptides, oligonucleotide aptamers, etc.) to surface protein markers on cancer cells. Unique surface proteins on CTCs can be a primary target. Studies have demonstrated that EpCAM can highly be expressed on CTCs from many human malignancies. Hence, anti-EpCAM molecules which specifically bind to EpCAM are often applied to screening the CTCs. Many cell surface markers, such as vimentin, glycan, major vault protein (MVP), androgen receptor, and fibroblast activation protein α(FAPα), have been studied for the detection of CTCs. However, a majority of these markers are only specific to certain cells, and many markers do not exist after CTCs on experienced EMT. More mesenchymal CTCs are seen in the metastatic stages of cancer, and thus, seeking proper EMT markers to evaluate prognosis and metastasis in cancer patients is important [28]. Table 2 shows recently identified cell surface protein markers for the detection of CTCs in different cancer types.

(c) Detection based on mRNA

With the help of NPs, it is also possible to detect intracellular mRNA in addition to extracellular. Nanoflares are specifically designed gold NP probes modified by oligonucleotides labeled with a fluorophore. It acts as a transfection agent and detects cellular mRNA in living cells [84]. Nanoflares overcome many technical challenges in the creation of effective and sensitive intracellular probes and show a large signal-to-noise ratio and sensitivity to changes in the number of RNA transcripts in cells. Nanoflares show high orientation, dense oligonucleotide coating and can enter cells without any cytotoxic transfection agents [85]. Quantification of intracellular mRNA at the single live cell level is possible with the help of multiplexed nanoflares. In some cases, the nanoflare platform can be extended to quantify intracellular RNA and detect spatiotemporal localization in living cells [84]. β-actin targeting nanoflares were incubated with HeLa cells that resulted in different intracellular distributions, showing strong colocalization with mitochondria. Smart flares were employed for studying melanoma tumor cell heterogeneity which is crucial for identifying novel biomarkers for early cancer diagnosis and metastasis [86]. Halo et al. [87] described nanoflares, which were applied to capture live circulating breast cancer cells. These nanoflares could detect target mRNA in model metastatic breast cancer cell (MBC) lines in human blood and displayed high recovery and 99% reliability. They also used nanoflares together with later cultured mammospheres to reimplant the retrieved live recurrent breast cancer cells into whole human blood. Only 100 live cancer cells could be detected per mL of blood.

Table 2 Cell surface protein markers used for CTC detection

Protein marker	Cell type	Cancer type	Reference
EpCAM	CTC	Colorectal Breast Head and neck	[71]
EpCAM and FRα	CTC	Non-small cell lung cancer	[72]
Glycan	CTC	Breast	[73]
Vimentin	CTC	Gastrointestinal	[74]
	EMT CTC	Prostate	[75]
	CTC	Sarcoma	[76]
Vimentin + PD-L1	CTC	Colorectal, prostate cancer	[77]
Synaptophysin	CTC	Castration-resistant prostate cancer	[78]
Major vault protein	Mesenchymal and intermediate CTCs	Hepatocellular carcinomas	[79]
Androgen receptor	CTC	Metastatic breast cancer	[80]
p75 neurotrophin receptor + EpCAM	CTC	Esophageal squamous cell carcinoma	[81]
Carbonic anhydrase 9 and CD147	CTC	Clear cell renal cell carcinoma	[82]
Excision repair cross-complementation group 1	CTC	Platinum resistance ovarian cancer	[83]

Relying on the nanoflare technology, it was possible to, simultaneously, isolate and characterize intracellular live cancer cells from whole blood. Lee et al. reported an approach based on a plasmonic NP network structure, generating a plasmon-coupled dimer able to detect single mRNA variants [88]. Two probes conjugated to NPs were connected to the *BRCA1* mRNA target in a sequence-specific manner, resulting in the spectral shift of spectra due to dimer formation. This method can detect and quantify of *BRCA1* mRNA splice variants in vitro and in vivo.

2.6 Nanotechnology for in Vivo Imaging

Imaging plays a vital role in the diagnosis and treatment of tumor tissues. NP of iron oxide has optical, magnetic, acoustic, and structural properties that can enhance imaging. NP probes can favorably accumulate in tumor tissues through active or positive targeting, thereby allowing imaging and diagnosis of cancer in vivo [89]. Interactions between NPs and blood proteins, penetration into solid tumors, uptake and clearance by the reticuloendothelial system (RES), and optimized active (vs.

Table 3 NPs applied for medical imaging

NPs	Size (nm)	Targeting material	Cell line	Imaging technology	Reference
MnO-TETT	6.7 ± 1.2	None	C6 glioma cells	Fluorescence/T1-MRI	[90]
USMO@MSNs	30–50	Dox	HeLa cells	MRI-guided chemotherapy	[91]
PLGA-mPEG	151.1 ± 1.3	cRGD	SKOV-3 cells	US	[92]
OINPs	300	Folate	SKOV3 ovarian cancer cells	US/PA	[93]
PEG-coated and Gd-loaded fluorescent silica	125.5 ± 9.9	YPSMA-1	LNCaP and PC3 prostate cancer cells	MRI/fluorescence imaging	[94]
SPIO/USPIO	50	None	4T1 murine breast cancer cells	MRI/MPI	[95]

passive) targeting are the main barrier to the clinical application of NPs. Table 3 lists some recent examples of NPs made with different materials for tumor imaging.

US ultrasound, *MSNs* mesoporous silica NPs, *USMO* ultra-small manganese oxide, *GEM* Gemcitabine, *OINPs* oxygen/indocyanine green-loaded lipid NPs, *PA* photoacoustic, *MPI* magnetic particle imaging, *MRI* magnetic resonance imaging, *SPIO* superparamagnetic iron oxide, *USPIO* ultra-small SPIO, Optical coherence tomography (OCT) is a non-invasive, micron-level resolution useful in the real-time diagnosis and surgical guidance. In this technique, the light source is separated into two individual light sources. When these beams are recombined, their resultant interference signal depends upon the distance traveled by each beam. As the beam traveled into the tissue, it scatters cells and other structures and some light sends backward. This scattered light is collected and made to interfere with the second beam. Using the resulting interference signal, the depth of all the tissues can be measured. By analyzing this optical scattering, properties of cancer tissue like blood vasculature, anatomy, and lymphatic vasculature can be measured. As normal OCT cannot detect elastic scattered light, the use of NPs can be able to change the amplitude of OCT. This new imaging technique is called magnetomotive optical coherence tomography (MMOCT) [96].

MRI is another extensively used non-invasive, most effective tumor detection method which measures the magnetization of hydrogen molecules in water

molecules. Each cancer tissue shows a different image as the protons of each tissue cause variation in magnetization. The visibility of images can be enhanced by utilizing more contrast agents [97]. Iron oxide magnetic NPs (IONPs) are presently the most common MRI nanoprobe contrast agent. Proper NP surface alteration and appropriate tumor-specific bio-oligomer embedding can improve the fixing of NPs in tumors, which gives clearer imaging and can be used for early micro-tumor imaging. For example, AuNPs targeted for human transferrin can successfully enhance the imaging of brain tumors [98].

3 Nanotechnology in Cancer Therapy

3.1 Targeted Drug Delivery

Chemotherapeutic drugs are the most frequently used treatment for tumors, but they are poorly targeted toward the malignant tumor and over accumulated in healthy tissue [99]. So, the cells which are actively growing such as hair follicles, bone marrow, gastrointestinal cells, and lymphocytes are adversely affected which may lead to bone marrow suppression, hair loss, mucositis, and even death. In targeted drug delivery, the nanotherapeutic drug should effectively differentiate between normal cells and cancer cells. Thus, it has low side effects than conventional chemotherapeutic drugs and better efficacy [99]. Last few decades, researchers are actively focusing on to produce a large arsenal of nanoplatforms with diversified capabilities for drug loading and releasing and also for tumor targeting. Several types of nanomaterials are being extensively used for this process. Liposomes [100, 101], Au NPs [102, 103], micelles [104], magnetic NPs, carbon nanotubes [105], mesoporous silica NPs [105], dendrimers [106], etc., are a few of them. The NPs used in cancer research are checked through their sizes, shapes, and surface properties for targeting specific tumors. NPs of different sizes are essentially important that travel through the bloodstream for delivering the nanocarriers to tumor tissues [107]. NPs can target chemotherapeutic drugs to tumor cells through active or passive targeting [108].

In passive targeting, abnormal vasculature of tumor tissue is utilized for targeting the nanomedicine to the target site. Blood vessels in tumors are leaky due to the presence of an enlarged gap junction of around 100 nm–2 μm [109]. Increase in hypoxia and metastasis is caused by an accumulation of interstitial fluid pressure due to leakiness of the vessels and irregular distribution of blood, nutrients, oxygen, etc. A tumor does not have a well-defined lymphatic system, so it cannot efficiently clean the macromolecules and drugs accumulated in it [110]. The enhanced vascular permeability and poor lymphatic drainage are collectively known as the enhanced permeability and retention effect (EPR), which is the gold standard for the delivery of nanomedicine and other types of drugs and imaging agents [111]. Passive targeting can be attained by utilizing the enhanced permeability and retention effect (Fig. 2a). Active targeting of nanocarriers is accomplished by decorating a variety of targeting

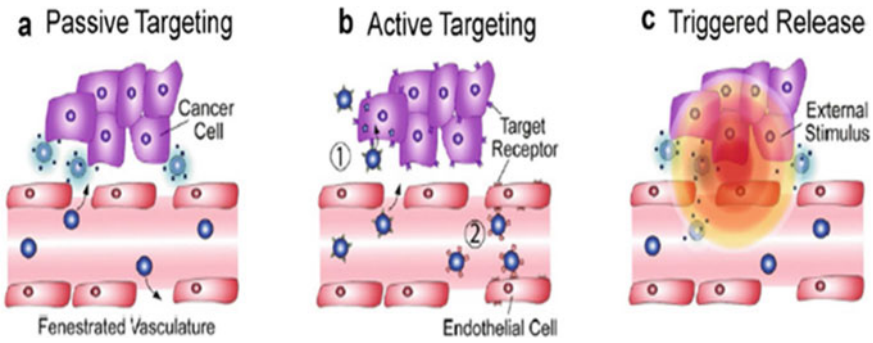

Fig. 2 Types of targeting nanomedicines for the tumor tissue [112]

ligands on the surface of nanomaterials, which can effectively recognize a target within the tumor affected organs, tissues, cells or intracellular organelles [112]. Ligands have a high specificity to receptors and other cancer-specific targets which are over-expressed on the surface of tumor cells, such as glycans [113]. These receptors must be expressed in high quantity and should be evenly distributed on the cancer cell's surface (Fig. 2b). Stimuli-responsive systems may decrease non-specific exposure to chemotherapeutic drugs. Internal and external stimuli can trigger the release of drugs by inducing a change in the nanocarriers. The pH, ionic strength, redox, and stress in target tissues are examples of internal stimuli, whereas temperature, light, ultrasound, magnetic force, and electric fields are external (physical) stimuli (Fig. 2c) [112]. Table 4 provides information on nanoplatforms used in targeted drug delivery.

3.2 Cryosurgery

In this technique, tumor tissues are destroyed by freezing which is advantageous because of low invasiveness, less intraoperative bleeding, low cost, and fewer postoperative complications. Still, this technique is facing the issue of insufficient freezing efficiency and freezing damage to surrounding tissues. Although protective agents for instance antifreeze protein-1 are being utilized to assist cold ablation, the effect is not satisfying [121]. With the expansion of cancer nanomedicine, the concept of nano-cryosurgery is proposed. In nano-cryosurgery, NPs with specific physical or chemical properties are introduced into tumor tissues. Special properties of NPs increase the efficiency and effectiveness of freezing and also control the direction of ice ball formation. Intracellular ice formation is the key to tumor cell damage. Meanwhile, research proves that NPs can effectively induce intracellular ice formation [122]. Tissues supplemented with NPs freeze faster than normal tissues and hence are more prone to heterogeneous nucleation. Under the same

Table 4 Typical NP platforms used in drug delivery

Agent of NPs	Vehicle	Size (nm)	Character	Effect	Reference
DNA and RNA	Exosomes	30–100	Small size, cellular origin, flexibility to incorporate macromolecules	Carrier for DNA, RNA, and micro-RNA Cross-stringent biological barriers, such as the blood–brain barrier	[114]
DOX	Polymer-lipid encapsulated manganese dioxide	170	Bioreactive and multifunctional	Downregulate TME-associated drug resistance and immunosuppression Enhancing chemotherapeutic efficacy and boosting antitumor immunity	[115]
5-FU	AuNPs/chitosan	100–400	Natural cationic, biodegradable and biocompatible	Enhance the curative effect for hepatocellular carcinoma cells (HepG2)	[116]
Tyrosinase-related protein 2 (Trp2) peptide	Layered double hydroxide (LDH) NPs	140–150	Provoking strong cell-mediated immune responses	Adjuvant multiple tumor-associated antigen peptides	[117]
Cisplatin; ICG	PLGA	90–100	Folate targeting Controlled drug release	Promoting the apoptosis of McF-7 tumor cells NIR sensitivity	[118]
IL-2	PEGylated liposomes with anti-CD137	80	Complete absence of systemic toxicity	Inducing intratumoral immune responses Initial antitumor activity	[118]
FA	Magnetic mesoporous silica	213	pH-sensitive drug release	Inhibiting proliferation of HeLa cell lines higher cytotoxicity effect	[115]

(continued)

Table 4 (continued)

Agent of NPs	Vehicle	Size (nm)	Character	Effect	Reference
PTX	Peptide H7K(R2)2-modified iron oxide NPs	168.3 ± 2.80	Few side effects	Excellent MRI imaging Inhibiting tumor growth	[119]
siRNA	RGDfC-SeNPs	150	No toxicity Multiple tumor targeting	Carrier for siRNA Inhibiting tumor Cells proliferate Promoting the generation of ROS	[120]

DOX doxorubicin, *5-FU* 5-fluorouracil, *FA* folic acid, *PTX* paclitaxel, *ROS* reactive oxygen species

freezing conditions, ice formation of tissue with NPs is easier and faster. Thus, nano-cryosurgery is effective in killing tumor tissue to prevent nearby healthy tissue from being frozen simultaneously [123]. Figure 3 schematically represents the advantages of nano-cryosurgery.

NPs of metal oxides can significantly improve the thermal conductivity in tumor tissue. The application of NPs in cold ablation can be divided into two types: synergistic effect and protective effect. Synergistic NPs are distributed inside the tumor and kill the tumor cells, while protective NPs are distributed around the tumor and protect the surrounding normal cells. Both these NPs are different in terms of the design requirements and the distribution in vivo [124].

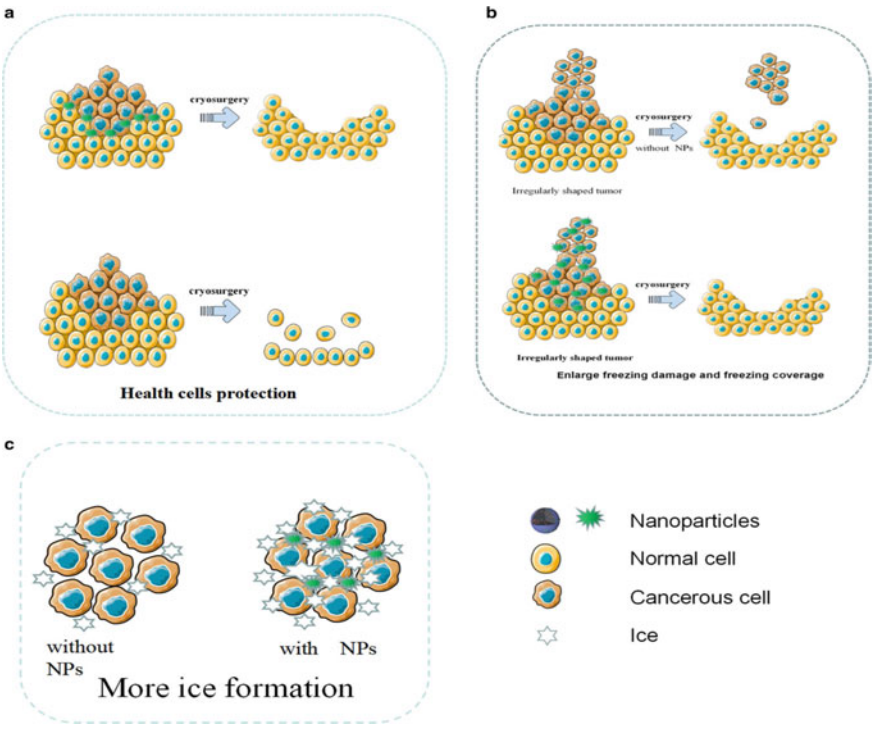

Fig. 3 Diagrammatic illustration of NPs for cryosurgery. **a** NPs protect healthy cells during cryosurgery, and **b** NPs enhance the freezing damage and control the freezing coverage, **c** with the help of NPs, more ice has been formed [124]

3.3 Photothermal Therapy (PTT) and photodynamic Therapy (PDT)

At present, PTT and PDT based on NPs have shown the virtues of strong efficacy, small invasion, and mild adverse effects during tumor treatment [125]. In addition to destroying tumor cells directly, fragments of dead tumor cells generated by PT and PTT treatment can act as potential antigens to trigger a continuous immune response, named photothermal and photodynamic immunotherapy [126]. NPs designed for PTT treatment are a new type of light-to-heat conversion nanomaterials, which can effectively convert light energy into heat energy to destroy cancer cells. The use of NPs in this method has two major advantages first, tumor targeted aggregation [127]. Second, NPs have better imaging capabilities which can be accurately positioned by CT, MRI, and photoacoustic imaging [128]. For example, targeted NPs can perform PTT under 0.2 W/cm^2 NIR to induce tumor cell apoptosis by destroying the tumor cell nuclear DNA and inhibiting the DNA repair process [129]. Table 5 lists some of the recent examples of NPs used in PDT and PTT.

3.4 Radiotherapy (RT)

RT is a tumor treatment technique that kills localized tumor cells by ionizing radiation produced by rays and is presently an effective treatment for many primary and metastatic solid tumors. Experiments prove that radiotherapy can effectively kill tumor stem cells [138]. In recent years, NPs in the field of radiotherapy have demonstrated strong radio-sensitization capabilities, tumor-targeted delivery of radio-sensitizing drugs, and imaging guidance enhancement [139]. At present, the most popular NPs for RT are made of high atomic number metal materials, which are featured by chemical inertness and strong radiation absorption capacity. They produce the photoelectric effect and Compton effect after absorbing radiation, thereby releasing a variety of particles such as optoelectronics, Compton electrons, and Auger electrons. These electrons react with organic molecules or water in tumor cells to generate a large number of free radicals, leading to synergistic chemotherapy [140].

4 Theragnostic Nanomedicine for Cancer Therapy

The heterogeneous nature of tumor tissue makes it difficult to present an exact diagnosis and consequently efficient treatment. The interpatient tumor heterogeneity rises due to unique genetics and epigenetics, the high diversity of cancer sub-types, and dynamic factors such as age, lifestyle, environment, and medical history [1]. Thus, for the development of effective treatments, patient stratification needs to be

Table 5 Typical NP platforms used in PDT and PTT

NPs	Photosensitizer	λ (nm)	Size (nm)	Outcome	Cell line	Reference
MnO_2	Chlorin e6	660	3.94	Upregulating the secretion of IL-12, IFN-γ, TNF-α. Inducing decomposition of tumor endogenous H_2O_2 to relieve tumor hypoxia	4T1 murine breast tumor	[130]
Au-liposome	None	780	100 ± 6.5	The cytotoxicity was enhanced to 90% upon laser irradiation for a duration of 5 min	B16 F10 (melanoma)	[131]
Silica-coated TiN	None	785	80	High nitridation temperatures and long residence times lead to increased NIR light absorption	HeLa cells	[132]
Silica	Verteporfin	425	160–168	Inducing singlet oxygen release 30% reduction in cell growth	SK-MEL 28 (melanoma)	[133]
Graphdiyne	None	808	160	Higher cancer inhibition rate compared both in vitro and in vivo Biocompatibility and no obvious side effects	MDA-MB-231	[134]
RCDs	Chlorin e6	671	3.7	Multimodal imaging capabilities Activating PTT and PDT at the same time	MCF-7,4T1 and Hela	[135]
CuSe	Non-porphyrin containing COF	808	150	Activating PTT and PDT at the same time Enhancing therapeutic effect on killing cancer cells and inhibiting the tumor growth	HeLa	[136]

(continued)

Table 5 (continued)

NPs	Photosensitizer	λ (nm)	Size (nm)	Outcome	Cell line	Reference
HSA	ICG and chlorin e6	808	120	Preventing the side effects of active Ce6 Activating PTT and PDT at the same time	PC3	[137]

RCDs amino-rich red emissive carbon dots, *COF* covalent organic framework, *ICG* indocyanine green, *HAS* serum albumin

optimal. However, conventional cancer therapeutic methods such as chemotherapy and radiotherapy are missing patient-specific individualized platforms to fight cancer effectively. These individualized platforms include the delivery of chemotherapeutic drugs in patient-specific clinical situations. The finest goal of nanomedicine is to develop therapeutic or diagnostic platforms using specially designed chemotherapeutic drug-conjugated nanocarriers to address cancer theranostics (therapy + diagnostics) [12, 13]. Hybrid nanoplatforms (HNPs) contain multimodal nanocarriers that have extraordinary surface functionality, which can enhance anticancer activity by boosting the triggered drug release directly at the tumor site [141]. HNPs have various advantages in the treatment of tumor tissue because (i) efficient accumulation and retention at tumor sites; (ii) high penetration abilities due to functionalization, (iii) HNPs carry and release chemotherapeutic drugs in response to internal and external triggers or stimuli, and (iv) pharmacokinetics of HNPs are similar to those of drugs or small molecules [142]. Nanotheranostics have a wide scope to integrate with next-generation cancer therapies such as PTT, PDT magnetic hyperthermia (MH), and external control, which facilitate excellent temporal and spatial control of acquisition aspects of cancer management [143]. The duplex effect of local heating can control the amount of drug released and the spatial control of the release. Furthermore, the higher temperature can increase the effectiveness of the drug, owing to the synergetic thermo-chemo effect [144]. Dual modalities of HNPs and preclinical reports have shown efficient photothermal damage of primary tumors under MRI-photoacoustic (PA) imaging guidance and a hyperthermia-mediated immunostimulatory effect on deep-seated tumors [145]. Figure 4 schematically presents an all-in-one nanotheranostics approach. The imaging-guided light and magnetic responsive immunostimulatory nanoagents (MINPs) are proposed to trigger cancer immunotherapy for primary-treated and distant-untreated tumors. Under laser irradiation, HNPs initiate a photothermal effect to disrupt the primary tumor cells and further achieve strong immune responses for long-term tumor inhibition under light and magnetic triggers [146]. In another approach, a reactive oxygen species-responsive core cross-linked HNP micellar system has been designed to enhance the circulation stability that allows on-demand chemotherapeutic drug release via far-red-light-induced ROS generation [147].

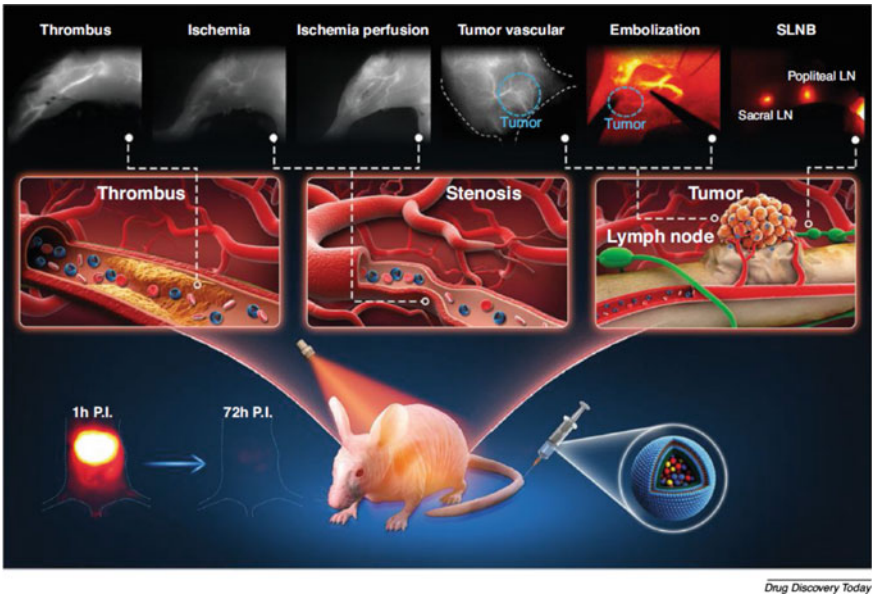

Fig. 4 Schematic illustration of next-generation HNP which consists of excretable lanthanide NPs for multifunctional biomedical imaging and surgical navigation in the second near-infrared window. The strategy reports innovative nano-theranostics using HNPs for proper real-time tumor imaging tools to assess the progression of diseases and their therapeutic response [146]

5 Challenges and Future Perspectives

In the past few years, using nanomaterials, many efforts have been made to develop assays for cancer diagnosis. In comparison with the presently available cancer detection methods, a variety of nanomaterial-based assays have exhibited improved selectivity and sensitivity or offered totally new properties that are not possible with traditional approaches. Thus, it will improve the survival rate of cancer patients by allowing early detection. Also, nanomaterial-based cancer diagnosis methods are used to monitor cancer progress in response to treatment. A large number of nanoplatforms are used for cancer treatment. The main goal of these nanoplatforms is to decrease the drug dose that is needed to attain a specific therapeutic effect ultimately, reducing the costs and side effects associated with them. Great efforts have been directed by the scientists in specifically targeting the chemotherapeutic drug at tumor site and theranostic applications. Multifunctional NPs will become the trend of future of cancer research. Many nanoplatforms have been evaluated for drug targeting; some of them have managed to get FDA approval and are routinely used in the clinic.

A large number of the NPs stay only in vivo and in vitro stages. There are the following reasons which hinder the clinical applicability of NPs.

(i) Lack of injection routes and methods.
(ii) Difficulty in localization of NPs in vivo.
(iii) Difficulty of degrading in the human body.
(iv) Difficulty in avoiding mononuclear phagocytic system.

Synthesis and reproducibility of homogeneous nanomedicines and stability of formulations under various conditions are still a challenge. Furthermore, studies and optimization are required to ultimately scale up the synthesis process from the bench to clinical applications. In future efforts, it will be important to not only make ever more nanomaterials but also to understand subcellular-level interaction between cancer cells and nanomaterials.

6 Conclusions

The poor therapeutic effect, inefficient targeting capacity, possible biological risk, and several side effects are some of the undesirable characteristics of existing cancer therapy and diagnosis. In the past few decades, advanced nanotechnology and molecular cell biology have endorsed the applications of NPs in the cancer field. Early detection is a key factor for successful treatment. Nanotechnology-based cancer diagnosis and our understanding in this field have greatly improved due to continuous efforts made by researchers worldwide. A variety of NP-based assays exhibited improvement in selectivity and sensitivity or offered new capacities that could not be attained with conventional approaches. Collaboration among researchers, engineers, and clinicians, a nanotechnology-based cancer diagnosis is poised to move into the clinic in the near future. High sensitivity, specificity, and multiplexed measurement capacity nanotechnology provides great opportunities to improve cancer diagnosis, which will ultimately lead to an improved cancer patient survival rate. Nanomedicine has the potential to effectively treat cancer by reducing the limitations of existing traditional cancer treatments. Various types of nanoplatforms are used in the treatment of cancer. For effecting targeting and therapeutic effect of chemotherapeutic drugs, passive and active targeting along with theranostic methods is now the main area for cancer research. Understanding tumor biology is essential for the development of successful theranostic applications because cancer cells have different capacities to grow, differentiate, develop drug resistance, and form metastases. A deep understanding between cancer cells and theranostic nanomaterials must be accomplished considering a biological perspective.

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Nanotechnology: Antidiabetics, Antioxidant and Anti-inflammatory

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Abstract Diabetes mellitus is one of the major health and economic concerns worldwide, because of a high rate of prevalence and complications. A stable and satisfactory level of glycemic control plays an important role in avoiding further complications related to diabetes. Therefore, persistent efforts with anti-hyperglycemic agents, herbal medications and routes of treatment are made for better control of this chronic disorder. Furthermore, novel drug delivery stems such as antidiabetic peptide delivery and nanotechnology-based therapies are playing a crucial role in the control of diabetes with elevated bioavailability, higher efficacy, minimal frequency of dosing and reduced toxicity. Among these, nanotechnology-based therapies and islet cell implantation have shown promising results in diabetic therapy. In this regard, the present chapter aims to provide insight into various novel therapies, nanocarrier delivery systems, antioxidant and anti-inflammatory agents used for the control and treatment of diabetes.

Keywords Diabetes mellitus · Antioxidant · Anti-inflammatory · Nanocarrier delivery systems

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R. S. Mane et al. (eds.), *Nanomaterials for Sustainable Development*,
https://doi.org/10.1007/978-981-99-1635-1_8

1 Introduction to Antidiabetic, Antioxidants and Anti-inflammatory Drugs

1.1 Antidiabetic Drugs

Diabetes also called diabetes mellitus is one of the chronic conditions caused by the inability to produce sufficient insulin by the pancreas or body cannot effectively utilize the insulin it produces. It is the 7th leading cause of death and accounts for 6.7 million deaths worldwide in 2021 [1]. In 2021, USD966 billion was incurred as a global health expenditure on diabetes [1]. Diabetes has been classified into three types: type 1, type 2 diabetes and gestational diabetes mellitus (GDM) [2]. According to International Diabetes Federation 2021 data, the worldwide occurrence of diabetes in adults was estimated to be 537 million. The total number is expected to increase to 643 million in 2030 and 784 million by 2045. In India, the incidence and death due to diabetes are estimated to be 74.2 million and 6.47 million, respectively, and ranks 2nd in the world concerning the prevalence of diabetes in adults [1]. Among all the types of diabetes, type 2 diabetes (T2D) is the most prevalent and accounts for about 90% of total diabetes globally. T2D is called non-insulin-dependent diabetes and is caused due to insulin resistance, resulting in hyperglycemia. The increasing trend of T2D is due to obesogenic environments, ageing, lifestyle changes and rapid urbanization [3]. In recent years, a higher incidence of T2D in younger adults with a longer survival rate also contributes to the overall rise in T2D prevalence. Apart from this, type 1 diabetes accounts for 5–10% of diabetic cases and is caused by the body's autoimmune reaction in which insulin is not produced by beta cells of the pancreas because of the destruction of beta cells by antibodies or the immune system resulting in a deficiency of insulin production [4]. Diabetes is clinically diagnosed based on any one of the four-plasma glucose (PG) criteria: (a) fasting plasma glucose (FPG) (> 126 mg/dl), (b) 75 g oral glucose tolerance test for 2 h resulting in > 200 mg/dl PG level, (c) random plasma glucose test (> 200 mg/dl) indicating hyperglycaemic condition and (d) > 6.5% of haemoglobin A1c (HbA1c) level [5].

Improper management of diabetes mellitus leads to life-threatening health complications such as lower-limb amputation, nerve damage (neuropathy), blindness, cardiovascular diseases and renal failure [4]. To prevent these complications and control diabetes, antidiabetic drugs or agents are used. Antidiabetic drugs are the agents used to reduce the blood glucose level concentration of people with diabetes mellitus. These agents lower the complications of diabetes by maintaining the blood sugar to the normal range [6]. Antidiabetic drugs and agents are used to treat both type 1 and type 2 diabetes by targeting and controlling ominous octet factors that contribute to the pathophysiology of diabetes such as neurotransmitter dysfunction, increased lipolysis, decreased insulin secretion, increased hepatic glucose production, decreased incretin effect, increased glucose reabsorption, increased glucagon secretion and decreased glucose uptake [7]. Figure 1 shows the site of action of antidiabetic drugs for the treatment of T2D.

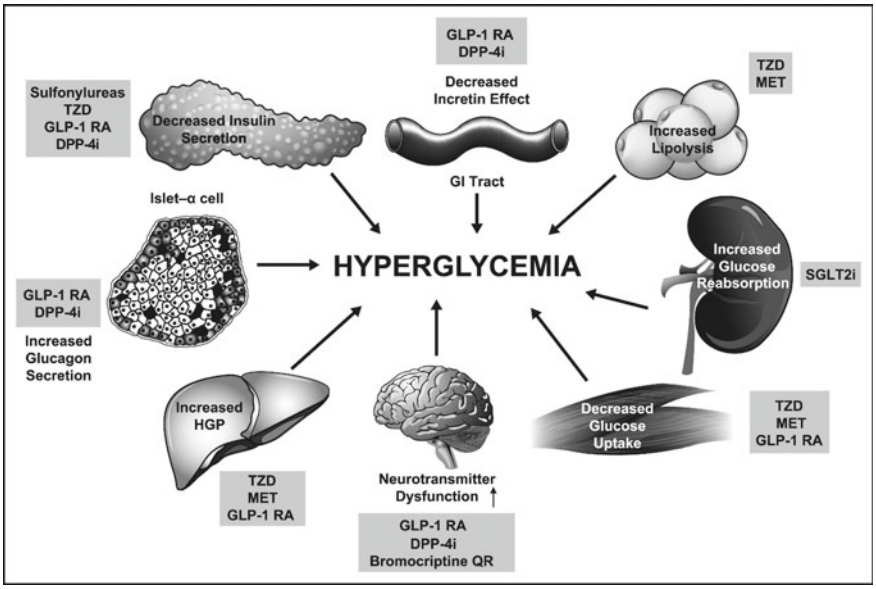

Fig. 1 Site of action of antidiabetic drugs against type 2 diabetes [7]

Antidiabetic drugs provide beneficial effects in lowering and controlling diabetes through: (i) insulin increase in the body; (ii) reducing the body's resistance to insulin; and (iii) lowering the intestinal absorption of glucose [8, 9]. Various hormonal (insulin) and non-hormonal antidiabetic drugs used for the treatment of diabetes include meglitinides, glitazones, sulfonylureas, alpha-glucosidase inhibitors (AGIs), biguanides, sodium-glucose co-transporter inhibitors and dipeptidyl peptidase-4 (DPP-4) inhibitors. The antidiabetic drugs are administered as monotherapy, dual-therapy or multi-agent therapy along with or without insulin administration [10]. Table 1 summarizes the classification of antidiabetic drugs with their route of administration and mechanism of action.

Further, insulin pump systems, immune modulation/incretins, stem cell mobilization, beta-cell (β-cell) encapsulation, microencapsulation interventions are used for the treatment of especially type 1 diabetes [13]. Due to several side effects of antidiabetic medications such as hypoglycemia, weight gain, mitogenetic effect, stigma, gastrointestinal effects, low durability, oedema/heart failure, increase risk of genital fungal infection and urinary tract infections (UTI), angioedema and high cost have led to a search of alternative treatments for type 2 diabetes [12].

The most common treatments for diabetes include antioxidants and anti-inflammatory drugs. The following sections provide insight into the role of antioxidants and anti-inflammatory drugs in the management of diabetes mellitus.

Table 1 Classification of antidiabetic drugs [11, 12]

Antidiabetic agents	Route of administration	Mechanism of action
Rapid-acting insulin		By inhibition of hepatic glucose production and stimulation of peripheral glucose uptake in skeletal muscle and fat lowers blood glucose level
Insulin lispro	Subcutaneous	
Intermediate-acting insulin		
Neutral protamine Hagedorn insulin (NPH insulin)	Subcutaneous	
Insulin (short-acting insulin)		
Insulin regular	Subcutaneous	
Long-acting insulin		
Insulin glargine	Subcutaneous	
Insulin detemir	Subcutaneous	
Rapid-acting insulin		
Insulin aspart	Subcutaneous	
Insulin sensitizers		
Biguanides—Metformin	Oral	By activation adenosine monophosphate kinase and hepatic gluconeogenesis inhibition
Thiazolidinediones or glitazones—pioglitazone, rosiglitazone	Oral	Activation of PPAR-gamma receptor by acting as agonist increases insulin sensitivity
Insulin secretagogues		
Sulfonylureas—gliclazide, glimepiride, glipizide, glibenclamide (glyburide)	Oral	By inhibition of potassium ATP channels insulin release is stimulated from beta cells of pancreatic islets
Non-sulfonylureas—repaglinide, nateglinide	Oral	
Alpha-glucosidase inhibitors		
Acarbose	Oral	Inhibits intestinal alpha-glucosidases and delay that converts carbohydrates into absorbable monosaccharide units
DPP-4 inhibitors		
Sitagliptin, vildagliptin, saxagliptin, linagliptin, alogliptin	Oral	Decrease the glucagon release by inhibition of dipeptidyl peptidase-4 increases the activity of glucagon-like peptide-1 resulting in increase in glucose-dependent insulin secretion
Sodium–glucose co-transporter 2 (SGLT2) inhibitors		
Canagliflozin, dapagliflozin, empagliflozin	Oral	Inhibits the SGLT2 co-transporter and reabsorption of glucose from proximal convoluted tubules and promote glycosuria

1.2 Antioxidant Drugs

Several studies have proved that diabetes mellitus and its complications along with macro- and microvascular dysfunctions are related to a reduction in antioxidant potential and elevated levels of free radical formation [14]. Because of this, the balance between protection and free radical formation within the cells is disturbed, resulting in oxidative stress or damage of cell components such as nucleic acids, lipids and proteins. Elevated levels of oxidative stress in both type 1 and type 2 diabetes play an important role in the progression and its complications [15, 16].

Many factors are responsible for elevated levels of oxidative stress in diabetes mellitus, which includes imbalance cellular oxidation, auto-oxidation of glucose leading to the formation of free radicals and decreased antioxidant defences such as cellular antioxidant property and activity of enzymes on free radicals. Further, five pathways activation occurs due to elevated production of superoxide leading to diabetes complications and pathogenesis, which includes the higher activity of hexosamine pathway, polyol pathway flux activation, higher rate of formation of advanced glycation end products (AGEs), protein kinase activation and expression of AGEs receptors and its ligands [17, 18]. The initiating factor for diabetes complications such as neuropathy, cardiomyopathy, nephropathy and endothelial dysfunction is superoxide formation through mitochondrial electron transport chain and neutralizing these reactive molecules leads to significant inhibition of complications [19]. Figure 2 presents the complications of diabetes due to oxidative stress.

Antioxidants can be used to overcome the diabetes mellitus complications due to oxidative stress via various mechanisms for counteracting free radical formation

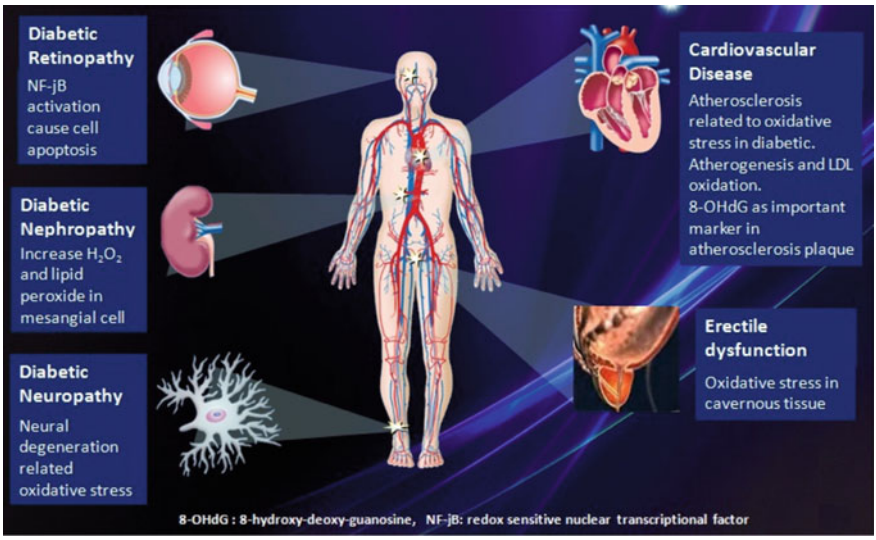

Fig. 2 Correlation of oxidative stress to complications of diabetes [15]

such as (a) degradation of free radicals by acting as enzymes, (b) by binding to metals that stimulate free radical production and (c) as free radical scavengers [20]. Some of the common deficiencies that are encountered due to lack of antioxidants in diabetes include reduced glutathione and superoxide dismutase, and reduced levels of ascorbate [21].

Antioxidants such as vitamins (C and E) and β-carotene are the most studied and ideal supplements for oxidative stress-induced pathophysiology of complications in diabetes. Apart from this, vanadium, zinc and selenium are also used along with plant-based active ingredients as natural antioxidants [14]. Tables 2 and 3 present the efficacy of antioxidants and plants and their antioxidant ingredients on diabetes and its complications.

In addition to the above antioxidants, studies in diabetic patients and streptozocin-induced diabetic rats by honey have contained polyphenols such as apigenin, quercetin, kaempferol, luteolin and catechin with antioxidant properties and reduced blood glucose level by following mechanisms; (i) oxidative stress reduction leading to protection of β-cell, (ii) α-amylase and α-glucoside enzymes inhibition, (iii)

Table 2 Efficacy of antioxidants on diabetes and its complications

Antioxidants	Target	Efficiency
Vitamin E	Streptozocin-induced diabetic rats	Decreases the activity of lipid peroxidation, glutathione S-transferase and glutathione peroxidase [22]
	Diabetic patients	Reduces oxidative stress indicators, glycosylation of protein and insulin resistance [23]
	Patients with type 2 diabetes	Reduces oxidative stress indicators, low-density lipoprotein oxidative susceptibility, haemoglobin A1c, levels of insulin and action of insulin improved [20, 21]
	Patients with type 1 diabetes	Reduces homodynamic abnormalities of retina, normalize creatinine clearance [24]
Vitamin C	Patients with type 2 diabetes	Reduces fasting plasma insulin and haemoglobin A1c, action of insulin improved [20]
β-carotene	Patients with type 2 diabetes	Reduces low-density lipoprotein oxidative susceptibility [25]
	Streptozocin-induced diabetic rats	Increases glutathione and glutathione peroxidase activity [26]
Zinc	Alloxane-induced diabetic rats	Induces synthesis of metallothionein, decreases lipid peroxidation in retina [27]
Vanadium	Streptozocin-induced diabetic rats	Free radical scavenging, reduces lipid peroxidation in pancreas [28]
Selenium	Alloxane-induced diabetic mice	Increases glutathione in brain and liver [29]

Table 3 Plants and their antioxidant ingredients on diabetes

Plant name	Active agent	Target	Efficiency
Eugenia jambolana	Flavonoids	Streptozocin-induced diabetic rats	Free radical scavenging [30]
Juglans regia	Pedunculagin	Type 2 diabetic mice	Reduces oxidative stress biomarkers [31]
Plants like ferula asafoetida	Ferulic acid	Streptozocin-induced diabetic rats and KK-Ay mice	Free radical scavenging and reduces lipid peroxidation [32]
Allium cepa	S-allyl cysteine sulfoxide	Alloxane-induced diabetic rats	Free radical scavenging [33]
Trifolium alexandrinum	Flavonoids	Streptozocin-induced diabetic rats	Free radical scavenging, reduces lipid peroxidation and increases hepatic reduced glutathione [34]

aldose reductase and gluconeogenic enzymes reduction and (iv) insulin cell receptor production and glucose transporter type 4 with increased absorption of glucose [35].

1.3 Anti-inflammatory Agents

Many factors play an important role in the development of diabetes and its complications. Among them, innate immunity is the main driving force for pathophysiology. Type 1 diabetes mellitus (T1DM) is caused due to autoimmune-mediated inflammation response failing β-cells of pancreatic islets. While the mediator for type 2 diabetes mellitus and its macro/microvascular complications is systemic low-grade inflammatory response [36]. T1DM incidence has increased dramatically in the past 10 years and accounts for about 5% of all diabetic patients. Pro-inflammatory cytokines (TNF-α, IL-6 and IL-1β) and cytotoxic T cells are predominant players responsible for the progress of TD1M [37]. Furthermore, cytokine-induced cytotoxicity has resulted in the death of pancreatic β-cells, since it possesses specific receptors in abundance for different cytokines [38]. Apart from this, T2DM is developed due to one of the major reasons called metabolic inflammation and accounts for about 90% of the cases. Aforementioned case, dysfunction of β-cells leads to excessive production of glucose and this promotes activation of pro-inflammatory cytokines (IL-1β) and chemokines (IL-33, IL-8 and IL-6). Furthermore, immune cells and macrophages recruit lead to an increase in IL-1β and impaired function [38, 39] (Fig. 3).

Uncontrolled diabetes leads to consequences such as stroke, eye damage, heart disease, digestion problems, dental problems and susceptibility to infection. Furthermore, metabolic inflammation results in the progression of diabetic complications

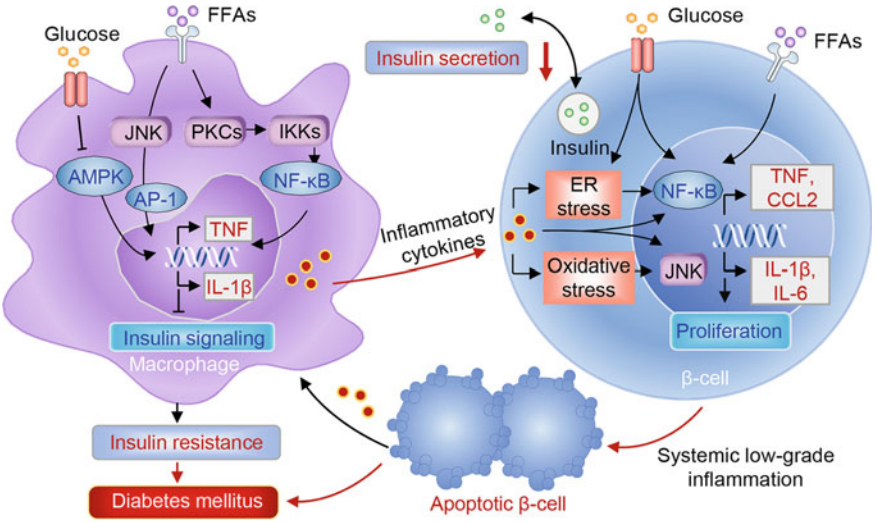

Fig. 3 Low-grade inflammation role in type 2 diabetes pathogenesis [36]

including neuropathy, retinopathy and kidney disease. Therefore, numerous anti-inflammatory agents are being used for the management of diabetes. Among them, phytochemicals have shown positive results in the treatment and prevention of diabetic complications in experimental models. Tables 4 and 5 represent molecular targets to reduce inflammation and anti-inflammatory mechanism of phytochemicals in the management of diabetes and its complications.

Table 4 Diabetes management by compounds and its target to reduce inflammation [40]

Compounds	Mechanistic target	Target organ	Consequence on the metabolism of glucose
Rapamycin	mTOR inhibitors	Artery	None
Resveratrol	Sirtuin 1 (SIRT1) activators	Adipose tissue	Insulin action improved
Metformin	AMPK activators	Liver	The output of hepatic glucose reduced
Anakinra	IL-1 receptor blockade	β-cell	Secretion of insulin improved
Etanercept, infliximab	TNF-α antagonists	Adipose tissue and muscle	Insulin action improved
Salsalate	IKKβ-NFkβ	Liver β-cell Muscle	Clearance of insulin reduced Insulin action improved Secretion of insulin improved

Table 5 Mechanism of representative phytochemicals as anti-inflammatory agents

Compound	Result		Animal model	References
	Downregulation	Upregulation		
Ellagic acid	TNF-α, IL-6, IL-1β, NF-κB activation	–	Diabetic kidney disease and peripheral neuropathy	[41, 42]
Naringenin	TNF-α, IL-6, TGF-β, NF-κB and ICAM-1	AMPK activation, PPARs	Gestational diabetes disease and diabetic kidney disease	[43–45]
Eriodictyol	TNF-α, IL-8	PPARγ2	Diabetic retinopathy	[46, 47]
Quercetin	IL-18, IL-1β and NLRP-3	Macrophages switching from M1 to M2 polarization	Diabetic kidney disease and diabetes	[48, 49]
Chrysin	TGF-β1, IL-1β, Smad 2/3,IL-6 and NF-κB activation	PPAR-γ	Diabetic kidney disease and peripheral neuropathy	[50–52]

In this regard, the present chapter aims to discuss recent advances in diabetic diagnosis, treatment, methods of drug delivery and challenges, and future perspectives.

2 Nanotechnology in Diagnosis, Treatment and Drug Delivery for Diabetics

Numerous synthetic drugs or agents and traditional medicines are used for the treatment of diabetes and its management. But, these agents have proven to cause severe side effects and insulin injections causes several problems such as allergies, weight gain and abnormalities in the site of injection like pain and swelling. Additionally, insulin pumps and glucose monitoring systems in combination have been developed to overcome these issues and found that it is only reasonably effective. Therefore, there is an immense demand for improved diabetic management tools [53].

Among several new technologies, nanotechnology has shown greater promise in solving the darkest avenues of medical diabetic management because of its unique physicochemical properties. Monitoring of blood glucose and delivery of insulin by various systems are the major improvements in the treatment of diabetes that nanotechnology has facilitated [54]. The most important aspect of diabetes is accurate and early diagnosis with optimal patient outcomes which is necessary to overcome diabetic complications. However, conventional diagnostic methods such as oral glucose tolerance test, HbA1c (glycated haemoglobin), or fasting glucose level analysis require constant and tedious glucose monitoring and insulin injections, impacting

the quality of life and falling short to overcome diabetic complications [53]. Additionally, autoantibodies measurement is used to as a test to diagnose and distinguish type 1 diabetes [55]. These methods depend on antibody titre, measurement of glucose levels and painful procedure, and results vary based on the physiological conditions of the person [56]. To overcome these problems, numerous nanotechnology methods have shown potential results in the early diagnosis of diabetes, which are non-invasive. Among them, quantification of β-cell mass and immune cell activity in diabetic patients using nanoparticle-based imaging techniques (MRI) has proven to be a novel route of diagnosis. For example, exendin-4 or ferumoxran-10 conjugated superparamagnetic iron oxide nanoparticles have been developed and used for the early diagnosis of diabetes [57–59]. This method has opened new avenues for treatment modalities and the identification of disease progression. Apart from this, a quantum dot-based gas sensor that analyses acetone levels has been developed for the diagnosis of diabetes [60].

Monitoring glucose levels is one of the prime importance in diabetes and one of the common approaches used is the finger-prick method. In this method, blood is drawn by pricking the finger with a sharp needle and loaded into the sample port of the standard glucose metre and the level of glucose is monitored. Several disadvantages are glucose measurement which is unreliable due to factors like age, mealtime and poor patient compliance [56]. Further, intermittent testing pattern leads to a higher risk of diabetic complications [61, 62]. Nanotechnology-based monitoring methods have provided a solution to the above limitations, which includes smart tattoos or fluorescence-based nanosensors (quantum dots and nano-optodes) [63, 64], layer-by-layer technique [65] for glucose monitoring and multiwalled carbon nanotubes-based sensor for insulin monitoring [66, 67].

One of the main challenges in diabetes treatment even though accurate diagnosis and constant monitoring is the delivery of insulin through the gastrointestinal tract. The traditional treatment includes insulin-based therapies in the form of oral, injectable, inhalable and insulin analogues (insulin aspart and insulin degludec U-200). These treatments cause the risk of hypoglycemia and unable to maintain euglycemia for a longer period. In recent decades, advances in nanotechnology have played a major role in the convenience, efficiency and safety of usage of insulin replacement therapies. In addition, nanotechnology-based therapies have been shown to provide strict glycemic control and reduce the continuous injections of insulin numbers. Novel methods used for the treatment of diabetes consist insulin patches and insulin nanogels [68–70], nanopumps [71], gene therapy [72] and cellular-based therapies [73, 74].

3 Recent Trends in Antidiabetic Treatment like Nanoencapsulation, Nanocarrier and Nanopolyphenols

Numerous conventional antidiabetic agents are being released into the market worldwide, but a complete cure for diabetes mellitus remains still untouched. Because of the reason that severe side effects of these drugs and many intrinsic deficiencies. Furthermore, lack of target specificity, ineffective dosage, diminished potency, high protein binding, short half-lives, low bioavailability and risk of hypoglycemia limit their usage [72, 75, 76]. Last few decades, several research studies have proved the potential of nanotechnology with the aid of nanoparticles to overcome the limitations of antidiabetic drugs. Therefore, nanotechnology-based novel drug delivery systems have gained attention in the treatment and management of diabetes including liposomes, niosome, dendrimers, polymeric nanoparticles, inorganic nanoparticles and polymeric micelles [77]. The advantages of the aforementioned drug delivery systems include a decrease in side effects, targeted therapeutic efficacy, reduced dosing frequency and prevention from acidic gastric environment degradation [78].

3.1 Liposomes

Liposomes are produced from cholesterol and non-toxic phospholipids of natural origin consisting of one or more phospholipid bilayers and are small vesicles. This acts as a transporter for active molecules, easily crosses the bio-systems, fuse with biological membranes and release the encapsulated drug into the cytoplasm resulting in pharmacological action [79]. Liposomes are used as a common choice of drug delivery systems because of target-specific action, low toxicity to encapsulate hydrophilic and lipophilic drugs, biocompatibility and biodegradability [75]. Numerous forms of liposomes are used for drug delivery including sodium glycocholate, glycerolphosphate-chitosan micro-complexation, chitosan-coated and anionic liposomes used for GLP-1, insulin and oral peptides protection from enzymatic degradation [80, 81]. Table 6 presents information regarding different liposomal approaches used for antidiabetic drug therapy.

3.2 Niosomes

Niosomes are formed from cholesterol as excipients incorporated into non-ionic surfactant with a nanometric scale and are micro-vesicles of synthetic nature. Niosomes can be classified based on their bilayer and size as small unilamellar, unilamellar and multilamellar vesicles with a size range of 10–100 nm, 100–300 nm and > 300 nm, respectively. Niosomes act as reservoirs for drugs with maximum entrapment efficiency for sustained and prolonged release of drugs. Furthermore,

Table 6 Liposomal mediated antidiabetic drug therapy

Polymer	Incorporated drug(s)	Outcome	Reference
Chitosan coated liposomes	Insulin	Improved the absorption of insulin from GI tract by decreasing enzyme activity	[82]
Glycerolphosphate-chitosan microcomplexation	Metformin	Improved oral availability and controlled delivery of water-soluble antidiabetic drugs to site of action	[81]
Sodium glycocholate liposomes	Insulin	Improved proteins and peptides through oral routes by reducing enzymatic degradation	[83]

drugs with varying solubility can be accommodated within niosomes. Moreover, these agents offer excellent low toxicity and bioavailability because of their non-ionic nature. Niosomes are used for the delivery of insulin through the vagina of alloxan-induced diabetic Wistar rats. The results indicated a reduction of blood glucose level and prolonged drug release with a higher hypoglycemic effect compared to subcutaneous injections [84]. In addition, the release of antidiabetic agents using niosomes enhances the bioavailability and reduces dosing frequency and adverse side effects [85]. Table 7 provides insight into antidiabetic drug therapy using niosome-based drug delivery system.

Table 7 Antidiabetic drug therapy using niosome-based drug delivery system

Polymer	Incorporated drug(s)	Outcome	Reference
Span 40, span 60 and cholesterol	Insulin	Effective delivery of therapeutics agents via vaginal administration indicated reduced glucose levels with prolonged release of insulin	[84]
Span 60 and cholesterol	Repaglinide	Decreased the frequency of dosing and enhanced the bioavailability of the entrapped drug	[86]
Span 60/cholesterol/N-trimethyl chitosan system	Insulin	4 times more insulin absorption was observed via Caco-2 cell monolayer than free insulin	[87]

3.3 Polymeric Nanoparticles

Nanoparticle usage has been widespread in drug delivery systems because of reduced adverse effects and enhanced drug utility. To increase the efficacy of nanoparticles loaded with drugs and aiming potential towards the targeted site, nanoparticles are capped with mucoadhesive agents, polyethylene glycol, etc. Since bioavailability of oral administration of insulin loaded nanoparticles is low, it is poorly adsorbed by the GI tract with low permeability. Whereas, insulin loaded mucoadhesive nanoparticles have shown increased bioavailability of insulin [88]. In addition, solid lipid nanoparticles incorporated with insulin exhibited have enhanced insulin adsorption and prevented degradation of insulin by proteolytic enzymes in the GI tract, thereby enhancing oral insulin tolerance, bioavailability and residence time in diabetic animals [89]. Examples of polymeric nanoparticle-based antidiabetic therapy are shown in Table 8.

Table 8 Examples of antidiabetic therapy based on polymeric nanoparticle drug delivery system

Carrier type	Polymer	Incorporated drug(s)	Outcome	Reference
Solid lipid nanoparticles	Cetyl palmitate-based solid lipid nanoparticles	Insulin	Lowered plasma glucose level compared to empty solid lipid nanoparticles and insulin solution administration	[90]
Nanoparticles	Chitosan or alginate-coated nanoparticles to form nano-network gel	Recombinant insulin	Threefold increase in release of insulin was observed as induced by higher glucose level in hyperglycemic stage. This would provide control over both long-term and self-regulated diabetes	[69]
Nanoparticles	PEG capped poly lactic-co-glycolic acid-loaded insulin nanoparticles	Insulin	Showed noticeable hypoglycemic effect with decreased cholesterol, lipid peroxidation and triacylglycerol with elevated level of HDL cholesterol	[91]

Table 9 Different dendrimers used in drug delivery systems for antidiabetic therapy

Carrier type	Polymer	Incorporate drug(s)	Outcome	Reference
PAMAM (G2, G3, G4)	–	Pancreatic insulin of human origin	Fibrillation of insulin was strong with PAMAM dendrimer generation and ratio of protein	[96]
PAMAM (G2, G3, G4)	Amidoamine	Pancreatic insulin of human origin	Secondary structure of inulin was not altered and did not enhance the aggregation of proteins	[97]
PAMAM dendrimer (G0, G1, G2, G3)	–	Calcitonin and insulin	Generation dependent increase of absorption of calcitonin and insulin was observed (G3 > G2 > G1 > G0)	[98]

3.4 Polyamidoamine Dendrimers

Dendrimers are nano-sized, polymeric globular hyperbranched macromolecules with tree-like morphology in 3D nanostructure which comprises a central core and branched monomers with different reactive end groups on the surface [92]. They are classified into glycol, peptide, liquid crystalline, core–shell, poly(propylene imine) (PPI), hybrid and poly (amidoamine) (PAMAM) dendrimers. Due to their unique physicochemical properties, dendrimers are widely used in biomedical and pharmaceutical applications as effective drug carrier. Based on the modification of functional groups and size, dendrimers with different hydrophilicity, molecular weight and effective diameters are obtained [93]. The insulin secondary structure is maintained when incorporated with dendrimer of class poly(amidoamine). In addition, poly(amidoamine) does not change the conformation of proteins and forms rigid protein interactions. Therefore, poly(amidoamine) dendrimers is one of the dendrimers commonly used as insulin delivery tool and reduces aggregation of insulin [94]. Apart from this, studies related to PAMAM G4dendrimers on diabetic animal models confirm a significant decrease in glucose level in plasma and hyperglycemic markers of long term with mimicking hypoglycemic action [95]. Table 9 provides insight into different dendrimers used as carriers for antidiabetic therapy.

3.5 Inorganic Nanocarriers

Inorganic materials such as metallic nanoparticles, mesoporous silica nanoparticles and carbon nanotubes are usually employed as nanocarriers with surface functionalization, size and controlled morphology. Thus, inorganic nanocarriers have brought

more options for drug delivery [99]. Metallic and metallic oxide nanoparticles such as silver [100, 101], selenium [102, 103], gold [104] and zinc oxide nanoparticles [105, 106] have demonstrated promising results for type 2 diabetes mellitus treatment [107]. However, the synthesis of metallic nanoparticles carried out by chemical and physical methods reveals several drawbacks such as toxic solvents usage, production of hazardous by-products and high energy consumption [108]. The synthesis of metallic nanoparticles using plant extract has gained attention over chemical techniques as an alternative [109]. Phytoconstituents having antidiabetic properties are used and act as stabilizing and reducing agents for the synthesis of metallic nanoparticles. The examples include docosahexaenoic acid zinc oxide nanoparticles [105], vicenin gold nanoparticles [110] and gymnemic acid gold nanoparticles [111]. All these nanoparticles have exhibited excellent antidiabetic properties in both in-vitro and in-vivo studies. In addition, metallic nanoparticles synthesized using phytoconstituents with antidiabetic properties have showed enhanced activity compared to bare metal nanoparticles. For instance, selenium nanoparticles prepared using polysaccharides of *Catathelasma ventricosum* exhibited enhanced antidiabetic effects compared to selenium nanoparticles and their counterparts [112].

3.6 Nanopolyphenols

Numerous treatments for diabetes mellitus are available worldwide, but they cause adverse side effects leading to find a natural alternative. Among them, polyphenols have been found as one of the alternatives [113]. Polyphenols are bioactive compounds as well as secondary metabolites produced by plants. They are chemogenic substances with phenolic rings of one or more and hydroxyl groups in their structure. Based on the phenolic ring numbers and attached groups, they are classified as polyphenolic amides, flavonoids, phenolic acids and non-flavonoids (tannins, lignans, diarylheptanoids and stilbenoids) (Fig. 4). Several reports indicate that polyphenols possess a wide range of biological activity like anti-inflammatory, antimicrobial, anticancer and antidiabetic effects [114]. In addition, polyphenols have been shown to exhibit antidiabetic effects via various mechanisms through their ability to: decrease hepatic glucose output, and insulin sensitivity, elevate insulin sensitivity, intestinal glucose uptake inhibition by sodium-dependent glucose transporter 1 [115–118]. This has been observed via animal models and clinical trials [119–121]. Due to their compound particle size, low bioavailability and instability at low pH have restricted its usage as antidiabetic agents. To overcome this problem, nanoencapsulation techniques are being utilized in which polyphenols can be encapsulated using nanocarriers [114]. Antidiabetic effects of various nanopolyphenols are provided in Table 10.

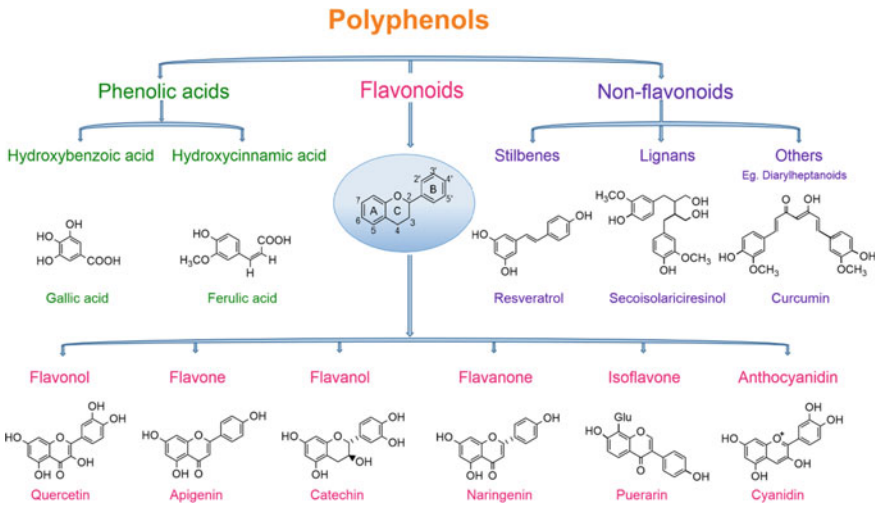

Fig. 4 Types of polyphenols [114]

4 Theranostics and Imaging

Theranostic is defined as an emerging field that combines the utilization of nanoscale materials for both therapeutic modalities and diagnostic imaging. Diagnostic imaging is carried out using a magnetic resonance imaging (MRI) facility and is not sensitive enough for early diagnosis. To increase the sensitivity for diagnosis novel, MRI agents are necessary. To overcome this problem, magnetic nanoparticles need to be used as contrast agents for MRI. Magnetic nanoparticles are not only useful as imaging tools but also as a carrier of therapeutic moieties and the release of drugs in a controlled manner makes MRI important modalities for theranostic imaging applications [127].

Theranostic imaging is a multidisciplinary field consisting of synthetic chemistry, nanotechnology and molecular biology. Various classes of nanoparticles are used for imaging which are categorized into inorganic and organic materials. Polymers, dendrimers and polymeric micelles are primarily used as nanocarriers for the delivery of drugs are grouped into organic materials. Magnetic nanoparticles, a class of inorganic materials, are commonly used for theranostic MRI than organic nanoparticles because of unique physical properties like size and composition. In addition, ease of synthesis, modifications of surface to incorporate therapeutic agents and target specificity have enabled its usage as a smart platform for theranostic MRI [128, 129].

The probes used for theranostic MRI for treatment and management of diabetes should: (i) biodegrade and produce safe by-products, (ii) accumulate in target tissues or cells specifically, (iii) deliver therapeutic moieties effectively and (iv) provide functional and morphological information of the area. The commonly used probes for theranostic MRI are manganese nanoparticles, iron oxide nanoparticles

Table 10 Effect of nanopolyphenols as antidiabetic agents

Polyphenol (class)	Nanocarrier (components used for delivery system)	Outcome	Reference
Naringenin (flavanone)	Polymeric nanoparticles (sodium alginate and chitosan)	Reduced blood glucose level and free iron content, architecture of hepatic revived and Langerhans cells structural complexity was regenerated	[122]
Resveratrol (stilbene)	Nanoemulsion	Decreased glucose level in serum, elevated insulin in serum and reduced glutathione, catalase, superoxide dismutase and glutathione peroxidase	[123]
Curcumin (diarylheptanoids)	Polymeric nanoparticles (polyethylene glycol—poly(lactic-co-glycolic acid, polyvinyl alcohol)	Decreased diabetes-induced oxidative stress and enhanced anti-oxidative enzymes	[124]
Quercetin (flavonol)	Inorganic nanoparticles (iron oxide nanoparticles)	Reduced blood glucose levels	[125]
Syzygiumcumini (L.) (extract rich in polyphenols)	Polymeric nanoparticles (polysorbate 80)	Reduced blood glucose, creatinine, cholesterol, pancreatic and serum advanced oxidation protein products and thiobarbituric acid reactive substance levels in renal	[126]

and gadolinium (Gd) loaded nanoparticles [127]. Pathological hallmarks of type 1 diabetes include β-cell destruction, microvasculature leakage and mononuclear cell infiltration of the pancreatic islets. Theranostic imaging with new strategies is designed to target these biomarkers to provide therapy and prevention. For diagnostic application, Gaglia et al. [130] reported on the development of a MRI method to visualize active insulitis in T1D patients using superparamagnetic iron oxide T_2 contrast agents which exhibited promising results in the detection of early insulitis caused due to inflammation of the islets of Langerhans (β-cells). In addition, Castillo et al. [131] studied the usage of fatty acid-containing protected graft co-polymer for the application of therapeutics like glucagon-like peptide-1 (GLP-1) to pancreatic β-cells for type 2 diabetes. The results indicated long circulation of blood pool agents

for the treatment of diabetes. Apart from this, fluorescently labelled nucleic acid polymer functionalized iron oxide nanoprobe exhibited the potential of quantifying pancreatic beta-cell mass as an efficient indicator of the onset of type 2 diabetes [132].

5 Efficacy and Toxicity Studies

Diabetes mellitus is one of the major concerns worldwide because it causes damage to many organs such as eyes, kidneys, heart, nerves and blood vessels as well as an elevated risk of several complications such as retinopathy, stroke, neuropathy, renal failure, blindness, cardiovascular diseases and peripheral vascular diseases. To reduce symptoms and save lives, antidiabetic drugs are used for the treatment of diabetes. In addition to this, the prime importance of using antidiabetic drugs is to eliminate risk factors to increase life span and to avert long-term complications of diabetes. The aforementioned complications and symptoms are reduced using various classes of antidiabetic drugs that have the intrinsic property of lowering blood glucose level. But these drugs have major drawbacks like severe side effects and to be taken lifelong. Therefore, the efficacy and safety of these drugs play an important role in the selection and utilization of appropriate drugs for diabetes therapy [133]. The different classes of drugs used for diabetes mellitus treatment and management are as follows; insulin, meglitinides, sulfonylureas, biguanides, thiazolidinediones, sodium-glucose co-transporter 2 (SGLT2) inhibitors, dipeptidyl peptidase-4 (DPP-4) inhibitors, alpha-glucosidase inhibitors (AGIs), glucagon-like peptide-1 (GLP-1) agonists and dopamine agonists [134].

Insulin is a hormone produced by beta cells of the pancreas endogenously. Patients suffering from diabetes, especially type 1 diabetes have insulin deficiency and reduced production of insulin in the case of type 2 diabetes. Type 1 diabetic patients require insulin as lifelong treatment. Whereas, in type 2 diabetic patients, insulin is used as monotherapy or adjunct therapy to oral antidiabetic agents. Various types of insulin are developed using natural insulin and components as substitutions. Depending on their pharmacodynamic and pharmacokinetic properties, they are classified as rapid-acting, short, long and intermediate-acting. Insulin therapy has many drawbacks such as low absorption from the subcutaneous tissue, 30–60 min for metabolic action and 2–3 h for attaining peak concentration. Neutral Protamine Hagedorn insulin (NPH) has different effects in lowering blood glucose levels. They are absorbed at varying rates from subcutaneous tissue and have a shorter action time. This causes an increase in blood glucose levels before breakfast and hypoglycemia at night-time [135]. To overcome this problem, insulin analogues are used as an alternative that absorbs more rapidly after subcutaneous injection compared to regular insulin and NPH with 15 min onset action [136]. Insulin therapy has the most common side effect called hypoglycemia. Apart from this, several other side effects are allergic reactions, pain, lower blood potassium, etc. [137]. The aforementioned

side effects have limited the usage of subcutaneous administration and necessitate the need for non-injectable methods.

Sulfonylureas are one of the oldest antidiabetic agents used for type 2 diabetes and act as insulin secretagogues [138]. Examples of this class include glimepiride, glibenclamide, glipizide, tolazamide, etc. [139]. They are effective only when some of the beta cells of the pancreas are effective and act by increasing the secretions of insulin. Sulfonylureas cause hypoglycemia and require hospitalization as they persist for several hours [140]. They are commonly used for patients with lower body weight and lowers glycated haemoglobin levels by 1.51% higher compared to placebo [141]. Among several forms of drugs in this class, glimepiride has been reported as effective in achieving control of glycaemia. In general, the side effects of sulfonylureas include nausea, vomiting, constipation and diarrhoea. Apart from this, hypoglycemic-associated symptoms are headache, dizziness, sweating, drowsiness and lack of energy. Therefore, they are not suggested for elderly persons and infrequently sulfonylureas can cause blood disorders and liver function disorders [140]. Metformin a class of biguanide group antidiabetic drugs has been used as primary treatment for type 2 diabetes worldwide. In recent years, metformin is also used for gestational diabetes treatment and prevention of diabetes. Alleviated glucose output is the consequence of biguanides by inhibition of gluconeogenesis in the liver and higher uptake of insulin-mediated glucose by skeletal muscle. Metformin improves the sensitivity of insulin, lowers blood glucose level, but causes weight loss and reduces food intake, and the absorption process of glucose is slightly delayed. They are beneficial in reducing diabetes-related complications and have a better safety profile compared to other antidiabetic drugs. Gastrointestinal problems are the common side effects of metformin with infrequent serious consequences of lactic acidosis [133].

In addition to the above, dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) agonists, etc., are used as a new class of therapy for diabetes in line with existing antidiabetic drugs as add on therapy.

6 Nanomaterials Used as an Antioxidant and Anti-inflammatory Studies

Patients with type 2 diabetes have elevated levels of oxidative stress and associated chronic inflammation. Oxidative stress causes a significant role in the onset of type 2 diabetes and tissue damage due to hyperglycemic conditions. Conventionally, exogenous antioxidants like glutathione, vitamin E, flavonoids and ascorbic acid are used to control higher cellular levels of reactive oxygen species (ROS) which leads to oxidative stress. Due to limited absorption profiles and low bioavailability of orally administered antioxidants, conventional therapies are proven to be ineffective. Therefore, nanotechnology-based approaches have gained moderate attention because of inherent properties such as high specificity, reduced frequency of

dosing, increased bioavailability and degradation prevention capacity from gastric environments. In this regard, metal nanoparticles (gold, cerium oxide, zinc oxide and magnetic nanoparticles like Fe, Ni, Co) have shown considerable potential in the prevention and treatment of hyperglycemic-triggered complications by excessive ROS generation. The nanomaterials that show antioxidant properties and can scavenge free radicals and reduce concentrations of ROS are called nanoantioxidants [107].

Nanoantioxidants include both nonorganic nanoparticles and functionalized nanoparticles with antioxidants. Higher antioxidant properties like superoxide dismutase (SOD), catalase (CAT) and glutathione peroxidase (GPX) mimicking activities are exhibited by metal nanoparticles obtained from iron oxide [142, 143], nanoceria [144–146], manganese dioxide [147], vanadium pentoxide [148] and copper oxide [149], gold [150, 151], platinum [152] and silver [153]. The behaviour of antioxidant capacity of metallic nanoparticles depends on oxygen vacancies and multioxidation state with oscillations. For instance, cerium oxide nanoparticles are considered as one of the prominent nanoantioxidants due to its better catalytic properties caused by surface oxygen vacancies and two oxidation states (Ce^{3+} and Ce^{4+}) with auto-regenerative cycles [154]. In addition, cerium oxide nanoparticles alter the main antioxidant pathway such as nuclear factor erythroid 2-related factor 2 (Nrf2) [155]. Furthermore, the interaction of nanoparticles with lipids, proteins and nucleic acids is the main factor for antioxidant properties. Table 11 provides insight into antioxidant outcomes of nanoparticles in streptozotocin-induced diabetic rats.

Apart from this, gold nanoparticles have exhibited anti-inflammatory effects that decreased production of pro-inflammatory cytokines and improved blood glucose level, liver and kidney performance causing hyperglycemic control in diabetic rats [159].

Table 11 Effect of nanoantioxidants in streptozotocin-induced diabetic rats

Nanoparticle-type	Route of administration	Outcome	Reference
Zinc oxide	Oral	Elevated levels of SOD, CAT, GPX; reduced malondialdehyde and elevated levels of glutathione in testicular tissue	[156]
Gold	Intraperitoneal injection	Elevated levels of SOD, CAT, GPX activities and reduced levels of oxidized glutathione	[157]
Cerium oxide	Intraperitoneal injection	Antioxidant enzyme activity is recovered	[158]
Liposome delivered selenium	Oral	SOD, CAT, GPX activities of the pancreas are recovered	[102]

7 Challenges and Future Prospectives

The major challenge related to diabetic treatment is to find individualized factors that result in the control of blood glucose levels [160]. For type 2 diabetes management, there is a need for control of the progressive deterioration of beta-cell function that results in loss of glycemic control. Insulin therapy and antidiabetic drug usage are efficient but not possible to avoid glucoregulatory and metabolic dysfunctions. To overcome this, targeted and combination therapies are needed such as peptide analogues and incretin-based therapy. This probably might restore the function of beta cells and stop type 2 diabetes and its complications. The efficiency of new therapies depends on the ability to relieve disturbances caused by metabolic alterations resulting in elevated insulin production and uptake of glucose by skeletal muscles [161].

The emergence of leptin therapy would be the prospect for future and nanotechnological-based therapies during diabetes treatment. Furthermore, leptin therapy via CNS-dependent mechanism in mice has improved insulin-deficient type 1 diabetes. Apart from this, novel therapies like the use of mucoadhesive microcapsules with glipizide drugs for achieving efficient targeting and controlling release of drugs are preferred [161]. Therefore, great efforts have to be made in the treatment, prevention and diagnosis of diabetes and there is no successful treatment to date. With the advent of nanotechnology, new therapies and efficient medication for diabetes treatment are not unachievable.

8 Conclusion

Diabetes mellitus and its complications are the primary consequences of death worldwide. Several types of therapeutic targets and anti-hyperglycemic drugs have been tested, and a few combination therapies have also shown better control over blood glucose levels and alleviated complications caused by diabetes. In addition to the above drugs, therapeutics have gained pace with innovation in science for a novel treatment for diabetic patients. Among these novel routes, nanotechnology-based drug delivery systems have proved greater potential with elevated bioavailability, higher efficacy, minimal dose frequency and lesser toxicity. In addition, nanoparticles synthesized from herbal extracts have demonstrated promising results as therapeutics for diabetes. Still, extensive research is needed to assess the underlying mechanism of new therapies and their effectiveness, safety and prognosis in diabetes treatment. Furthermore, it is essential to covert basic research into clinical medications for social benefits.

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Nanotechnology for Sustainable Agricultural Applications

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Abstract Engineered nanoparticles have attracted much attention due to their successful implementation in different fields such as health, industry, and the space sector. Sustainable agriculture is a continuously evolving practice of various technologies working in a sustainable and eco-friendly manner. Further, recent advancements in sustainable agriculture practices can be attributed to nanotechnologies applied for different purposes in agricultural sectors. Studies suggest that nanoparticles of various materials can induce positive or negative effects on many plant growth parameters and regulate their hormones. Plant hormones such as auxin, gibberellin, cytokinin, ethylene, and abscisic acid can be regulated through nanoparticles to maintain plant growth, especially in stressful conditions for plants. Studies also suggest that these engineered nanoparticles exert a toxic effect on soil enzyme properties such as dehydrogenase, urease, and phosphatase that may negatively affect plant growth and also degrade soil quality in the long run. Further, many nano-based technologies used for disease control and pest control have also come into the picture. In this chapter, the readers will gain deep insights into nanotechnology for plant growth and disease control with sustainable agriculture practices in mind, exploring different technologies in practice and constraints related to them.

Keywords Nanotechnology · Sustainable agriculture · Disease control · Plant growth

1 Introduction

Global population is increasing at a rapid pace. The world's present-day population is 7.7 billion, and it will increase to 9.7 billion in 2050. The United Nations report 2019 data indicates it could be highest at nearly 11 billion around 2100. Overpopulation has led to crisis of good nutritious food and agriculture land. To address the rising

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R. S. Mane et al. (eds.), *Nanomaterials for Sustainable Development*,
https://doi.org/10.1007/978-981-99-1635-1_9

demands of food for increasing population, certain measures are taken such as application of chemical fertilizers and chemical pesticides to the crop fields. Further with the advent of concerns regarding the toxic nature and adverse effects of chemicals used for agricultural applications, a shift from chemical fertilizers was promoted [1, 2]. Biofertilizers and bio-pesticides have tremendous applications with respect to the sustainability of agricultural soil maintaining its fertility as well as promoting high yields in the crops [3–5]. The major problems caused due to chemical fertilizers were more due to its uncontrolled and indiscriminate use rather than the toxic nature of the chemicals. Sustainable agriculture practice refers to the minimum use of agrochemicals for maximum increase in the production of crops [6, 7]. Nanotechnology comes to the rescue of indiscriminate chemicals use by promoting the minimal chemicals with high precision results and therefore would be sustainable in nature. Nanoparticles in the form of fertilizers can help to reduce the indiscriminate use with plant growth promotion [6, 8]. The use of nanotechnology reduces the uncertainty levels with respect to the yields of the crops which is a major factor for the indiscriminate use of the chemicals by the farmers. Nanotechnology not only enables increase in plant growth with high precision under normal conditions but also makes sure the plants growth in stress conditions with changing climates, reduced water, reduced minerals, high temperatures, and good yield even in the presence of toxic metals. In addition to the use of nanotechnology for plant growth, nanotechnology has also enabled the monitoring of the plants' growth and response, their physiological variation over time at very precise and small levels, thus accelerating the response mechanism if the need arises. The use of nanotechnology not only promotes the plant growth and meets the food demands of the increasing human population but also doesn't harm the thriving living species in the surrounding area, thus promoting the aspect of sustainability. Nanotechnology offers different solutions by a simple technique, i.e. by offering more surface area required for the action of growth and development for the plant.

2 Nanotechnology for Plant Growth and Disease Control

There have been many studies suggesting the use of nanomaterials for the promotion of plant growth and development (shown in Fig. 1). These nanomaterials bring about changes at the cellular level and hormonal level which induces changes visible in terms of their yield and productivity. In a study by Pallavi et al. [9], it was observed that silver nanoparticles increased the growth of wheat plants by increasing root nodulation at 50 ppm concentration while improvement in shoot growth parameters was observed at 75 ppm concentration. A study by Krishnaraj et al. [10] reported enhanced catalase and peroxidase activity on addition of silver nanoparticles to the plants of *Bacopa monnieri* L. which in turn enhanced plant growth and yield. Another study by Gruyer et al. [11] reported that the addition of silver nanoparticles to the plants of barley increased the root length, thereby affecting its yield parameters. Studies on effect of the gold nanoparticles done by Ferrari et al. [12] showed that

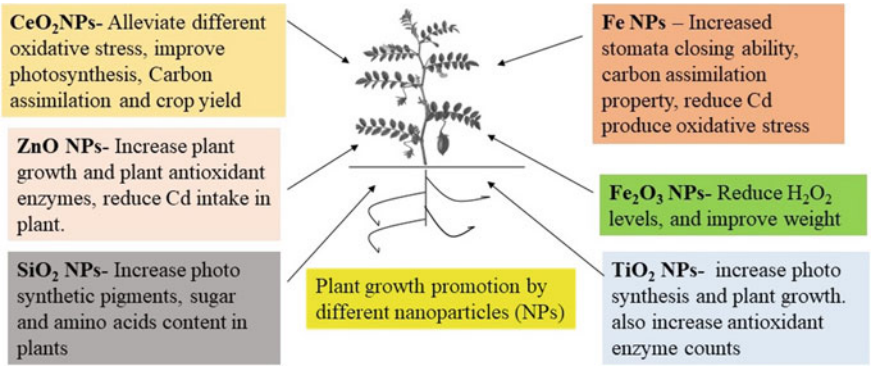

Fig. 1 Nanomaterials used for plant growth and promotion

the application of gold nanoparticles enhanced the growth of Arabidopsis plants by reducing oxidative stress elicited by immune-stimulatory PAMP flg22. Studies on zinc or zinc oxide nanoparticles by Nandhini et al. [13] on *C. americanus* reported that it helped in the inhibition of disease-forming spores which ultimately reflected in the growth yield parameters of the plants. Another study on zinc oxide nanoparticles by Keerthana et al. [14] reported that improvement in the growth and yield parameters of *Abelmoschus esculentus* plants. It also served as a great antimicrobial agent (Table 1).

Plant growth parameters are generally governed by the regulation of plant hormones. Therefore, it becomes imperative to study the effect of nanoparticles on plant hormones if they affect plant growth in any way. In studies by multiple authors [17–22] it was revealed that on application of different types of nanoparticles such as graphene oxide, zinc oxide, copper and silver nanoparticles the production of indole acetic acid (IAA) in plants greatly increased. Increase in IAA activity of plants in roots or shoots is directly associated with the increased plant yield. On the other hand, different studies on copper nanoparticles [18, 23] reported inhibition in the production of IAA in plants, thereby resulting in the decreased growth of the plants. Studies on the enhancement of gibberellins by multiple authors [24–26] suggested that, on application of various nanoparticles, levels of gibberellins could be regulated in the plants. Similarly, studies on cytokinin regulation [23, 27–30] and ethylene regulation [31–35] showed that nanoparticles of silver, gold, zinc, and copper could directly influence plant hormones by affecting its growth (Table 2).

3 Nano-Bioformulations for Agricultural Development

The worldwide increasing food demand prompts for high-yield crops production. Excessive use of chemical fertilizers and pesticides to increase the crop yield is surely not an appropriate choice for long term because they make a deleterious impression

Table 1 Effect of various nanoparticles on the plant growth promotion

Nanoparticles type	Plant used	Synthesis type	Effect	References
Silver NPs	*Triticum aestivum*, var. UP2338), *Vigna sinensis*, var. Pusa Komal, and *Brassica juncea*, var. Pusa Jai Kisan	Chemical reduction of silver nitrate by tri-sodium citrate salt	Growth promotion and increased root nodulation at 50 ppm treatment in cowpea; improved shoot parameters at 75 ppm in *Brassica*	[9]
Silver NPs	*Bacopa monnieri*(Linn.)	Treating $AgNO_3$with aqueous leaves extracts of *Acalypha indica* Linn	Enhanced peroxidase and catalase activity, simulated the stress conditions	[10]
Silver NPs	Using barley as a reference plant (e.g. radish and lettuce)	NA	Root length increased for barley, but was dramatically inhibited for lettuce	[11]
Silver NPs	*Trigonella foenum*-graecum	Chemical reduction of silver nitrate with tri-sodium citrate	Improved the growth parameters of fenugreek plant	[15]
Silver nanoparticle	*Arabidopsis*	NA	Induced bifacial effects on plant growth, effectively inhibited ethylene perception	[16]
Gold nanoparticle	*Arabidopsis*	Aqueous dispersions of citrate-stabilized AuNPs	Enhanced growth of the plants, reduced oxidative stress responses elicited by the immune-stimulatory PAMP flg22	[12]
Zinc oxide	*C. americanus*	Retentate of aqueous *E. alba*extract mixed with 80 ml of zinc sulphate	Prevention of disease, inhibition of spore germination of *S. graminicola*zoospore	[13]
Zinc oxide	*Abelmoschus esculentus*	Aqueous peel extract of *Citrus medica*	Improve the growth and yield; excellent antimicrobial potential	[14]

Table 2 Effect of nanomaterials on plant hormones

Plant hormone	Nanomaterial used	Plant tested	Effect	References
IAA	Graphene oxide	Rice	Increase IAA in root	[17]
	Zinc oxide	*Cicer arietinum*	Increased IAA in roots	[18]
	Copper and Silver	*A. muricata*	Increased activity of IAA in leaves	[19]
	Graphene oxide	*Brassica napus*L.	Modulates IAA in root growth	[20]
	Graphene oxide	*Brassica napus*L.	Regulates IAA in root growth	[21]
	Zinc oxide	*Pyrus*sp.	Increase indole-3-acetic acid and indole-3-butyric acid in roots	[22]
	Copper oxide	Cotton	Decreases in IAA in plant	[23]
	Graphene oxide	*Brassica napus*L.	Co-regulate contents of IAA, cytokinin, and ABA in root	[28]
	Silver NPs	Wheat	Increase in gibberellins and decrease in cytokinin	[36]
	Silver NPs	*Triticum aestivum*L.	Increase in IAA	[37]
	Silver NPs	*Arabidopsis thaliana*	Regulate IAA and ethylene signalling pathway	[38]
	Copper oxide	Cotton	Inhibit IAA and ABA concentrations	[18]
Abscisic acid	Graphene oxide	*Brassica napus*L.	Modulates ABA and IAA in root growth	[20]
	Graphene oxide	*Brassica napus*L.	Regulates IAA/ABA in root growth	[21]
	Graphene oxide	*Brassica napus*L.	Co-regulate contents of IAA, cytokinin, and ABA in root	[28]
	Silver NPs	*Triticum aestivum*L.	Stimulating indole-3-butyric acid (IBA), 1-naphthalene acetic acid (NAA), 6-benzylaminopurine (BAP) contents and reducing abscisic acid (ABA) content	[37]

(continued)

Table 2 (continued)

Plant hormone	Nanomaterial used	Plant tested	Effect	References
	Copper oxide	Cotton	Inhibit indole-3-acetic acid (IAA) and abscisic acid (ABA) concentrations	[18]
Cytokinin	Silver NPs	*Capsicum annuum*L.	Increased the level of Cytokinin in plant	[27]
	Zinc oxide	*Arabidopsis thaliana*	Suppressed biosynthesis of the cytokinins and auxins in shoot apical meristems (apices)	[39]
	Silver NPs	*Capsicum annuum*	Increased the level of Cytokinin in plant	[23]
	Graphene oxide and IAA co-treatment	*Brassica napus*L.	Co-regulate contents of IAA, cytokinin, and ABA in root	[28]
	Zinc oxide	*Arabidopsis Thaliana*	Induced the expression of ethylene and reduced the expression of cytokinin response genes	[29]
	Chitosan microparticles	Tomato	Participation of cytokinin and auxin signalling pathways	[30]
	Titanium dioxide	Barley (*Hordeum vulgare*L.)	Play a role similar to plant hormones such as cytokinin and gyberline	[26]
	Graphene oxide	Apple	Affected cytokinin by regulating the expression levels of cytokinin-related genes	[40]
Gibberellins	Silver and zinc oxide	Maize	Synthesis of plant hormones, such as gibberellins	[24]
	Polyglutamic acid/chitosan	*Phaseolus vulgaris*	Regulates gibberellic acid in seed	[25]
	Silver NPs and Silver ions	Wheat	Increase in gibberellin content and the accompanying decrease in cytokinins	[36]

(continued)

Table 2 (continued)

Plant hormone	Nanomaterial used	Plant tested	Effect	References
	Titanium dioxide	*Hordeum vulgare*L.	Play a role similar to plant hormones such as cytokinin and gibberellins	[26]
Ethylene	Zinc oxide	*Arabidopsis*	Ethylene signalling and biosynthesis	[31]
	Silver NPs	Plant tissue culture	Inhibitory effects of plant senescence phytohormone ethylene	[32]
	Silver NPs	*Swertia chirata*	Ethylene interceptions	[33]
	Potassium permanganate-coated zeolite	Peach and Nectarine	Inhibitory effect of ethylene gas	[34]
	Gold NPs	*Brassica juncea*	Ethylene interceptions	[35]
	Silver NPs	*Arabidopsis thaliana*	Inhibitors of ethylene	[16]
	Silver NPs and silver ions	*Arabidopsis thaliana*	Regulate auxin and ethylene signalling pathway	[38]

on the soil micro-flora and decline soil fertility, multi-nutrient deficiencies, shrinking of agriculture land. Synthetic fertilizers are not only costly but also lead to soil, air and water pollution [41, 42]. Nowadays, attention to nano-bioformulations an innovative approach of using green fertilizers, known as biofertilizer has increased due to their ability of N_2-fixation, phosphate solubilization, production of plant growth hormones, biocontrolling properties and sustenance of soil quality. Also increase of plant height, branch numbers and fresh and dry weight of plant in comparison with chemical fertilizers application alone has been observed [43]. Nanofertilizers are the important assets of nanotechnology, and nanofertilizers are the nanomaterials ranging from 1 to 100 nm at list in one dimension that should be classified as a nanomaterials size that supplies at least one or more types of nutrients to the plants. Different types of nanotechnological materials such as carbon nanotubes, zinc, iron, silicon, copper, manganese, molybdenum their oxides and nano-formulations are commercially used in agricultural inputs like urea, phosphorus and sulphur. Nanomaterials demonstrate a high surface area, absorption capacity and controlled release kinetics to the active sites with a smooth delivery system [44]. The NPs synthesized by novel methods are basically environment-friendly; i.e. no toxic chemicals are used during synthesis. Nano-bioformulation has come out as a tool in the agriculture sector to achieve novel approach in sustainable agriculture goal, and it has gained a rapid momentum in the modern agriculture system and is expected to become a main thrust in near

future by offering potential applications. Nano-bioformulation of biofertilizers has emerged as one of the most promising techniques to achieve sustainable agriculture goal. Nano-bioformulation of biofertilizer NPs is obtained from both organic and inorganic substances that interact with micro-organisms and increase their survival by providing protection from biotic and abiotic factors [45]. Nanobiotechnological products obtained through nanomaterials together with plant growth-promoting rhizobacteria (PGPR) will be more advantageous than conventional methods (such as direct application of biofertilizer).

Plant growth-promoting bacteria such as *Paenibacillus elgii, Pseudomonas putida, Pseudomonas fluoresce*ns, and *Bacillus subtilis*, treated with silver, aluminium, and gold NPs have been shown to support plant growth and increase pathogen resistance [46]. Green nanosilver bioformulation of *Trichoderma* (Fu21) an efficient and eco-friendly bio-efficacy show and biocontroling activity against stem rot (*Sclerotium rolfsii*) in groundnut (Arachis hypogaea L.) [47]. Iron, manganese, phosphorus, calcium, magnesium, nano-zeolite, molybdenum, titanium, copper, zinc, carbonaceous materials, etc., are envisaged to *Bacillus* sp, *Rhizobium* sp and *Pseudomonas* sp. as bioagents with nanoparticle formulations for enhancing in yield quality and decreasing environmental deleterious effects for the plants [48]. The effect of silicon nanoparticle-mediated seed priming on *Pseudomonas* species enhanced growth, physiology, antioxidant metabolism, plant biomass indices, the relative water content of leaves, photosynthetic pigment values, and essential oil yield. All major components in *Melissa officinalis* L. seed priming, pre-sowing, and seedling inoculation with bio-elicitor improve plant growth and phytochemical constituents [49] (Table 3).

Nano-biofertilizer contains micronutrients and macronutrients together with plant growth for enriching micro-organisms (*Azotobacter, Azospirihum, Azolla, Beijerinckia, Bacillus, Cyanobacteria, Pseudomonas,* and *Rhizobium*) that assist to fix atmospheric nitrogen, phosphate solubilizing, restoring soil nutrient richness, and capable to transform and mobilize nutrients in the rhizosphere from complex organic matter into simple compounds and shown greater potential in plant growth in different agricultural plants [58–60]. The *Bacillus* species such as *B. stearothermophilus, B. laterosporus, B. circulans, B. licheniformis, B. amyloliquefaciens, B. pabuli, B. megaterium, B. thuringiensis,* and *B. subtilis* are known to secrete 8% of the total secondary metabolites with antagonistic properties [7].

Biodegradable nano-biofertilizer in agriculture has been preferred as an emerging alternative to conventional farming due to some benefits such as less nutrient loss and controlled release of nutrients to the plant. Previous research shows that iron oxide NPs may have been a possible source of iron for soybean for reducing chlorotic symptoms of iron deficiency [61]. Oil-based nanoemulsion formulation have a small size, large surface area, durability, increased effectiveness, high solubility, versatility with *Beauveria bassiana* conidia as biopesticide can be used as a biopesticide in agricultural sector and effective, eco-friendly, long-lasting management of plant diseases [62]. The combination of silver nanoparticle and PGPR increases water uptake and nutrient from salinity condition, and *Pseudomonas moraviensis* is most effective to enhance total chlorophyll and carotenoids contents, sugar, protein,

Table 3 Nano-bioformulations for enhancement of plant growth parameters

Nanoparticles	Micro-organisms	Function	References
Ag, ZnONPs	R. *leguminosarum*(MTCC 10096)	Known symbiotic nitrogen fixer, biofilm former	[50]
	Klebsiella *pneumoniae*clsxc_AZ2 (MH884598)	Adherent biofilm former, free living nitrogen fixer, phosphate solubilizer	
	*Bacillus*sp. clsxc_NPS (MH884601)	Phosphate solubilizer, air–liquid interface biofilm former, amylase producer	
Gold NPs	*Pseudomonas fluorescens*, *Bacillus subtilis*, *Paenibacillus elgii*, and *Pseudomonas putida*	Significant increase in activity of *P. fluorescens, P. elgii*, and *B. subtilis*	[46]
Nanogypsum	*Pseudomonas taiwanensis*BCRC 17751 (MK106029)	Improving the structure and function of soil and plant health	[51]
ZnO, MnO_2, and MgO	Paenibacillus *polymyxa*strain Sx3	Combat the antibiotic resistance of Xanthomonas oryzae pv. oryzae (Xoo)	[52]
ZnO	*Bacillus cereus*RNT6	ZnONPs could be used as nano-pesticides against rice panicle blight	[53]
Titanium dioxide	*Bacillus thuringiensis AZP2, Paenibacilluspolymyxa* A26, Paenibacillus *polymyxa* A26Δsfp, *Alcaligenes faecalis*, *Fusarium culmorum*	Positive effect against abiotic stress (drought, salt) and biotic stress (*Fusarium culmorum)*	[54]
Zn–Fe oxide	*Azotobacter chrocoocum*, *Azospirillum lipoferum*, *Pseudomonas putida*	Improved wheat yield under salinity condition	[55]
TiO_2	*Bacillus amyloliquefaciens*UCMB5113	Biocontrolling against fungal pathogen *Alternaria brassicae*in *Brassica napus* plant and promotes plant growth	[56]
SiO_2	*Pseudomonas stutzeri*,*Mesorhizobium* spp.	Increased shoot and root dry weight of land cress (*Barbareaverna*) plant and increased nitrogen and phosphate in the soil	[57]

proline, flavonoids, and phenolic content in onion (*Allium cepa* L.) plants [63]. Combination of nanogypsum and *Pseudomonas taiwanensis* in maize (*Zea mays*) helps in improving the structure and function of soil which affects the plant health (enhance chlorophyll, total phenolic content, total sugar, protein content) without causing any toxic effect and increase in total bacterial counts, nitrogen, phosphorus, potassium (NPK) solubilizing bacterial population and soil enzyme activities (alkaline phosphatase, β-glucosidase, dehydrogenase, arylesterase, fluorescein diacetate, and amylase [51]. The concentration of NPs in the soil may have neutral, negative, or positive effects and interactions with NPs mycorrhizas/rhizobia. The link to viability and functionality of the symbioses have been explored including the germination of mycorrhizal fungal spores, hyphal growth and function, multiplication of bacteroides in rhizobial nodules, and nutritional symbiotic benefits [64]. The different types of carrier-substrates used in bioformulation include plant waste materials (sawdust), inert materials (Vermiculite), soil (Peat), and plain lyophilized microbial culture (bioformulation of *Rhizobium* and *Azospirillum*). The NPs' of carrier substrate-based bioformulations has been beneficial to soil in increasing its nutrient uptake and enhancing growth of plants. Therefore, the use of NPs with different application in field of agriculture led to their efficacy and toxicity assay as well so that the NPs do not harm the environment. Nano-bioformulation is advantageous as it delivers the selective potential micro-organism at site of delivery in accurate concentration that avoids the suppression of cell numbers by indigenous population [65].

4 Inhibitory and Toxic Effect of NPs

There have been a lot of applications of NPs for enhancing the growth and development of plants, either in the form of direct application or in the form of bioformulations mixed with microbes. However, the less studies part of the nanoparticle on plants is their inhibitory effects on growth and development (shown in Table 4). Water-soluble fullerenes exerted an inhibitory effect on the growth of the plants by disrupting auxin distribution, abnormal hormone distribution and cell division, and abnormal microtubule distribution and mitochondrial activity [66]. In another study by Salama et al. [67], it was found that silver NPs possessed a positive effect at lower concentrations but inhibited growth of the plants at concentration higher than 60 ppm. The possible reason for this inhibitory effect could be the accumulation of silver NPs in the roots of the plants. Another study by Lin and Xang [68] concluded that higher concentrations of Zn or ZnONPs totally stopped the elongation of root in plants species tested. Furthermore, it was found that the inhibition occurred at the seed incubation process stage. The study by Nekrasova et al. [69] revealed that the copper ions and copper oxide NPs suppressed photosynthesis at a concentration of 0.5 mg/l and 1.0 mg/l, respectively. At higher concentration of NPs, catalase and peroxidase activities were also decreased. Among copper ions and NPs former inhibited the enzyme activity more strongly. Inhibitory effect on photosynthesis also followed the same trend, stronger in copper ions than in nanoparticle which could

be credited to the disturbance in the pigment complex or due to RuBP carboxylase inactivation. Germination percentage reduced on exposure to silver and copper NPs and severe reduction in root and shoot length of plants observed when exposed to copper NPs [70]. Another study by Wang et al. [71] demonstrated the inhibitory effect of ZnONPs on the root and shoot growth development of tomato plants. Their enzymatic activity had also been disrupted and also decreased the content of chlorophyll a and b in the plants. In conclusion, the effect of nanomaterials or NPs on the plant is highly varied and even small variations in its concentrations can lead to the developmental activity being inhibited. In some studies, smaller concentrations have inhibitory effect but higher concentration could enhance the growth and production of plants. Therefore, it becomes highly important to take care of the concentration of NPs being applied to plants.

5 Critical Literature Analysis

The literature analysis was done only in the context of keywords to extract the information out of studies done on nanotechnology (Figs. 3 and 4) for sustainable agriculture. All the type of bibliographic analysis has been excluded as that would have been beyond the scope of this chapter. The literature analysis was done using literature extraction from web of science database and with the topic, "*nanotechnology for sustainable agriculture*". There were no limits with regard to time span or the type of articles set for analysis. It was found that most of the research is focussed upon silver NPs followed by ZnO and gold NPs, as evident from Fig. 2 (co-occurrence network map of the keyword plus). In the same map, it was observed that the literature keywords are basically categorized into three different domains, one in which nanotechnology aspects related to NPs have been discussed, second in which in-vitro studies ranging from drug delivery, encapsulation, controlled release and antifungal and antimicrobial activity keywords have been highlighted. Third domain is perhaps the field aspect in which toxicity, growth are highlighted. The thematic evolution map suggests the phases in which the study on NPs and nanotechnology has emerged with progress in time.

6 Future Perspectives and Challenges

The use of nanomaterial for the promotion of growth in plants has long been studied at the experimental level but its implementation at the farm level still remains in infancy. The situation arises due to the limited knowledge, and alterations in the effect even at minute concentrations of nanomaterials. Therefore, more studies are required to study their effect on plants along with their inhabiting micro-flora in the region. With expanding knowledge and their huge potential in agriculture, nanomaterials could play a pivotal role in the enhancement of plant growth promotion sustainably.

Table 4 Inhibitory effect of various NPs on different plants

Nanoparticle	Plant	Method used	Effect	References
Water-soluble fullerenes	*Arabidopsis thaliana*	Transgenic seedling lines expressing fluorescent makers	Disrupted auxin distribution, aberrant spindle, abnormal microtubule arrangement	[71]
Silver NPs	*Phaseolus vulgaris*L., *Zea mays* L.	Plant application	At a concentration > 60 ppm the growth of the plants was inhibited	[67]
Multi-walled carbon nanotubes, aluminium, alumina, zinc, and zinc oxide	Radish, rape, rye-grass, lettuce, corn, and cucumber	Seed application	Suspensions of 2000 mg/L Zn and ZnO solution terminated root elongation of the plants	[68]
Copper (II) ions and copper oxide NPs	Elodea densa Planch	Plant treatment	At high concentration of NPs photosynthetic activity was inhibited and the inhibition increased with increasing concentration	[69]
Silver, copper, and iron NPs	Wheat (*Triticum aestivum*)	Seed treatment	Copper inhibited while iron stimulated wheat germination and growth	[70]
Zinc oxide NPs	Tomato plants *Solanum lycopersicum*L.	Seedling (3 weeks)	Significantly inhibited tomato root and shoot growth, decreased chlorophylls **a**and **b**, and reduced photosynthetic efficiency	[71]
TiO_2NPs	*Triticum aestivum*L.	Seed treatment	At suitable concentrations of NPs seed germination was increased but very low concentrations of NPs actually decreased the seed germination	[72]
Aluminium oxide, silicon dioxide, magnetite, and zinc oxide	*Arabidopsis thaliana*	Plant treatment	Direct exposure to NPs causes phytotoxicity in plants	[73]
Aluminium oxide NPs	*Nicotina tabacum*L. cv. Bright Yellow-2 suspension-cultured cells (BY-2)	NA	Aluminium oxide NPs induce programmed cell death in plant cells	[74]

(continued)

Table 4 (continued)

Nanoparticle	Plant	Method used	Effect	References
Ceria NPs	*Lactuca*plants	Plant treatment	CeO_2NPs were toxic to three kinds of Lactuca plants and their toxicity varied	[75]
ZnO NPs	*Arabidopsis thaliana*Columbia wild-type, the ROS-deficient mutants respiratory burst oxidase homologue D (rbohD) and rbohF	Seed treatment	ZnO and Zn^{2+}inhibited primary root growth; ZnO strongly inhibited elongation zones, whereas Zn^{2+} had a stronger toxic effect on meristem cells	[76]

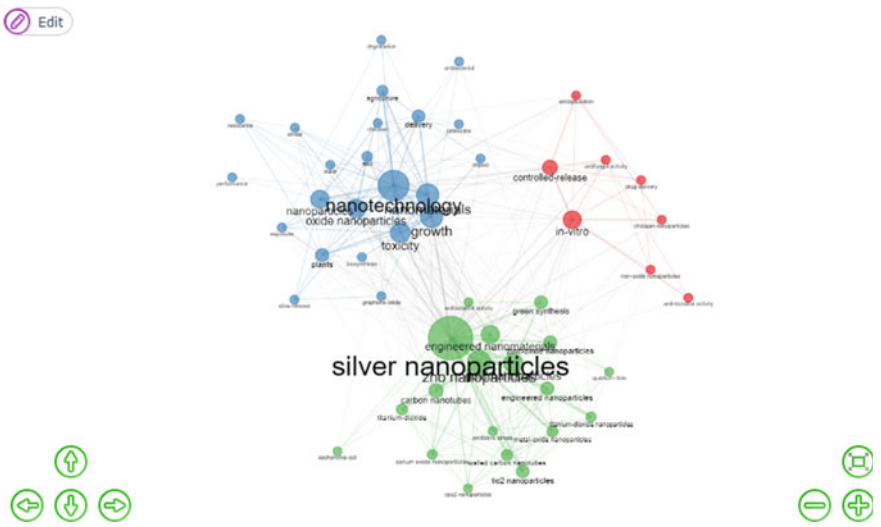

Fig. 2 Co-occurrence network map of the keyword plus

7 Conclusions

NPs of metals and metal oxides have long been used in the treatment of diseases and delivering effects in humans with high precision due to their small size. The time has come to use nanotechnology in a very efficient manner for the promotion of plant growth as well. Various studies are being carried out to assess the positive effects of the nanomaterials on plant growth. There are also few studies showing the toxic effect of nanomaterials on plants if the slight changes in their concentration occur. Various metal NPs such as Ti, Ag, and Au are showing positive effects on plant growth promotion, while Cu has relatively proven to be toxic. Other nanomaterials such as

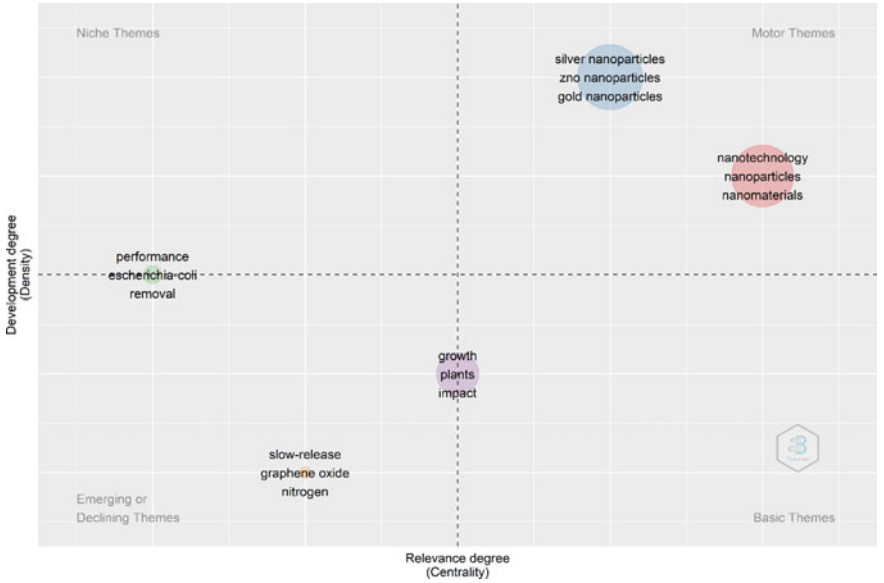

Fig. 3 Co-occurrence development degree of keyword plus

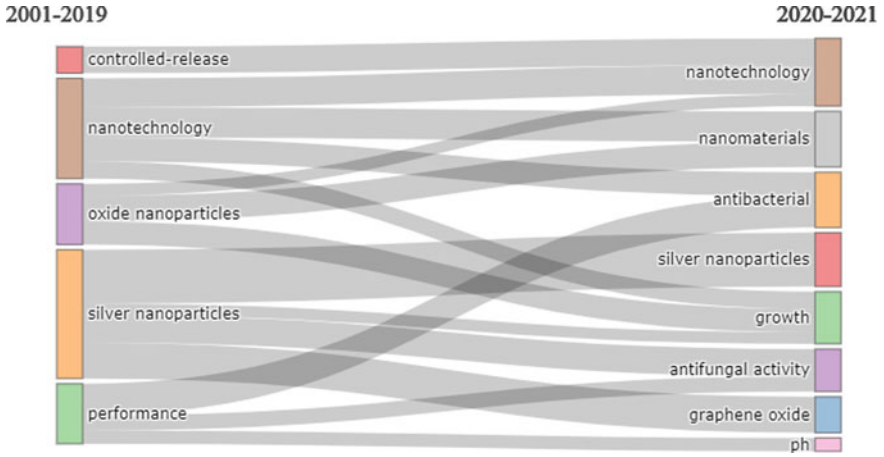

Fig. 4 Thematic evolution map of the keywords analysed during literature survey

graphene oxide and fullerene have also shown positive effects for the promotion of plant growth and if precise standardizations are carried out, nanomaterials could prove to be phenomenal. Therefore, at the farm level precise standardization of nanomaterials is required for mass-scale usability and acceptance among common people.

Acknowledgements Saurabh Singh is highly grateful to the University Grants Commission (UGC Ref No.3819)/(NET-JULY-2018) for providing the Junior Research Fellowship and Senior Research Fellowship, and Banaras Hindu University, IoE for providing Teach for BHU fellowship to support the research work.

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Nanotechnology for Bioenergy and Biofuel Production

Amruta P. Kanakdande and Rajaram S. Mane

Abstract Biofuel is one of the best alternatives for petroleum-derived fuels globally, especially in the current scenario, where fossil fuels are day-by-day depleting. Biofuels are viable source of renewable energy in contrast to the finite nature, geopolitical instability, and deleterious global effects of fossil fuel energy. The use of nanotechnology in the field of biofuel and bioenergy is emerging as a novel and efficient way to produce and enhance the eco-friendly production of renewable biofuels. Several methods have recently been proposed and adopted to prepare metallic, magnetic, and metal oxide nanoparticles (NPs) for enhancing biofuel production yield. The unique properties of NPs, such as easy design, high chemical stability, greater surface area-to-volume ratio, catalytic activity, and reusability, have made them as effective biofuel additives. In this context, current chapter explores the use of nanomaterials for biofuel production application. In addition to this, various types of nanocatalysts and their comprehensive applications in the production of biofuels followed significance have also been briefed.

Keywords Bioenergy · Biofuel · Nanoparticles · Nanocatalyst

1 Introduction

Environmental impact of conventional fossil fuel has pushed researchers to explore substitute fuel which addresses the concern of cost, environmental issues like global warming, and security [1]. In this context, nanotechnology plays a crucial role in the development of sustainable bioenergy and biofuel production. Different nanomaterials like metal nanoparticles, nanofibers, nanotubes, and nanosheets are being

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R. S. Mane et al. (eds.), *Nanomaterials for Sustainable Development*,
https://doi.org/10.1007/978-981-99-1635-1_10

reported to have their direct or indirect applications in the production of biofuels such as bioethanol and biodiesel. Basically, these biofuels are eco-friendly, renewable energy resources due to which they have gained special attention as an alternative energy source [2]. The core principle to explore nanotechnology in biofuel industry provides scientific (clean, green, and catalytic chemistry) and engineering solutions together in the quest of eco-friendly energy sources [3]. Also, the advances in the nanoscaffolds design (nanomaterials support) for immobilizing bioenergy-producing enzymes and the recent trends in biomass processing (untreated/treated agriculture, municipal and food waste, grasses, algal, etc., using advanced nanobiocatalysts for biofuel production) are useful essence of nanotechnology toward bioenergy sector. Also, the scale-up study of bioenergy production using nanomaterials/nanoparticles (NPs) immobilized enzymes and biofuel harvesting using nanomaterials; in this approach, nanotechnology contributed toward bioenergy sector [4]. Nanotechnology offers a significant deal of interest for the optimization of biodiesel production using nanomaterial-based catalysts for efficient, durable, economic, and stable nanocatalysts for attaining the higher production yield and quality of biodiesel. Various metal oxide nanocatalysts such as titanium dioxide (TiO_2) [5], calcium oxide (CaO_2) [6], magnesium oxide (MgO_2) [7], and strontium oxide (SrO) [8] have been used for high catalytic performance followed biodiesel production. Scientists and engineers are continuously researching to improve the various components of biodiesel including biomass/feedstock pretreatments, process optimization parameters, reactor designs, product quality and yields, capital cost, public acceptance, and market availability [9]. One of the greatest advantages of using nanomaterials for biofuel is their high surface area and unique characteristics like high degree of crystallinity, catalytic activity, stability, adsorption capacity, durability, and efficient storage which could collectively help to optimize the overall system. Use of nanomaterial's of high potential for recovery, reusability, and recycling ability [10]. The combination of these unique features of nanomaterials has proven to be the efficient, economical, and mature which are still mostly at laboratory and pilot scales. The conventional systems should be replaced on developing them at commercial scale [11]. Biofuel generation from multiple approaches such as physical, biological (includes microbial and enzymatic), chemical, and biochemical catalysis with the flavor of nanotechnology from multiple feedstocks is the key factor for biofuel production. A suitable conversion technology for lignocellulosic biomass *via* lignin valorization can be the key for complete utilization of lignocellulosic waste.

Cellulose and hemicellulose mainly consist of monomeric sugar units, and after proper pre-treatment, lignocellulosic biomass sugar components via further saccharification are converted into suitable biofuel [12]. However, the lignin component consists of phenyl propane unit, which is more recalcitrant than the cellulose and hemicellulose. During kraft pulping process lignin is utilized for the co-power generation which can be separated and suitably valorized into useful precursors for biofuel generation. The optimization process for biofuel production is normally done by understanding the whole process. Even biofuels productions have a direct impact on carbon sink; therefore, biofuels produced from oil-based fuels have a better choice as compared to greenhouse gas emissions into the environment critics of

biofuels, which ultimately depends on the route of production. Therefore, majority of the governments of the various countries are taking initiatives to establish several biofuel industries by generating and providing funds for research and development along with mandating laws of Environmental Protection Agency (EPA) for specific percentage of blending of biofuel with conventional fuel. Renewable Fuel Standard (RFS) provides harness power of biofuels and infrastructure, and high production of biofuels must be widely available for customers with the competitive price of conventional biofuel [13].

2 Classification of Biofuels

Biofuel is broadly classified by the raw materials or sources used for its production. Basically, biofuel is classified into two types, i.e., primary and secondary. Primary biofuels are derived from plants, animals waste, forests, and crop residues while secondary biofuels are directly synthesized by using microorganisms [14]. Another basis for its classification is origin of raw material; biofuels are classified into first-generation (1G), second-generation (2G), third-generation (3G), and fourth-generation (4G) [15] (Fig. 1). In the first-generation biofuel, sugar, starch, vegetable oils, and fats are converted into bio-alcohol from ($n = 1$–4) fatty acid methyl esters (FAME). Second-generation biofuel production depends on the carbon negative in terms of the carbon dioxide concentration in the environment, which majorly depends on the lignocellulosic biomass (plant material) [16]. The third and fourth generations of the biofuel utilize the algae and the blue-green algae (BGA) machinery for converting lipid into biofuel. Basically, in third-generation biofuel, algae is directly used for the production of the biofuel, where in the fourth generation, metabolic engineered algae from the oxygenic photosynthetic microorganism creates artificial carbon reservoir [17].

Furthermore, they are known as chemically synthesized biofuels and biologically synthesized biofuels. In chemical synthesis, in addition to catalyst various process parameters like pH, temperature, and pressure are playing significant role in process control. Due to more specific product formation rate and low cost for separation catalysts are preferred over the various physical processes. In biological methods, with the help of bacteria, halophilic archaea, fungi, and algae the complex lignocellulosic biomass is treated microbially. Moreover, other than this, several biological processes include various kinds of biocatalysts, i.e., enzymes for the production of the biofuels (Fig. 2).

These enzymes include cellulases, xylanases, and lignolytic enzymes such as lignin peroxidase (LiP), manganese peroxidase (MnP), laccase, lytic polysaccharide monooxygenase (LPMO), multicopper oxidases, cellobiose dehydrogenase (CBDH), and lipases. To date, all the biological processes demand a high production cost than the chemical process. The cost-effectiveness of the biological process can only be possible to reduce by understanding the microbial pathways, enzymatic reduction, and substrate utilization strategy. However, new mutated strains (modified

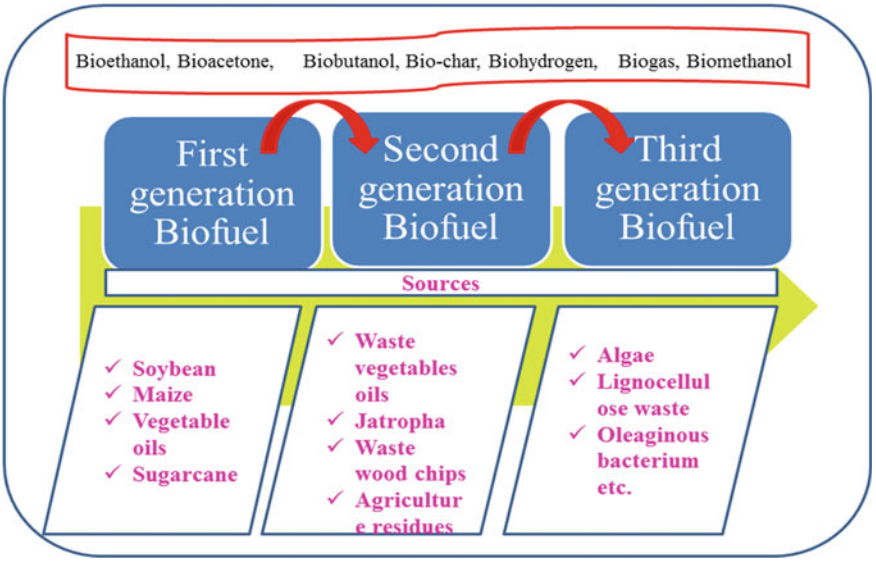

Fig. 1 Types and sources of biofuels

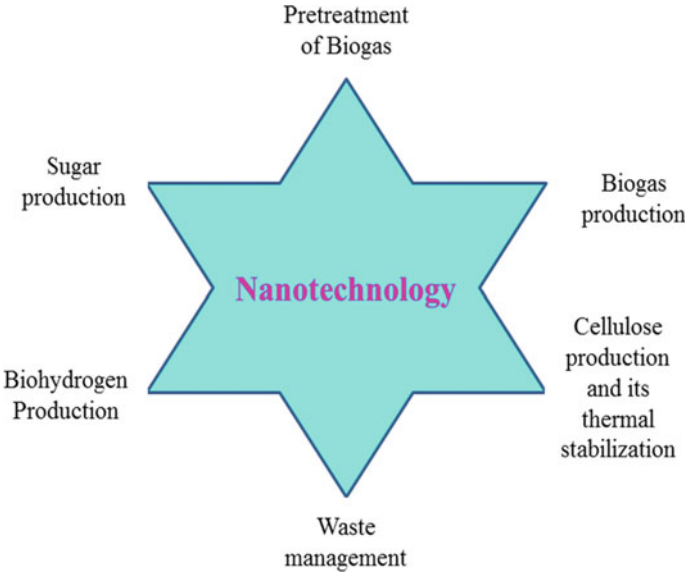

Fig. 2 Applications of nanotechnology in biofuel

for special character) have shown various promises to overcome all the barriers. The nanostructure offers large surface area for high enzyme loading, higher enzymatic stability, and possible chances of enzyme reusability, which might reduce the operational cost for large-scale biofuel production plants [18]. The techniques developed for enzymes immobilization using nanotechnology include nano-encapsulation, self-entrapment with silaffin, and adsorption. NPs have also been used for extracting the oils from algae without harming the cells. More specifically, for algal fuel production, nanomaterials like silica, metal oxide, single-walled carbon nanotubes, and nano-clay have been applied in various stages of lipid accumulation, extraction, and transesterification reaction [19]. Use of these techniques could reduce the production cost of algae biofuel plants at commercial scale. Another application of nanoparticle includes fuel additives to encourage blending performance of fuel which is another growing application of nanotechnology. The utilization of NPs like alumina and hollow carbon nanotubes showed enhanced combustion characteristics of biodiesel-operated engines with less harmful emissions [20]. In the anaerobic digestion, the employment of nano-iron oxide, zero-valence iron, nano-fly ash, nano-bottom ash, and bioactive nano-metal oxides has increased the performance of methane production [21].

3 Nanotechnology for Producing Biofuel

3.1 Nanoparticles in Biofuel Production

The NPs possess a large surface area and super-magnetic properties under the applied field which makes ease for the separation from biofuel cell and helps in their cycling of enzymes. Several NPs act as a supporting system for the nanocatalyst to apply for biofuel production. For example, magnetic NPs and carbon nanotubes (CNTs) act as a supporting system for enzymes. Other than these, metals, metal oxides, heterogeneous catalysts, acid-functionalized particles, etc., are also used. A range of nanomaterials like NPs, nanotubes, and nanosheets of carbon-based nanocatalysts like carbon nanotubes [22], carbon nanofibers [23], graphene oxide [24], and biochar [25] hold great potential for biodiesel production from a wide range of feedstocks, especially from non-food ones. These nanocatalysts are majorly used in the transesterification reactions. The transesterification reaction is used to reduce viscosity of oil and to produce the best quality biodiesel. Mainly two types of transesterification process are there: (a) with catalyst and (b) without catalyst. The biodiesel conversion rate and yield improve with the consumption of catalysts [26, 27]. Utilization of nanomaterials like nano-MgO, potassium bitartrate ($KC_4H_5O_6$), and lithium ion impregnated with calcium oxide and nanocrystalline calcium oxides were reported previously to produce biodiesel from various feedstocks [28].

3.2 Carbon Nanotubes

CNTs are allotropes of carbon formed by rolling up sheets of graphene to a cylindrical shape. Due to their potential in carrying redox reactions and electron transfer kinetics, NCTs are primarily used in the fabrication of biosensors and microbial fuel cells [29]. The CNTs are of two types, multi-walled carbon nanotubes (MWCNTs) are having multiple layers of graphene, whereas single-walled carbon nanotubes (SWCNTs) are consisting of a single atomic layer of carbon atoms [30–32]. These CNTs demonstrate application in a diesel engine when ethanol was blended with fuel [33, 34]. Moreover, ethanol has been employed as a carbon source to obtain high-quality CNTs by using a chemical vapor deposition (CVD) in the past [35, 36]. Also, even in the flame process using a burner, with the supply of ethanol as feed gas CNTs were also synthesized [37]. During the anaerobic digestion process, employment of CNTs resulted in a reduction of start-up period and enhanced performance as compared to other activated carbon (AC) particles. In a similar kind of study, the immobilization of *Enterobacter aerogenes* over functionalized MWCNT-COOH was used to enhance the hydrogen production rate (2.72 L/L/h), hydrogen yield (2.2 mol/mol glucose), and glucose degradation efficiency (96.20%) in comparison with the free cells [38]. Furthermore, employment of CNTs in biofuel generation increases the overall enzyme concentration and few properties of CNTs like porosity and conductivity due to which they are important for enzyme immobilization process [39].

3.3 Acid–Functionalized Nanoparticles

The core–shell structured heteropoly acid (HPA)-functionalized zeolitic imidazolate frameworks-8 (ZIF-8) NPs were highly porous and heterogeneous catalysts for synthesis of biodiesel. Bifunctional heterogeneous catalyst was synthesized by using HPA functionalization on ZIF-8 nanoparticles. The HPA-functionalized ZIF-8 catalyst showed a high reaction efficiency of the benzyl alcohol oxidation process, suggesting as an effective catalyst for wide range of applications. These bifunctional core–shell materials are environmentally friendly heterogeneous catalysts in transesterification of rapeseed oil with methanol to produce a high-quality biodiesel [40]. A robust, magnetically recoverable Fe_3O_4@SiO_2-SO_3H core@shell nanoparticulate acid catalyst as a heterogeneous catalyst for the process of transesterification and esterification of triglycerides and free fatty acids in *Jatropha curcas* oil (JCO) to a FAME mixture has successfully been synthesized by a stepwise co-precipitation, coating, and functionalization process. Thus as-obtained core–shell catalyst showed 98 ± 1% conversion yield under optimized reaction conditions such as 9:1 methanol:oil molar ratio and 8%wt. catalyst loading at a temperature of 80 °C with the time duration of 3.5 h. The transesterification of JCO to FAME using the present catalyst was benefitted from very low activation energy 37.0 kJ mol^{-1}. The

solid acid catalyst can exhibit excellent chemical and thermal stability and also reusability based on easy separation from the reaction mixture due to its inherently magnetic nature [41].

3.4 Magnetic Nanoparticles

Characteristics of magnetic NPs include (a) high surface-area-to-volume ratio, (b) quantum size effect, and (c) ability to carry other compounds, such as drugs due to their small sizes. An additional advantage of magnetic NPs over others is that they can be utilized as a highly useful catalyst, making immobilized particles which are easily recoverable by applying suitable magnetic field without exerting any toxic effect [42, 43]. Enzymes like cellulases and lipases are frequently used in the biofuel industries [44, 45]. Many studies on magnetic NPs have mentioned their role in immobilization of enzymes for biofuel generation. Enzymes can be reused after immobilizing them to a support matrix coated with certain nanomaterials. This process is suitable for hydrolysis of lignocellulosic biomass [46]. The super-magnetic properties of magnetic NPs are useful in separation of immobilized enzymes which in fact increases their reusability [47]. Many such attempts have been made to immobilize cellulose on magnetic NPs for hydrolysis of biomass [48]. Due to biodegradable nature, enzymes are widely used for different biotechnological applications. However, their instability, high cost of operability, hard recovery, and non-reusable ability have made them the most critical and challenging which can be solved by the immobilization of enzymes in nanostructured materials as nanobiocatalysts. It has been reported that the surface coating or modification of magnetic NPs with a variety of complex materials, such as polymers, silica, metallic-organic frameworks (MOFs), and carbon-based materials, might allow to improve few properties by providing potential industrial exploitability [49].

Methyl-functionalized silica and methyl-functionalized cobalt ferrite–silica ($CoFe_2O_4@SiO_2–CH_3$) NPs were used to improve syngas–water mass transfer. Of these, $CoFe_2O_4@SiO_2–CH_3$ NPs showed a better enhancement of syngas mass transfer. These NPs were recovered by using a magnet which were reused for five times to evaluate reusability [50]. Under optimum conditions, biodiesel production from crude Jatropha was measured at 94%, but after four cycles, it was decreased to 85% and then, due to the inactivation of the NPs, gradually decreased further. The reason behind the inactivation of NPs is that the deposition of components of the reaction medium could block the pores after the fourth, seventh, and ninth cycles. The surface area was also reduced to 252 m^2/g, which was less than earlier [51]. In biodiesel production, magnetic nano-ferrites doped with calcium have a significant effect, enhancing production yield by almost 85% when used soybean cooking oils. It was demonstrated that employing sugarcane leaves and MnO_2 nanoparticles increased bioethanol production [52]. Research work has demonstrated the potential of implementing MNPs to hydrolyze the microalgae cell wall by immobilizing the cellulose enzyme on MNPs accompanied by lipid extraction [53].

In the absence of a magnetic field, MNPs get dispersed in the same manner as any other nanoparticles. MNPs are not only applicable as an enzyme immobilization support, as they can also be coated or used for attachment of other catalytically active nanomaterials, making them useful nanocatalysts for various applications. These nanocatalysts are promisingly used for hydrogenation, photo-oxidation, inductive heating by application of high-frequency magnetic fields [54, 55].

In addition to zero-valent nanoparticles, iron oxide nanoparticles, such as Fe_2O_3 and Fe_3O_4, have been explored for the bio-hydrogen production using glucose, wastewater, and sugarcane bagasse [56–58]. Nano-zero-valent iron (nZVI) and Fe_2O_3 were used for the enhancement of biogas production using waste-activated sludge [59]. The addition of 10 mg/g of total suspended solids (TSS) nZVI and 100 mg/g TSS Fe_2O_3 NPs increased the methane production by 120 and 117% of control, suggesting the addition of a low concentration of NPs can promote microbial growth as well as activities of key enzymes for higher biogas production.

3.5 Metallic Nanoparticles

Metallic NPs have so far not been explored widely. Various studies have to be performed to evaluate their performance toward biofuel production. Metallic NPs are known for their higher surface area, enabling many enzymes like oxidoreductase to bind with magnetic NP, as a result of improving electron transfer capability [60]. Metallic NPs may merge with structured way to enhance their electrocatalytic activity and create a biofuel cell with high loading capacity and good electron transfer rate when employed in a layer-by-layer assembly with suitable polymers and enzymes [61]. Biofuel cells can be configured with gold (Au), platinum (Pt), and $Pt_{0.75}$-$Sn_{0.25}$ supported by MWCNTs, whereas Au NPs demonstrate great electrical conductivity and biocompatibility, and better catalytic activity than PtNPs. The combination of Pt and Sn NPs showed high oxidation activity for ethanol [62]. These Au NPs (5 nm) have ability for improving substrate utilization capacity by 56% due to which promoted biohydrogen generation rate by 46% can be achieved [63]. Because of their smaller size and larger surface area, silver (Ag) NPs facilitate biohydrogen generation by adhering microbial cells to active sites.

3.6 Metal Oxide Nanoparticles

Metal oxide NPs are best known for their uses in sensors, catalysts, and electronic materials. Metal oxides like KOH, MoO_3, ZnO, V_2O_5, Co_3O_4, and NiO are used for the conversion of vegetable oil to biofuel and have the capacity to catalyze the transformation of oil into organic liquid products [64]. Metal oxides are being used as a support system for synthesis of biodiesel because of their high catalytic activity. Biodiesel production using nanocatalysts like CaO and Al_2O_3 is carried out efficiently

in the past. Jatropha oil acts as a good source of feedstock, wherein biodiesels are synthesized by transesterification reaction process with 82.3% yield using methanol and oil [65].

4 Tailoring the Nanocatalysts for Biodiesel Production

Industrially, conventional homogeneous catalysts have long been used in the transesterification reaction for biodiesel production [66]. However, the catalyst requires extensive washing and purification steps, causing undesired saponification when treated with high-FFA content feedstocks [67]. The enzymatic transesterification of lipases is commonly associated with a high production cost and fast deactivation under severe reaction conditions, limiting the production of scalable commercial applications [68]. An alternative method to overcome these challenges is to use heterogeneous catalysts.

An effective ZrO_2-based bifunctional heterogeneous catalyst is used to convert microalgae lipid into biodiesel in transesterification reaction. The effect of several process parameters on the surface area of ZrO_2 prepared by surfactant-assisted sol–gel method followed by a hydrothermal treatment using non-ionic and cationic surfactants under basic conditions is investigated. Hydrothermal energy, a non-conventional energy source for synthesis of NPs, prevents particle agglomeration and allows for uniform grain size with regular morphology [69]. The optimization of process parameters was investigated by using response surface methodology central composite design. Mathematical models were developed and validated to predict the maximum surface area of ZrO_2. The acidic and basic properties of ZrO_2 were tailored after modification with bismuth oxide (Bi_2O_3) via incipient wetness impregnation method. The Bi_2O_3 was supported on the ZrO_2 via incipient wetness impregnation method. The catalysts were characterized by using different of techniques where the surfactant-assisted ZrO_2 NPs possess higher surface area, better acid–base properties, and well-formed pore structures than bare ZrO_2. The highest yield of fatty acid methyl esters (73.21%) was achieved for the Bi_2O_3/ZrO_2. The catalytic activity of the developed catalysts was linearly correlated with the total densities of the acidic and basic sites [70].

Extensive research has been focusing on synthesizing the novel solid acid catalysts using organic polymer and imidazole salt-based bifunctional catalysts under milder reaction conditions as compared to previous reported literature [71]. Pan et al. reported the synthesis of an imidazole salt-based catalyst, namely 1, 3-disulfonic acid imidazolium tetrachloroferrate bifunctional catalyst possessing Lewis (L) acid and Brønsted (B) acidic properties. In another study, synthesis of heterogeneous solid acid catalysts using ionic liquids functionalized with melamine formaldehyde polymer was reported. The as-obtained catalyst explored for biodiesel production from oleic acid under mild reaction conditions demonstrated reusability with the production efficiency of 88% in four runs [72].

Dai et al. reported the synthesis of Si and Al-doped lithium carbonate compound derived from clay materials using one-pot blending and grinding method. The optimum doping and air calcination temperature significantly increase the number of active basic sites followed by the catalytic activity. Beyond optimum calcination temperature, the surface morphology reveals high agglomeration capability, which further decreases the pore size and diameter. The catalyst was utilized for biodiesel production using soybean oil with optimum reaction parameters such as reaction temperature of − 65 °C, time of 4 h, 36:1 methanol:oil molar ratio with 8 wt% catalyst loading capacity that produces 98–99% yield. The catalyst was however recycled for seventh runs with insignificant loss of activity [73]. Nanocatalysts immobilized over enzymes can be a new perspective in the production of biodiesel. However, it still cannot be used on commercial scale due to some limitations like long reaction time, type of enzyme immobilized, operating conditions like pH and temperature [74, 75].

As a bulk, metal oxide-based catalysts confirm instability at high temperatures, which leads to catalyst deactivation along with the metal leaching and surface deformation creating major hindrance in increased biodiesel production. To overcome these serious drawbacks, several recent studies have been focused pertinently on developing a wide range of nanocatalysts based on supported materials like zeolites, zirconia, polymers, and heteropoly acid catalysts, which significantly impart chemical and structural stability to sustain at high reaction temperature followed longevity for obtaining increased catalytic activity [76] (Fig. 3).

5 Conclusions and Future Perspectives

Nanomaterials have promising application in biofuel production due to their small size, large surface area-to-volume ratio, and good catalytic properties which are responsible for enhancing the production of various types of biofuel such as biohydrogen, biodiesel, and bioethanol. The present chapter discussed the different types of nanomaterials applied in the bioenergy field to act as a nanocatalyst efficiently. In addition to this, the chapter discussed the extended strategies for recycling of nanocatalyst. From an up-to-date study in nanotechnology, we conclude that these approaches can be used in biofuel industries to enhance biofuel production and minimize the cost of biofuels due to unique structural properties of nanomaterials used as a nanocatalyst. Also, in the future the study can be extended toward the different waste materials that can be explored as a nanocatalyst, and also with the implementation of some of these key strategies, we can increase its efficiency also.

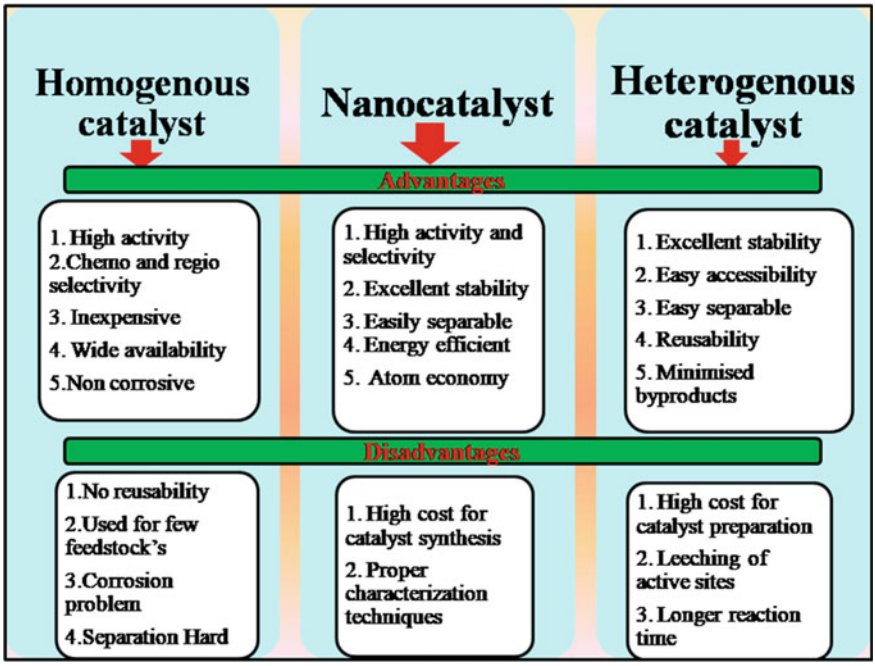

Fig. 3 Comparative snapshot showing different types of catalysts

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Potential Nanomaterials for the Treatment and Management of Diabetes Mellitus

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Abstract Diabetes mellitus (DM) is an emergent, severe health issue, widely spread throughout the world that needs to be tackled with enormous concern. There has been great interest in the use of nanomaterials for the treatment and management of diabetes mellitus due to their versatile theranostic applications and improved patient compliance. Nanoformulations can deliver drugs at the targeted sites, in a controlled manner for a prolonged period. They reduce drug toxicity and enhance drug stability, solubility, absorption, permeation, and bioavailability. Lipid-based nanoformulation has shown great potential in delivering the active therapeutic ingredient to the intestinal lymphatic system, thus avoiding the first-pass metabolism and eliminating P-glycoprotein (P-gp) efflux and permeability-related issues. The use of nanocarriers can ameliorate the accumulation of ASOs in organs and tissues pertinent to diabetes and their delivery into a specific cell. Encapsulating insulin into nanocarrier can overcome problems like short half-life, low intestinal permeability and bioavailability. This chapter explores the therapeutic potential of advanced nanomedicines like liposomes, niosomes, nanocarriers, magnetic and polymeric NPs, carbon NPs, Au NPs, Ag NPs, and ASOs for the treatment of diabetes mellitus. Nanomaterials of hypoglycemic drugs can offer enhanced diabetes management along with the minimized threat of acute and chronic complications.

Keywords Diabetes mellitus · Nanomaterials for treatment of diabetes mellitus · Antidiabetic therapeutics · Nano-based drug delivery

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R. S. Mane et al. (eds.), *Nanomaterials for Sustainable Development*,
https://doi.org/10.1007/978-981-99-1635-1_11

1 Introduction

Nanomaterials have enormous pharmaceutical applications; for instance, nanoparticle drug delivery systems are becoming emerging technologies. Pharmaceutical nanomaterials include nanostructured lipid carriers (NLCs), nanosuspensions, nanoemulsions, carbon nanotubes, nanocomposites, solid lipid nanoparticles (SLNs), magnetic nanoparticles, lipid–drug conjugates, nanocrystals, dendrimers, liposomes, niosomes, etc., for targeted drug delivery. Nanomaterials are nano-sized particles of sizes less than 100 nm [1]. Nanoparticles exhibit excellent physical as well as chemical stability, lower density, high surface area, improved solubility, and bioavailability which have made them excellent drug carriers. Nanomaterials have several applications including bio-inspired wearable electronics, biomedical, renal management, treatment and diagnosis of cancer, diagnosis, and treatment of diabetes mellitus, Alzheimer's disease, targeted drug delivery systems, MRI, biomedical engineering gene delivery, immunotherapy, 3D printing, and theranostic materials. Theranostic exhibits simultaneous diagnostic and therapeutic applications, in the field of precision and personalized medicine [1, 2].

Functional nanomaterials have been widely used in life sciences as they demonstrate excellent physicochemical properties, bioavailability, and good biocompatibility [2]. In the last few decades, nanomaterials have received huge importance. The applications of nanotechnology and nanomaterials to drug delivery include the use of precisely engineered materials to develop novel therapies and devices that may decrease toxicity as well as augment efficacy [2, 3]. As nanomaterials are extremely small in size, they can cross through various tissues, barriers, organs, and even cells to exert favourable therapeutic effects after critical and careful modification and engineering. Diabetes, being a chronic, lifelong metabolic disorder, is characterized by impaired secretion of insulin or deficiency in insulin secretion which leads to hyperglycemia. Diabetes mellitus type I is an autoimmune, juvenile diabetes that results from an insulin deficiency. Diabetes mellitus type II is non-insulin-dependent diabetes, which accounts for around 95% of diabetes [4].

If the diabetes is not cured properly, it may result in severe complications. Diabetes mellitus, one of the most common chronic metabolic disorders, is characterized by hyperglycemia that results from insulin resistance, or no insulin secretion, or both. Pancreas secret hormone is called insulin. Insulin metabolizes glucose that can be obtained from food for energy. People with diabetes mellitus type II, the pancreas either does not produce enough insulin or the pancreas can produce insulin but the liver, muscle, and fat cells do not use it. This condition is known as insulin resistance. When a cell becomes insulin resistant, it requires more insulin to convert glucose into energy, which leads to hyperglycemia or increases blood sugar. Diabetes mellitus is characterized by hyperglycemia, insulin resistance, and relative insulin deficiency. Type II diabetes mellitus (TIIDM) may result due to lifestyle-related factors, genetic factors, and environmental and behavioural risk factors [5, 6]. Due to the progressive nature of the disease, the management and treatment of TIIDM is a challenging and complex issue. To reduce the overall risk in patients with TIIDM monitoring multiple

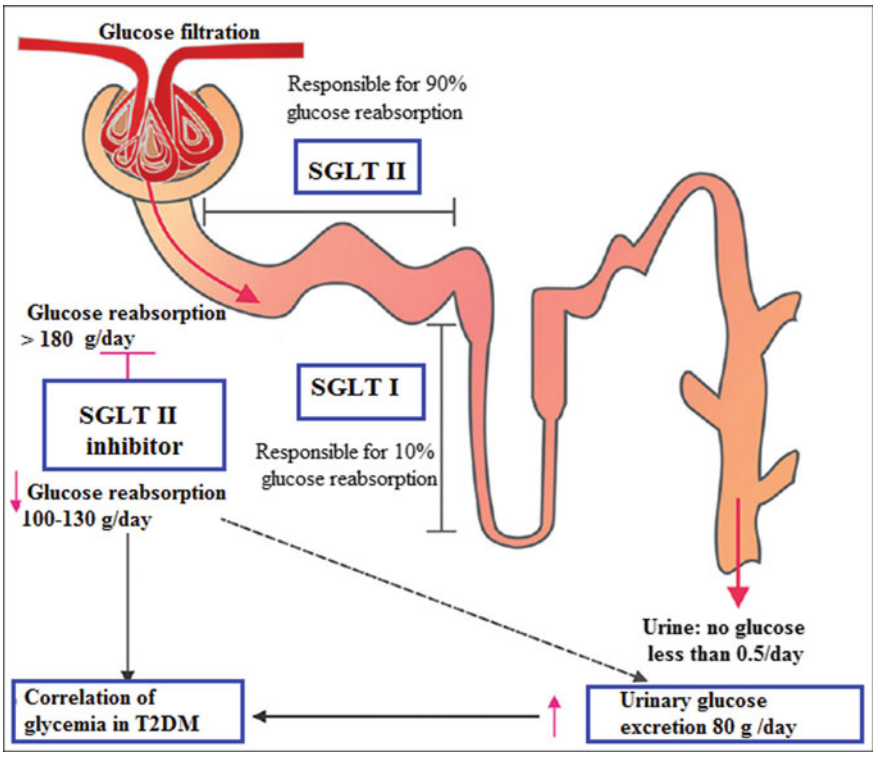

Fig. 11.1 Role of SGLT II inhibitors in diabetes mellitus type II

treatments like glucose, blood pressure, and lipids is essential [6, 7]. Insulin therapy is used in almost every diabetic patient to provide insulin replacement (Fig. 11.1).

2 Need of Nanomaterials in Diabetes Management

Conventional drug delivery system exhibits certain limitations like lack of efficacy due to improper dosage, first-pass metabolism, P-gp efflux, reduced potency or effects due to drug metabolism, and lack of target specificity [6, 7]. Nanoformulations offer certain advantages over conventional formulations, including enhanced intestinal drug permeation, enhanced gastric retention time, inhibits P-gp efflux, high specificity, improved efficiency, targeted drug delivery, sustained and controlled drug release, enhanced bioavailability, etc. Insulin delivery through nanoparticles is more significant as it is a more convenient, safe, and non-invasive route for insulin delivery in order to overcome limitations like insulin resistance in diabetes management [8].

3 Nanomaterials for Oral Delivery as Antidiabetic Drug

Drug loading into nanomaterials can improve the stability of the drug as it protects the drug from enzymatic and chemical degradation in the gastrointestinal tract (GIT). Nanoformulations enhance drug contact with GIT, gastric residence time, drug absorption as well as oral bioavailability. NPs can enhance intestinal permeation of insulin, mean residence time (MRT), and lymphatic uptake thereby avoiding first-pass metabolism. Over the last decade, nanoformulations have been studied for the administration of insulin [8, 9]. Insulin encapsulation into polymer-based nanoparticles can improve the oral bioavailability of insulin. In the last few decades, different nanoformulations and polymers are being used to encapsulate insulin and deliver insulin orally. Various nanoformulations including nanostructured lipid carriers, niosomes, liposomes, solid lipid nanocarriers, nanocomposites, polymeric, gold nanoparticles, phospholipid micelle, lipid drug conjugate, dendrimers, etc., have been designed and studied for the management and treatment of diabetes mellitus [10, 11]. Carbon nanomaterials play important role in the biomedical field, drug delivery system, imaging, and biosensing. Shao et al. developed carbon nanoparticles by carbonization using a polysaccharide from *Arctium lappa* L. root as the carbon source; these inhibit A-glucosidase activity and thereby induce a hypoglycemic effect in diabetic rats [12].

4 Role of Nanoparticles as Antidiabetic Therapeutics

NPs offer many advantages including improved efficacy, reduced toxicity, enhanced biodistribution, improved bioavailability, and improved patient compliance [10, 11]. NPs can enhance the oral absorption rate of the antidiabetic drug which can be formed with biodegradable and biocompatible polymeric systems. They also can enhance the bioavailability of insulin. By formulating NP-based antidiabetic formulations, drugs can be delivered precisely and safely in a controlled manner. NPs containing lipids increase lipophilicity and thus enhance the drug permeation across the gastrointestinal tract (GIT) wall. Partially water-soluble antidiabetic drugs can be formulated as NPs for improving solubility and bioavailability. Nanoparticles have several advantages over conventional dosage forms. Nanostructure-based sensors and imaging strategies like implantable nano-sensors or biosensors can be implanted into the body for continuous glucose monitoring and early diagnosis of diabetes [8–13].

4.1 Nanoparticles in Diabetes

Nanoparticles are the carrier of choice for antidiabetic drugs as these are showing higher intracellular and gastric uptake, thus enhancing solubility, bioavailability, and stability (Table 11.1) [14]. NPs can be formulated by various methods including emulsion solvent evaporation, spray drying, solvent displacement, diffusion solvent evaporation, supercritical fluid, supercritical antisolvent, ionotropic polyelectrolyte pre-gelation, nanoprecipitation, polyelectrolyte complexation, dispersion polymerization, interfacial polymerization of the micro-emulsion, ionic gelation, solvent precipitation/dispersion, etc. [13]. They are of different types including polymeric NPs, magnetic NPs, metal-based or gold NPs, smart NPs, lipid-based NPs, solid lipid NPs, and biogenic NPs (Fig. 11.2) [14]. Diabetes patients should maintain glucose levels either through controlled monitoring or by oral insulin administration. Smart insulin is a commercially formulated nanoparticle formulation that releases insulin depending on lectin-mediated glucose binding [15].

Metallic NPs like zinc (Zn), gold (Au), silver (Ag), iron (Fe), and metal oxides have enormous medical and biological applications. Alkaladi et al. [27] studied the antidiabetic activity of zinc oxide and silver NPs which would significantly reduce blood glucose by acting as potent antidiabetic agents. MNPs with good biocompatibility and excellent magnetic responsiveness are an outstanding class of materials that can be used for targeted drug delivery. Superparamagnetic iron oxide nanoparticles (SPIONs) are biocompatible nanoparticles that are used as magnetic resonance imaging (MRI) contrast agents in magnetic resonance imaging for diagnostics and targeted drug delivery. Magnetic NPs labelled T-cells can be used as a non-invasive method for imaging the diabetic pancreas for diagnosis and treatment of diabetes. Ali et al. performed a comparative study of the antidiabetic effect of superparamagnetic iron oxide nanoparticles on Type II diabetic rats and compared their effect to metformin treatment, wherein SPIONs significantly lowers blood glucose and lipid consequently plays a vital role in diabetes treatment. SPIONs extensively ameliorate glucose sensing and are the foremost component of the insulin signalling pathway. SPIONs are effective through multiple pathways as the used doses of SPIONs have produced an antidiabetic effect equivalent to metformin [28]. Zhao et al. formulated insulin NPs for transdermal drug delivery, using a supercritical antisolvent (SAS) micronization process where ultra-fine insulin NPs can be formulated with DMSO as a solvent and carbon dioxide as an antisolvent for the high rate of permeation [29].

4.2 Nanostructured Lipid Carriers

Nanostructured lipid carrier is the next, and advanced generation solid lipid nanoparticles consist of solid and liquid lipid (oil) to form unstructured matrices, which fundamentally improves the drug loading and decreases the drug expulsion from the matrix during storage. NLCs are lipid-based NPs, which are being introduced as

Table 11.1 Nanoformulation delivery systems used for the treatment of diabetes mellitus [8, 16–26]

Nanoformulation	Antidiabetic drug	Route of administration	Outcome
Nanostructured lipid carrier—NLC gel	Gliclazide	Transdermal	Enhanced drug permeation and bioavailability of gliclazide
Niosome	Glipizide and Metformin Hydrochloride	Oral route	Niosomes are capable for sustained release of the drugs
PEGylated liposomes	Glibenclamide	Injection through transdermal route	Encapsulating the drug in the liposome core enabled sustained release
Lipid-polymeric nanoparticles	Insulin	Oral route	Nanoparticles provide insulin stability and intestinal permeability
Zinc oxide NPs	Docosahexaenoic acid	Oral route	Enhanced glucose lowering effects; Reduced insulin resistance
Nanoliposomes	Resveratrol	Oral route	Liposomal formulations have significantly decreased high glucose levels on enhancing the bioavailability of the drug
Nanostructured lipid carriers	Canagliflozin	Oral route	NLC has enhanced drug solubility and bioavailability
Niosomes	Metformin Hydrochloride	Oral route	Controlled release drug delivery of metformin hydrochloride with enhanced bioavailability
Tegaderm™ silver nanoparticles	Silver-containing alginate dressing	Topical route	This can be effectively used for the healing and management of the diabetic wound
Solid lipid nanocarriers	Repaglinide-loaded SLNs prepared using various surfactants	Oral route	Slow release of the drug repaglinide was observed from all formulations
Lipid-based nanoparticles	Gliclazide	Oral route	Prolonged drug release with a fivefold increase in oral bioavailability of gliclazide
Chitosan-based glucose-responsive nanoparticles	Insulin	Oral route	Prolonged intestinal residence time of insulin

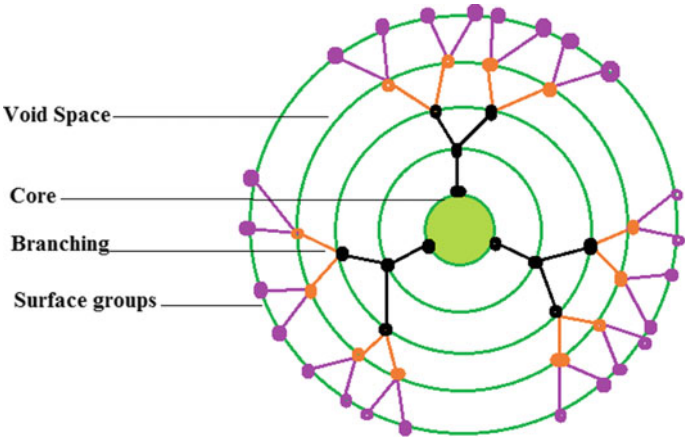

Fig. 11.2 Structure of dendrimers

the latest pharmaceutical delivery system. NLCs exhibit excellent solubilization and dispersing capacities and act as promising nanocarriers for oral drug delivery [30].

Lipids as carriers in drug delivery provide numerous opportunities due to their ability to enhance gastrointestinal solubilization and absorption of the drug by selective lymphatic uptake of week bioavailable drugs. Lipids in NLC possess various advantages like biocompatibility, high solubilization potential, easy manufacturing, and ability to enhance oral bioavailability of sparingly water-soluble drugs. Lipids eliminate various physiological barriers such as pre-systemic metabolism, gastrointestinal degradation of drugs, P-gp efflux, and permeability-related issues enhancing the bioavailability of biopharmaceutical classification system (BCS) class II and IV drugs. Lipid-based nanoformulation such as nanostructured lipid carriers has shown great potential in delivering the active therapeutic ingredient to the intestinal lymphatic system and to avoid the first-pass metabolism. After oral administration, NLC exhibits better-controlled release than other lipid-based formulations in the gastrointestinal tract. Nanostructured lipid carriers of poorly water-soluble drugs can maintain sufficient solubility at the intestinal absorption site on account of the small particle size and lipid solubilization. Among the various lipid nanocarrier formulations, NLCs have grabbed more attention due to their unique binary lipid constituent of different chemical structures which provides an enormous scope of exploration of lipid vehicles that could improve in-vivo release through poorly water-soluble drugs.

4.3 Nanostructured Lipid Carriers (NLCs)

NLCs are administered by various routes like oral, parenteral, pulmonary, dermal, and ocular [31]. These NLCs have shown great potential in delivering therapeutic agents to the intestinal lymphatic system and to avoid the first pass metabolism

and proved to enhance oral bioavailability and other pharmacokinetic properties of drugs to be administered orally. NLC can be prepared by using various methods including high-pressure homogenization, displacement or injection method, melting dispersion method, solvent emulsification-diffusion method, spray drying, hot melt emulsification, probe sonication technique, phase inversion method, ultrasonication technique, emulsification-solvent evaporation technique, solvent emulsification-diffusion method, and micro-emulsion-based method [31, 32]. Pandey et al. formulated repaglinide-loaded NLC gel using Gelucire as solid lipid, and Tween 80 as a surfactant. Formulated NLC has improved the pharmacokinetics and bioavailability of repaglinide by transdermal route to manage diabetes mellitus [32]. Pioglitazone (PGZ) loaded NLCs fabricated using different concentrations of the surfactants (Tween 80 and Span 80), Compritol® 888 ATO was used as solid lipid, and Labrasol® was used as liquid lipid. It was found that PGZ-NLCs could be a promising drug delivery for the management of type II diabetes [33].

4.4 Liposome-Based Drug Delivery System

Liposomes are nano- to micro-sized, comprising one or more phospholipid bilayers that are made up of natural non-toxic phospholipids and cholesterol, and surround an aqueous core. Phospholipids are major components of all biological membranes. Liposomes are showing excellent biocompatibility. Liposomes are nanocarriers that have the ability to encapsulate or entrap both hydrophilic as well as lipophilic drugs. Liposomes exhibit certain advantages including biocompatibility, biodegradability, and low toxicity that facilitate targeted or site-specific drug delivery. Liposome-based delivery systems have been studied for their application in the oral delivery of therapeutic proteins and peptides; mainly for the oral delivery of the insulin hormone. Liposomes can be used to carry insulin as a targeted drug delivery system [34, 35]. Amjadi et al. [36] formulated betanin-loaded sustained release nanoliposomes study revealed that nanoliposomes improved the stability as well as the therapeutic potential of betanin. Dwivedi et al. [37] formulated silica-coated liposomes for insulin delivery that was effective in reducing glucose levels. Ye et al. developed novel multivesicular liposomes DepoFoam™ technology for designing sustained release formulations of a protein like insulin and peptides like leuprolide, enkephalin, and octreotide. DepoFoam system has effectively encapsulated therapeutic proteins and peptides like biologically active macromolecules with higher drug loading, narrow particle size distribution, and controlled release profile [38].

Karathanasis et al. formulated insulin-loaded liposomes as aerosol insulin carriers based on the agglomerated vesicle technology. Cross-linking of liposomes with chemical bridging cleavable by cysteine was prepared. Liposomal carriers with cysteine encapsulated insulin release rapidly in the lungs [39].

4.5 Niosome-Based Drug Delivery System

Niosomes are non-ionic surfactant-based vesicles having a lamellar structure that is formed by the self-assembly of surfactant molecules. According to their structure, they can be administered through subcutaneous, intramuscular, pulmonary, intraperitoneal, intravenous, ocular, oral, and transdermal routes [40]. Niosomes can be formulated by various methods like thin-film hydration (handshaking) ether injection, reverse phase evaporation, emulsion, and bubble. Niosomes demonstrate potential applications in drug delivery system. It has several advantages including chemically stable, biocompatibility, biodegradable, and osmotically active. Niosomes, the potential drug carrier in drug delivery, act as reservoirs for drugs to attain maximum drug entrapment for sustained and prolonged drug release which enhances drug permeation across the skin and improves the bioavailability of sparingly water-soluble drugs. Peptides like insulin can be fabricated as niosomes which prevent degradation of insulin by encapsulation of the drug along with the surfactant in their hydrophilic matrix, and thus sustained drug release can be achieved [40, 41]. Insulin-loaded niosomes of polyoxyethylene alkyl ethers (brij) have shown sustained release, good stability, and reduced toxicity in the presence of proteolytic enzymes of GIT [41].

4.6 Gold Nanoparticles in Diabetes Treatment

Various nanodevices, nanotechnology-based biosensors, diagnostics therapeutics, and targeted drug delivery systems are being designed for theranostic applications in the management of various diseases. Gold nanoparticles (Au NPs) range from 2 to 100 nm in size and can be synthesized in various shapes like hollow, rod, diamond, sphere, and prism as core–shell or solids, for excellent physicochemical properties. AuNPs image can be observed using transmission electron micrograph (TEM). Au NPs are stable, biocompatible, and effective that show pharmaceutical applications like imaging, labelling, and sensing [42]. Omolaja et al. [43] designed and formulated chalcone-capped Au NPs of South African medicinal plant *Helichrysum foetidum* extract, which were effective against diabetes. Opris et al. designed and formulated Au NPs using *Sambucus nigra* L. (SN) plant extract that revealed great adjuvant in the management of diabetes [44]. As Au NPs are biocompatible and biodegradable, they are widely been used in diagnostic imaging, sensing, labelling, and biomedical applications. Au NPs have been designed to determine blood glucose level in patients [44]. Nair and Sreenivasan designed non-enzymatic colorimetric glucose estimation device using cyanophenyl boronic acid (CPBA) and β-cyclodextrin (βCD) stabilized AuNPs. These glucose sensors were designed by green one-pot tandem method to estimate glucose in human blood serum [45]. Nanomaterials improve biosensor sensitivity, performance, and response time. Recently developed novel AuNPs biosensors serve as diagnostics and theranostics thus these integrate nanomaterials as lab-on-chip [46].

Nowadays, nano-biosensor devices are being developed for in-vivo and in-vitro glucose sensing. Many commercially available glucose biosensors are used for glucose monitoring [46]. Examples of these marketed glucose biosensors include the OneTouch Ultra2 by LifeScan, FreeStyle Lite by Abbott, Accu-Chek by Roche, and the Contour by Bayer. Electrochemical glucose biosensors measure electric signals directly in proportion with the glucose concentration. This biosensor monitors oxidative current generated by glucose oxidase. Ag NPs reveal antibacterial and anti-inflammatory properties, and thus, they exhibit the exceptional potential to promote wound healing in diabetic condition [16].

4.7 Nanocarriers of Antisense Oligonucleotides in Diabetes

Antisense oligonucleotides (ASOs) are short, chemically synthetic DNA oligomers that can alter RNA and shrink, refurbish, or modify protein expression through numerous distinct mechanisms. ASOs are capable of blocking gene expression and thus, obtaining a therapeutic outcome. ASOs are used in the development of antidiabetic agents as they can regulate the expression of disease-causing genes at the ribonucleic acid (RNA) and protein level. Nanocarriers are used for delivery of ASOs and targeting. Oligonucleotide therapy uses ASOs, siRNA, or aptamers. This approach blocks proteins expression using different intracellular mechanisms. Nanotechnology-based ASOs can be successfully used as antidiabetic agents with improved potency and delivery [47]. ASOs, being genetic materials, are promising tools used to regulate unsuitable expression of genes in pathological condition by the specific inhibition of expression of their mRNA targets [48]. Carbon nanotubes, dendrimers, protein or peptide conjugates, liposomes are used to deliver ASOs. ASO drugs have been investigated to use in combination with nanoparticles. In this approach, genes involved in the pathogenesis of insulin resistance and hyperglycemia can be identified. Therapeutic oligonucleotides reduce the production of target proteins or RNA level by inhibiting gene expression. ASO-induced gene inhibition is useful in the identification, functionalization, and validation of target genes concerned in diabetes pathogenesis. Various small molecule drugs ASOs have been approved for using in the treatment of type II diabetes mellitus. Various classes of antidiabetic drugs including SGLT II inhibitors like Dapagliflozin, Canagliflozin, Empagliflozin, Ertugliflozin, Sotagliflozin; alpha-glucosidase inhibitors like Acarbose, Miglitol; Dipeptidyl-peptidase 4 inhibitors like Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin are approved as small molecule drugs. Various antisense-based drugs like ISIS 113715, ISIS 325568, IONIS-GCGRRX (ISIS 449884), Volanesorsen (ISIS 308401) are in various phases of clinical trials [47, 48].

4.8 Dendrimers in Diabetes Treatment

Dendrimers are basically three-dimensional, nano-sized, homogenous, polymeric globular hyper-branched macromolecules, with tree-like branched structure (shown in Fig. 11.3). Dendrimers consist of three regions: a central core, branched monomer, and different terminal functional groups on the external layer of repeat units. Polyamidoamine (PAMAM) dendrimers and polypropylene imine dendrimers are frequently used dendrimers. Dendrimers consist of hydrophilic surface and hydrophobic core manufactured by convergent or divergent polymerization of branching units. Dendrimers are nanomaterials with great physicochemical stability that have ability to functionalize their end groups with different therapeutic agents. Thus, these are potential carrier for targeted drug delivery [49]. The muco-adhesive property of dendrimers increases drug residence time at intestinal epithelium; they get penetrated inside intestinal membrane through lymphoid tissues, thereby enhancing drug absorption. Surface-modified dendrimers inhibit P-glycoprotein efflux effect by enhancing drug gastric retention time, thus improves bioavailability [50]. Dendrimers have grabbed an enormous attention as drug delivery as well as for personalized medicines. It has been found that PAMAM G4 (generation 4) dendrimers imitate hypoglycaemic behaviour, through reduction of higher plasma glucose level and long-term markers of hyperglycemia in diabetic animal model [51]. Dong et al. conducted an experiment to study the effects of PAMAM dendrimers of various generations on the pulmonary absorption of insulin and calcitonin in rats. It was found that PAMAM dendrimers significantly increased the pulmonary absorption of insulin and calcitonin in rats [52].

4.9 Different NPs for Transdermal Drug Delivery of Antidiabetic Drugs

Oral bioavailability is one of the major concerns for insulin delivery. Nowadays, parenteral route is mostly used for insulin delivery. NPs designed with biodegradable and biocompatible polymeric systems improve the bioavailability of insulin. Transdermal and pulmonary routes are used for effective delivery of insulin. Insulin inhalation can be used for the treatment of T1DM and T2DM [53]. Transdermal drug administration is alternative to subcutaneous delivery. Skin is the largest organ of the human body; transdermal drug delivery system has potential advantages over other drug delivery including reduced systemic side effects, non-invasive drug delivery, patient compliance, self-administration, and controlled drug delivery. NPs-encapsulated polymeric microneedles (NPs-MN) have been used for transdermal drug delivery of hydrophilic and hydrophobic drugs. NPs-MN has been successfully used in diabetes therapy, for enhanced bioavailability [54]. Insulin-loaded nanoparticles can be formulated by encapsulating drug in various delivery systems like electrosomes, liposomes, nanoparticles, niosomes, and nanodispersions for transdermal

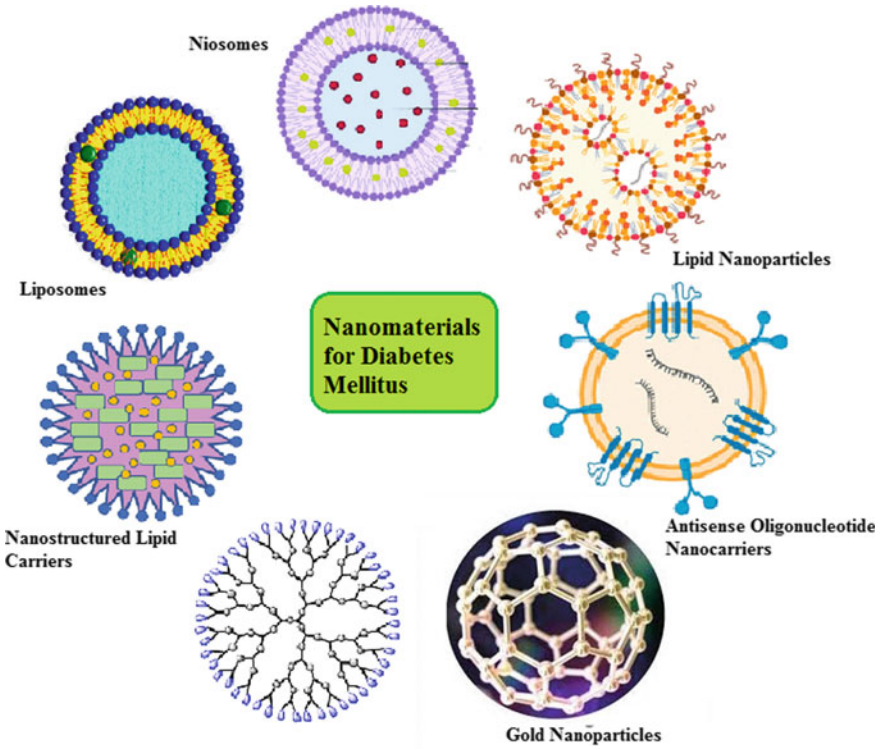

Fig. 11.3 Nanomaterials in treatment and management of diabetes mellitus

applications. Technologies like iontophoresis, electroporation, sonophoresis, and microneedles are used to enhance transdermal delivery of insulin-loaded nanoparticles. NPs containing hydrogel are used to promote diabetic wound healing by loading bioactive molecules like growth factors, genes, and proteins/peptides [55]. Nanofiber-based systems can be intended for diabetes. Nanofibers can be formulated using natural and synthetic or both materials for the delivery of biomacromolecules like insulin and antidiabetic drugs. Insulin can be incorporated in nanofiber patches for administration via dermal, transdermal, or sublingual to lower blood glucose level [56].

5 Challenges and Future Perspectives

Challenges associated with nanomaterials include toxicity, shorter shelf-life, toxicity, pharmacokinetics, stability, expensive formulations, reduced entrapment efficiency, poor drug loading, etc. There is a need to develop smart nanoformulations for the future to overcome these challenges. While nanomaterials have already made

a significant impact on management of diabetes, there are numerous areas where further developments are expected, particularly the design of biosensors, medicinal nano-sized devices, nanodiagnostic, and nanotherapeutics. Nanoparticles can deliver proteins and genes with improved therapeutic outcomes. The development of nanomaterials for gene therapy can be one of the best future prospects for nanomaterials. There is need to develop easy and cost-effective methods for the fabrication of nanomaterials of different functionalities and morphologies.

6 Conclusions

The application of nanomaterials in diabetes includes diagnosis, glucose sensing, glucose monitoring, insulin delivery, drug delivery, and wound healing. In the biomedical field, NPs are primarily used in drug delivery, imaging, and theranostic processes. Nanomaterials can be formulated as various types of drug delivery systems, like NLC, liposome, niosome, nanosuspension, and SLN, which improves drug bioavailability. Nanocarriers can be administered through oral, parenteral, transdermal route of administration that enhances patient compliance. Nanoparticles, being small in size, get penetrate throughout minor capillaries and are taken up by cells, which permit competent drug accumulation at the target sites. Nanoparticles have been shown to be the most safe and proficient vehicle for delivery of drugs at targeted site. Insulin after oral administration goes through enzymatic degradation. Encapsulation of insulin in the nanocarriers can eliminate this issue to some extent. In nutshell, nanomaterials are the most promising drug delivery for the treatment of diabetes mellitus.

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Nanomaterials for Biosensing Applications in the Medical Field

Rakesh K. Sahoo, Saroj Kumar Singh, Rajaram S. Mane, and Shikha Varma

Abstract The combination of nanotechnology and biotechnology has emerged as an integrated technology for medical applications. Over the world, day by day, numerous researchers are developing novel materials using the suitable platform to detect pathogenic, mutagenic, or toxic compounds or any biological effect. This chapter addresses the classification of biosensors, especially for medical applications based on the two most important parameters: bio-recognition element and signal transduction. Furthermore, several grooming biosensing technologies are also addressed. Subsequently, more emphasis has been added to nanomaterial classification employed in the biosensors based on their chemical contents and structural dimensions. Additionally, more insight into the current challenges in the application of nanomaterials in biosensors, especially for medical applications, has been demonstrated.

Keywords Biosensors · Biomedical detection · Nanomaterials · 2D materials · Carbon materials

1 Introduction

The alarming rise in several pandemic and epidemic diseases like severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), black fungus, cancer, etc., has forced the researcher to think up more advanced biological detection and monitoring systems

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R. S. Mane et al. (eds.), *Nanomaterials for Sustainable Development*,
https://doi.org/10.1007/978-981-99-1635-1_12

to detect carcinogenic, mutagenic, and toxic elements [1–4]. Although modern technologies and industrialization have simplified our lives to a new level, others left behind several environmental issues leading to serious health issues [5]. Thus, it is highly desirable to design and explore the challenges in developing advanced detection and monitoring systems, especially bio-detection and bio-monitoring systems, to better human health. The potential of biosensors in various functional fields is schematically presented (Fig. 1). The technology that highly depends on genetically modified organisms can be treated as biosensor technology which is emerging in advancement. The research in biosensor had drawn attention when Gary Sayler's group reported the report of the genetically modified microbial biosensor in the early 1990s [6]. According to van der Meer and Belkin biosensor [7], a device detects the chemical and biological changes in the system and transforms them into a measurable signal when the biological materials interact with this engineered device. Based on the type of biological materials interacting with the bio-reporter, the sensor is nomenclatured by different names. When the biological material is an antibody or whole-cell or nucleic acid, it is termed as an immunosensor or microbial biosensor, or DNA aptamer [8], respectively. Basically, there are four major components in the biosensor namely; (i) bio-receptor, (ii) transducer, (iii) a signal processing unit, and (iv) a display or interface unit that showcases the output signal (schematically shown in Fig. 2).

Fig. 1 Potential of biosensor in various fields of application in schematic form

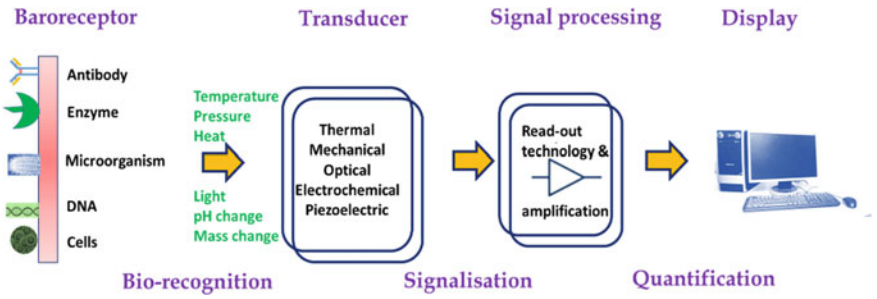

Fig. 2 Schematic of the biosensor

More research in experimental and theoretical aspects is timely required to use the biosensors as the first filter for pre-screening the samples. The potential of synergetic research in engineering with biology has an enormous potential in designing biosensors for advanced applications. Thus, it is highly desirable to understand the fundamental changes in the biological sensing behavior of living beings. Some of the natural examples are (i) vibration, tactile, and airflow sensors in spiders, (ii) fast response of the plants toward the change in luminous intensity, osmotic pressure, temperature, water availability, etc., (iii) the snapping system in venus flytrap, (iv) dogs possess a sense of smell far beyond the sensing behavior of the artificial sensor. More significantly, dogs can detection system is so sensitive that it can detect the concentration of parts per billion, and (v) the system for controlled bending of trees, etc. In the above, all cases functional outputs are highly correlated to materials behavior with biological needs.

The biosensing platform is expected to be mechanically robust, versatile, and high throughput that will simplify the life in developing individual medicine, in vivo-drug development, genomic-proteomic research, and point-of-care medical diagnosis [9]. Integrated technologies where nanotechnologies coupled with micro-fabrication technologies are able to develop new biosensors for medical applications [10]. However, the above type of advanced biosensor fabrication is in the embryonic stage and needs more research and development to enhance sensitivity, specificity, and high throughput. In this contest, designing the building blocks of the biosensor, i.e., the sensing materials in different scales and dimensions, has received considerable attention. Especially, nanomaterials in various dimensions and squeezing the atomic scale dimension have demonstrated fascinating bio-molecule detection behaviors. The work of Nam et al. [11] using nanoparticles and Liber et al. [12] using nanowires to design ultrasensitive biosensor is the pioneer in this area of research.

Several up-to-date sensor platforms are tested and proposed [13–16], especially for bio-molecule detection; additionally, few integrated technologies are in the next research phase before the medical diagnosis [10, 17–20]. In this chapter, the classification of biosensors based on bio-recognition elements and signal transduction has been described. The electrochemical, optical, thermal, and piezoelectrical sensors

based on the signal transduction perspective are proposed. Additionally, the enzymatic, protein receptor, immunosensors, DNA aptamer, and whole-cell biosensors based on bio-recognition elements are expressed. In the next section of the chapter, the nanomaterials of different dimensions and compositions applied in biosensor design have thoroughly been elucidated. Very concisely, nanomaterials, especially the two-dimensional materials used in designing flexible energy harvest and sensing for biomedical applications, are presented. Further, the current challenge and future prospective design of nanomaterials for biosensing, particularly for biomedical applications, are outlined.

2 Biosensors for Medical Applications

Technically, the entire class of biosensors has been classified based on two critical perspectives out of several, i.e., signal transduction and biorecognition element. In the subsequent section, the above two prospectives are briefly elaborated as follows.

2.1 Signal Transduction Perspective

Based on the signal transduction perspective, biosensors are categorized as electrochemical, thermal, optical, and piezoelectric sensors [3]. The electrochemical sensors are the most advanced and vastly investigated sensors for vivo monitoring or on-site monitoring. Low detection limit, high sensitivity, and generalizability are the advantages of this sensor compared to other category sensors. This category of the sensor is miniaturized to a lab-on-chip. Based on the signal from the sensor measured, it is subcategorized as amperometric (measuring the current produced during oxidation and reduction of the electroactive species), voltammetry (measuring the change in voltage of the working electrode concerning the reference electrode), and conductometry (measuring the alteration in conductance due to biochemical reaction). During the ongoing COVID-19 pandemic, electrochemical biosensors have been considered a crucial tool for rapid, accurate, and large-scale diagnosis of severing acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) [2, 4, 21–23]. During the biochemical reaction, the absorbed or emitted photons are measured through an optical transducer. The optical phenomena studied to observe the alteration in biological responses include fluorescence, surface plasma resonance, and absorption. In parallel, the advancement of fiber optics technology has boosted optical sensor research to an extent level.

A thermal sensor, the most basic version, is a thermometer that is used to measure body temperature. However, the temperature range and toxicity of mercury limit its uses. Modern thermal sensors or enzyme thermistors are designed with a principal component called a sensitive thermistor based on similar working mechanisms. The function of the thermistor is to accurately estimate the change in enthalpy of the

system during the biochemical reactions [24]. The piezoelectric sensor reciprocates the relationship between the resonant frequency change with respect to the mass of the molecule absorbed or desorbed on the crystal surface. The direct, label-free interaction with analyte mode is an efficient way of piezoelectric sensing platform. It is observed that the antibody or antigen is the best bio-molecule to be compatible with the piezoelectric sensor surface [25, 26].

2.2 Bio-recognition Perspective

Based on the bio-recognition perspective, the biosensors are categorized as enzymatic, protein receptor, immunosensor, DNA aptamers, and whole-cell biosensors. Each of the categories is elaborated as below.

a. Enzymatic biosensors

This type of sensor enzyme is the primary component that recognizes and reacts with the analyte to produce the electrochemical outcome. The brief sketch consists of analytes, receptors, an electrochemical transducer, and a signal amplifier. Here, the enzyme acts as a catalyst. And the function of the electrochemical transducer is to convert the chemical signal from the bio-reaction into a measurable physical signal which is further amplified by an amplifier. Most enzyme-catalyzed reactions release oxygen, carbon dioxide, and residual ionic species, measured by a transducer [27]. Two types of analytical enzymes such as hydrolases and oxidoreductases are used in the enzyme biosensor.

b. Protein receptor-based biosensors

The role of protein is opposite to enzyme as discussed previously in enzyme sensor. In this case, the protein present in the cell membrane acts as a receptor and reacts in a non-catalytic way with the signal from the transducer and produces the detectable signal by the process of metabotropic receptors through enzyme secretion or ionotropic receptors. Optical transduction has a significant role in this type of sensing platform [28, 29].

c. Immuno-sensors

This is a solid-state device wherein the immunochemical reaction is coupled to a transducer which is a basic design to detect the direct binding between antibodies to an analyte. Due to direct detection, faster and more cost-effective detection is possible using this type of sensor. A most exciting feature of immune-sensor is their selective and sensitivity in detecting multiple analytes by designing new recombinant antibodies [30].

d. DNA aptamers biosensor

Aptamers are short, single-standard DNA or RNA, and less than a hundred nucleotides are arranged/assembled in a specific sequence. This aptamer can interact

selectively with superior specificity and affinity forms bonding with a particular type of analyte, virus, bacteria, proteins, small molecules, toxins, hormones, etc., by hydrogen or Van der Waal binding force for biosensing. The beauty of these aptamers is that they can rearrange to form a variety of shapes and dimensions [31, 32]. Compared to immune sensor, DNA aptamer sensor is more specific, stable, and has a simple detection ability and also the cost is relatively lower. Due to its high stability, low cost, and superior specificity the DNA aptamer sensor is considered an alternative to antibodies.

e. Whole-cell biosensor

This type of sensor consists of two working components, i.e., the sensing element and reporter. The reporter element is a gene or gene cassette that has catalytic as well as non-catalytic functions. Catalytically, it accelerates the biochemical reaction to a detectable signal, and in a non-catalytic way as coding for the genes for metabotropic or ionotropic signal generation. The sensing element observes the gene or sets of gene's transcription initiation point similar to a promoter. The microbial sensor is the widely used whole-cell biosensor [33, 34]. Functional information rather than analytical information can be obtained using the whole-cell biosensor. The functional information can be obtained from the living cells by understanding the stimulus on a living system which can be applied in pharmacology, toxicology, cell biology, and many more. For example, the bacteria whole-cell biosensors can be genetically modified to sense mercury, nitrogen oxide, and hydroxylated polychlorinated biphenyls in urine and serum.

2.3 Limitations of Bio-based Biosensor

The major limitations that lag behind the bio-based biosensor are

1. First, low sensing performance with the low sensitivity and high limit of detection value of the designed sensor.
2. Due to limited active catalytic sites and surface area, bio-based biosensors have less chemical and catalytic activity.
3. The mechanical and cyclic performance stability and work life span of this type of sensor are very low.
4. Relatively low diffusivity of the bio-based biosensors. Especially in the electrochemical sensing case where the rate change of Faradic current is proportional to the diffusivity of the analyte on the electrode probe surface.

The above short-coming of the bio-based biosensors are tactically overcome by the use of engineered nanomaterials in the biosensor. Nanomaterials based biosensors are the rapidly growing research, especially for biosensor applications. Nanomaterials are basically used as transducer materials in biosensor development.

3 Nanomaterials in Biosensors

3.1 Metal Oxide Nanostructures

The beauty of the metal oxide nanostructures lies in their inherent functional biocompatibility, abundant active surface area in absorbing the bio-molecules, and high catalytic property in immobilizing the biomolecules in a non-toxic way to enhance electron-transfer kinetics for effective sensing characteristics. Various metal oxides from metals like Fe, Zn, Ce, Mg, Zn, Cu, Ti, and Zr are extensively explored in the literature for biosensor applications (shown in Fig. 3) [35–37]. These oxides of different morphologies and dimensions are synthesized using various synthesis methods like hydrothermal, sol–gel, radio frequency sputtering, soft chemistry, etc. [3].

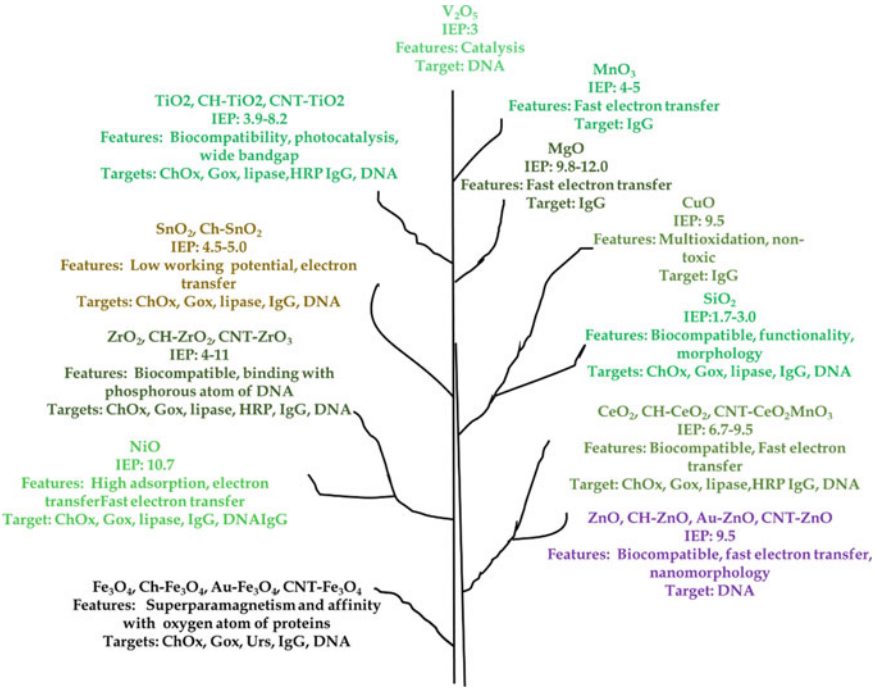

Fig. 3 Typical metal oxide nanostructures and their biosensing characteristics. The abbreviations in this picture can be read like this IEP as iso-electric point; ChO_x as cholesterol oxidase; GO_x as glucose oxidase; HRP as horseradish peroxidase; IgG as immunoglobulin G; Urs, as urease (adopted from Solanki et al. [35])

3.2 Chalcogenide Nanostructures

In biosensors, to enhance the optical, opto-electrical, electrical, and magnetic properties of the semiconducting oxides are deliberately used with metal oxide as a hybrid structure. Additionally, several semiconducting sub-atomic scale particles demonstrate fascinating biosensing characteristics. The use of semiconductor and semiconductor chalcogenide nanostructures is reported in optical transduction. As reported in the literature, semiconducting quantum materials are deliberately used in biosensing applications due to their superior photo-stability, size-dependent photoemission, and broad absorption. However, the structural defects in fine quantum dots enhance the radiative recombination leading to inaccurate emission estimation.

Several soft techniques are adopted to overcome such defects and make the transducer more sensitive toward analyte detection and bio-immobilization. Those are as follows.

(i) In the case of CdS, a layer of ZnS is coated on the surface to form a core–shell structure which acts as a photo-quencher: *Encapsulation*
(ii) Functionalization of the quantum dots to enhance biomolecule immobilization and minimize the chance of toxicity with a broad idea not to hamper the photophysical recombination: *Ligand exchange*
(iii) An extension of the previous step where the quantum dots are coated with silica to enhance the stability: *Silanization.*

This type of non-radiative or Fluro-quenched nanostructures is used as Förster/fluorescence Resonance Energy Transfer (FRET), especially for detecting optical DNA and oligonucleotides. Recently, two-dimensional nanomaterials and their derived quantum structures have demonstrated high potential donors in FRET-based sensing applications. These materials are graphitic carbon nitride (g-C_3N_4) [38], perovskite materials [39], selenium [40], 2D metal–organic/covalent organic frameworks [41], and their derived 2D quantum structures [42, 43]. The details of the above materials are tabulated in Table 1.

Bioluminescence resonance energy transfer (BRET) is another type of biosensing technique where semiconducting quantum nanostructures are used as the acceptor. It is a distance-dependent non-radiative energy transfer from a bioluminescent donor to a fluorescent acceptor through resonance energy transfer. Using this technique, the blood glucose level can be estimated from teardrops. Bioluminescence donors are natural enzymes collected from marine animals. Certain donors have specific functions based on their structural arrangement. Some of the BRET donor–acceptor pairs reported in the literature are listed below in Table 2. Recently, several quantum dots are used as the acceptor in BRET sensors due to their distinct advantages. Mattoussi et al. [60] tunable emission from Ag: ZnInSe QDs can be obtained by varying the In/Zn feeding ratio. This Ag: ZnInSe QDs demonstrates robust behavior in terms of tuning the emission to align the protein emission in the BRET sensor for several cycles. Some of the reported functionalized semiconducting quantum dots used in BRET sensors include polymer-coated CdSe/ZnS core–shell nanostructure [61],

Table 1 Summary of the FRET sensing applications of 2D nanomaterials as donors

Target analyst	Donor: acceptor pairs	Dynamic range	Detection limit	References
Bilirubin	MoS_2 QDs: bilirubin	0.5–10.0 μm	2.1 nm	[44]
MicroRNA	MoS_2 QDs: FAM-MBs	5–150 nm	0.38 nm	[45]
EP	MoS_2 QDs: $P_{EP\text{-}PEI}$ copolymers	0.2–40 μm	0.05 μm	[46]
AA	MoS_2 QDs: $P_{EP\text{-}PEI}$ copolymers	0.5–40 μm	0.2 μm	[46]
6-MP	MoS_2 QDs: DAP	0.5–70 μm	0.29 μm	[47]
BSA	MoS_2 QDs: RGO	5–50 nm	Not mentioned	[48]
Dopamine	MoS_2 QDs-aptamer: MoS_2 nanosheets	0.1–1000 nm	45 pm	[49]
BSA	MoS_2 QDs: polyaniline	10–70 nm	9.86 nm	[50]
GSH	MoS_2 QDs: R6G	5–50 nm	2.7 nm	[51]
Nitrite	MoS_2 QDs: BSA-Au NCs	0.5–20 mg/l	0.67 nm	[52]
NFZ	WS_2 QDs: NFZ	0.17–166 μm	0.055 μm	[53]
DNA	BP QDs: Dabcyl-L probe	4–4000 pm	5.9 pm	[54]
GSH	g-C_3N_4: MnO_2	NM	0.2 μm	[38]
H_2O_2	g-C_3N_4: MnO_2	0–130 μm	1.5 μm	[55]
Glucose	g-C_3N_4: MnO_2	0–150 μm	1.5 μm	[55]
Ricin	g-C_3N_4: MnO_2	0.25–50 μg/ml	190 ng/ml	[56]
Riboflavi	g-C_3N_4: riboflavi	0.4–10 μm	170 nm	[57]
Metronidazole	g-C_3N_4: metronidazole	0.01–0.10 μg/ml	0.008 μg/ml	[58]
Dopamine	BSA-Au NCs/g-C_3N_4: dopamine	0.05–8.0 μm	0.018 μm	[59]
Hg(II)	Perovskite: RBED	20–90 μm	2.36 μm	[39]

semiconductor polymer nanoparticles with poly[2-methoxy-5-((2-ethylhexyl)oxy)-p-phenylenevinylene] (MEH-PPV) [62], carboxylated quantum dots (Qd-625) [63], annexin V·RLuc-QDs [64], and glutathione-coated CdSeTe/CdS QDs [65].

Table 2 Summary of bioluminescent proteins used in BRET sensing application

Bioluminescent proteins	Emission (nm)	Substrate	References
Vargula luciferase (Vluc) or Cypridina luciferase	460	Vagulin (Cypridina luciferin)	[66]
Bacterial luciferase (Lux)	490	$FMNH_2$ long-chain aliphatic aldehydehdacf	[67]
Gaussia luciferase (Gluc)	480	Coelenterazine	[68]
Metridia luciferase	480	Coelenterazine	[69]
Renillaluciferase (Rluc)	480	Coelenterazine	[70]
Aequorin	469	Coelenterazine	[71]
Firefly luciferase (Fluc)	562	D-luciferin	[72]
Nanoluciferase (Nluc)	460	Furimazine	[73]

3.3 Magnetic Nanoparticles

Intrinsic magnetic nanoparticles [74] and functionalized or coated nanoparticles have been applied in various biological applications like DNA [75] or cell separation [76], biological missiles [77], radio-immunoassay [78, 79], and in several varieties of biomolecule immobilization [80–87], especially for biosensor applications. Core–shell nanostructures of Fe_3O_4@polydopamine [88], Ferrocene-modified Fe_3O_4@SiO_2 nanoparticles [89], Au@Ni [90], Ag NPs@Fe_3O_4 [91], Fe_3O_4/Au @γ-Fe_2O_3/Au [92], etc., are designed for biosensor applications. Grancharov et al. [93] reported that the functionalized magnetic nanoparticles are used as biomolecular labels in magnetic tunnel junction-based biosensor. Chuang et al. [94] interpreted the time scale of Brownian relaxation of magnetic nanoparticles suspended in liquid obtained from the susceptibility variation as a function of frequency as a bio-magnetic target molecule sensor. Simultaneous detection of the magnetic field-assisted DNA hybridization is sensed using a spin valve sensor reported by Graham et al. [95]. Liu et al. [96] fabricated a phenol biosensor where carbon paste is used as the supporting substrate for chemically immobilized and functionalized core–shell magnetic nanoparticles.

Research on magnetic nanoparticle-based biosensors is limited to lab-scale devices and medical diagnosis instruments in miniature form for bedside medical diagnosis. Several NPs are used in medical diagnosis devices; their sensitivity, the minimum sample volume, and the analyte that can be detected using these instruments are listed in Table 3 which is adapted from Koh et al. [97]. One pioneer example is the μ-NMR designed by Weissleder et al. [10] using 39 nm functionalized iron oxide nanoparticles in the microfluidic network. Further, the improved version of the microcoils is embedded in PDMS to increase the filling factor and decrease the signal-to-noise ratio. Also, this instrument can detect a minimal amount of sample, i.e., 1 μl of the device [19, 20, 98].

Table 3 Magnetic nanoparticle used in different medical diagnosis instruments with their sensitivity [97]

	Analyte	Magnetic particle/instrumentation	Sensitivity	Sample volume (μL)	References
MRSw type I	Nucleotide	CLIO, benchtop relaxometer	Low nM-pM	300	[99]
	Proteins	CLIO, benchtop relaxometer	Low nM	300	[100]
	Virus	CLIO, MRI	50 virus/100μL	100	[101]
	Bacteria	Core/shell, DMR	20 CFUb/100 μL (membranefitered)	5	[20]
	Cancer cell	Mn-MNP, DMR	2 cells/1 μL	5	[19]
MRSw type II	Antibody	MP, bench top relaxometer	< 1 pM	300	[102]
AC susceptometer	Antibody	Iron oxide nanoparticles	< 1 nM		[103, 104]
SQUID	Bacteria	Iron oxide nanoparticles	1.1 × 105 bacteria/ 20 μL		[103, 104]
	DNA	Magnetic bead	3–10 pM (signal amplification)		[105]
GMR	Protein	Cubic FeCo NP	2 × 106 proteins	2	[106]
	DNA	Antiferromagnetic NP	10 pM		[107]
	Protein	Iron oxide NP	2.4 pM		[108]

3.4 Carbon Nanostructures

The beauty of carbon-based nanomaterials from its bulk count part is

It is easy to electrochemically recognize a specific type of biomolecule (such as ascorbic acid and uric acid.) mixed with carbon nanomaterials and quantify it which is impossible with glassy carbon electrodes. In potentiodynamic analysis, carbon nanotubes act as an ion–to–electron transducer for biosensing analysis.

a. The outstanding electrical transport properties of carbon nanomaterials like carbon nanotubes and graphene. Intrinsic single-wall carbon nanotubes and graphene possess ballistic transport properties with high electron mobility which is necessary for high-speed biosensors.
b. Using carbon nanomaterial in particular single or bilayer defect-free graphene which has high conductivity with low thermal noise and due to fewer defects, the pink noise (*i/f* noise) is also very low and can be effectively utilized in designing ultrasensitive biosensors.
c. For flexible biosensor design, carbon-based nanomaterials are considered the best selection based on cost, stability, and performance.

d. Carbon nanodots/quantum particles are the best fluorescent centers for effective optical biosensor applications.

3.5 Hybrid Nanostructures

Hybrid nanomaterials are a promising platform for biosensor application, especially for the sensor in bio-medical diagnosis consisting of a unique conjugate of inorganic and organic components. The beauty of these hybrid nanomaterials lies in

a. Fine inorganic nanoparticles (< 100 nm) have an enormous potential to be applied in electronics, catalysis, bio-medical, etc. However, for bio-medical applications, the inorganic particles must be bio-compatible and have colloidal stability in the aqueous environment without agglomeration and degradation. Thus, the organic material is widely hybridized with this inorganic particle to improve bio-compatibility, processability, and chemical stability.
b. The organic/inorganic hybrids are mechanically robust and thermally more stable systems than individuals. Most importantly, the internal porosity of the hybrid can be tuned by anchoring the inorganic component which is highly desirable for ultrasensitive biosensor design and to increase the drug loading efficiency.
c. The biological fluid when interacting with finer in-organic particles, the protein corona forms on the surface of the inorganic nanoparticles. The size and surface properties of the nanoparticles are highly dependent on the protein corona formation and cell-nanoparticle interaction. Additionally, the selection of organic components of the hybrid especially for biomedical application needs depth understanding of the protein corona formation and growth for effective biomedical application of the hybrid nanomaterial.

Based on recent literature, we are citing some of the recent works on the use of hybrid nanomaterials in biosensing applications. The list of carbon materials in hybrid form, reported in the literature in tabulated form (adapted from [3]) is cited in Table 4.

4 Challenges and Future Perspectives

Most importantly, the modern biosensor device can be miniaturized to a portable form for bedside clinical applications with effectively high throughput. Some of the new detection techniques that sound well from a scientific point of view and technological importance are grooming as next-generation electronic sensing chips such as field-effect electrolyte–insulator-semiconductor (FE–EIS) sensors and capacitive FE–EIS. Recently, the application of 2D materials like nanocarbon, metal dichalcogenides, hexagonal boron nitride, black phosphorous, and metal oxides has highly impacted the research in the FE–EIS-based sensors. However, there remain several challenges

Table 4 Represents the list of carbon and carbon-based hybrid nanomaterials employed in the development of biosensors (Adopted from Ref. [3])

Nanomaterial	Analyte	Transducer	Linear range	Detection limit	References
Ag@CQDs-rGO	Dopamine	Electrochemical	0.1–300 μm	0.59 nm	[109]
Ag NP-MWNT	Glucose	Electrochemical	0.025–1.0 mM	0.01 mM	[110]
Pd/Co-NCNT	Hydrazin	Electrochemical	0.05–406.045 μm	0.007 μm	[111]
Pd/CNF/$[M3OA]^+[NTF2]^-$	H_2		1.00–35.0 nM	0.33 nM	[112]
Cu NPs/Rutin/MWCNTs/IL/Chit/GCE	H_2O_2	Cyclic voltammetry	0.35–2500 μM	0.11 μm	[113]
Cu/rGO-BP	Glucose	Electrochemical	0.1–2 mM	11 μm	[114]
Ni/Cu MOF	Glucose	FET	1 μM–20 mM	0.51 μM	[115]
NiO/PANINS	Glucose	Amperometric	1–3000 μM	0.06 μM	[116]
MnO-Mn_3O_4@rGO	H_2O_2	Impedimetric	0.004–17 mM	0.1 μM	[117]
ZnO-rGO	Dopamine	Cyclic Voltammetric	0.1–1500 pM	8.75 ± 0.64 pM	[118]
MoO_3@RGO	Breast cancer	Electrochemical	0.001–500 ng mL^{-1}	0.001 ng mL^{-1}	[119]
Graphene QDs	Cu^{2+}	Electrochemical	0.015–8.775 μM	1.34 nM	[120]
Graphene QDs	Lung $cancer^+$	Fluorescence	0.1 pg mL^{-1}–1000 ng mL^{-1}	0.09 pg mL^{-1}	[121]
CdTe/CdS//ZnS core/shell/shell QDs	l-ascorbic acid	Fluorescence	8.0×10^{-9}–1.0×10^{-7} M	1.8×10^{-9} M	[122]
NSET amptamer@Fe_3O_4@GOD and MoS_2	Tumorcell(EpCAM)	Magnetic fluorescence	2–64 nM	1.19 nM	[123]
Au NPs@PDA@CuInZnS QDs	P53 gene	Electrochemiluminescenece	0.1–15 nmol L^{-1}	0.03 nmol L^{-1}	[124]
CaM/SiNW-FETs	Protein	FET	10^{-8}–10^{-6} M	7 nM	[125]
G/Au NR/PT	HPV DNA	Electrochemical	1.0×10^{-13}–1.0×10^{-10} m L^{-1}	4.03×10^{-14} m L^{-1}	[126]

(continued)

Table 4 (continued)

Nanomaterial	Analyte	Transducer	Linear range	Detection limit	References
Graphene-Au NRs	NADHEthanol	Amperometric voltammetric	20–160 μM5–377 μM	6 μM1.5 μM	[127]
LAC-CNTs-SPCE	Para-cresol	Electrochemical	0.2–25 ppm	0.05 ppm	[127]
Co_3O_4-CNT/TiO_2	Glucose	Photoelectrochemical	0–4 mM	0.16 μM	[128]
CNT thin-film transistor (TFT)	DNA	Thin film transistor (TFT)	1.6×10^{-4}–5 μmol L^{-1}	0.88 μg L^{-1}	[129]
GQDs-MWCNTs	Dopamine	Electrochemical	0.005–100.0 μM	0.87 nM	[130]
CNT/Au NPs	Choline	Amperometric	0.05–0.8 mM	15 μM	[131]
PAMAM dendrimer	DENV 2E	Optical fiber	0.1 pM–1 μM	19.53 nm nM^{-1}	[132]
SAM/NH_2rGO/PAMAM	DENV 2E	SPR	0.08 pM–0.5 pM	0.08 pM	[133]

in biosensor-based materials design, especially for medical applications which are as follows

a. In enzyme-based biosensors, the presence of fouling agents and endogenous interfaces present in the sample has significantly hampered the sensor's sensitivity and specificity. Though this issue was partially addressed by making hybrid biomaterial, still the interface effect persists.
b. Generally, doped semiconductor nanostructures have particular importance in biosensor design. However, the synthesis of doped semiconductor nanostructures is carried out in a harsh environment, and it isn't easy to achieve it on a large scale. Scale-up synthesis with high-quality control is highly desirable.
c. Real-time in-vivo monitoring in complex media such as tissues and blood is still challenging. Moreover, it is highly desirable to establish a robust detection platform for in-vivo analysis, especially from a pharmacokinetic and pharmacodynamics point of view.
d. Toxicity of the nanomaterials (carbon nanomaterials such as carbon whisker and carbon fiber.) in biosensors remains a significant challenge, especially for medical diagnosis.

5 Conclusions

This chapter comprehensively summarized the present scenario of nanomaterials in biosensors for medical applications. An attempt was made to summarize several chemical compositions and dimension nanomaterials applied in various biosensors in worldwide research. Additionally, the classification of biosensors based on the biorecognition and signal transduction mechanism was discussed. In recent decades, biosensors have demonstrated their potential to detect various quantitative and qualitative targets, especially for medical diagnosis. Due to the high stability and lower price, biosensors such as aptasensors and DNA-modified electrodes are being used as point-of-care devices for quick diagnosis of the SARS COVID-19 virus during ongoing pandemic emergencies across the globe. Modern biosensors have a vast perspective and high compatibility compared to conventional biosensors in medical applications due to their real-time diagnosis capability, high specificity, and sensitivity with minimal sample preparation.

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