Nanotechnology in the Life Sciences

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Biobased Nanotechnology for Green Applications

Springer

Nanotechnology in the Life Sciences

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

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

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Preface

The current book will be useful for different industrial sectors such as the biofuel industry, agriculture, food protection and food packaging, plant and crop protection, the pharmaceutical industry, advanced medical technology such as neurodegenerative diseases, 3D/printing, environmental rehabilitation such as in controlling pesticide, and water and wastewater treatment. The biobased nanomaterials could provide new insights into the fast-moving fields of biomedical and environmental sciences by demonstrating the efficacy of such nanomaterials in biomedicine and environmental remediation. These nanosize particles are extremely useful and are likely to become the next-generation nanosize factories with vast applications in these fields. Research is therefore continuing and the data produced in the environmental and biomedical fields will have the potential for a sustainable future. As bioremediation, a green and sustainable approach is rapidly gaining momentum; the chapters in this book would be quite apt for future research that could be of benefit to all concerned stakeholders. The chapters in this reference book are a special selection covering the most recent studies, contributed by eminent experts in the aforementioned fields. We hope that this book covering and highlighting significant research and development in the field will immensely help researchers a great deal and will also add a new dimension to the sustainable use of biobased nanomaterials.

The book comprising 22 chapters has been contributed by 80 authors from leading nanotechnology research groups from Brazil, Costa Rica, Czech Republic, India, Iran, Ireland, Malaysia, México, Oman, Slovakia, and the USA. The introductory chapter critically evaluates nanotechnology for green applications, with specific emphasis on machine learning. Other chapters highlight copper and iron-based bio-nanocomposites; applications in agriculture; magnetic nanoparticles from bacteria; benefits of chitosan-based and cellulose-based nanocomposites in food protection and food packaging; nanotechnology for biofuels; biosynthesis of nanoparticles by bacteria and thallophytes; nanotechnology for detection and diagnosis of plant diseases; organic carbon dots for mitigating neurodegenerative diseases; characterization and biocompatibility of a poly lactic acid (PLA) 3D/printed scaffold; nanoparticles as artificial chaperons suppressing protein aggregation:

remedy in neurodegenerative diseases; metal-organic framework-based nanostructures for biomedical applications; biological conjugates: potential role in biomedical and pharmaceutical applications; biosurfactants-based nano micelles for extraction of biomolecules; implications of nanoscopic surface modification on protein adsorption and cell adhesion; nanotechnology as an effective tool for improved crop production under changing climatic conditions; silver nanoparticles as a fungicide against soil-borne *Sclerotium rolfsii*: a case study for wheat plants; novel strategies for environmental remediation of pesticides using nanocatalysts; synthesis of novel metal/metal oxide-based nanomaterials using plant derivatives and their potential environmental applications; dry deposition of atmospheric nanoparticles—a case study; and biochar-based nanocomposites: a sustainable solution for water and wastewater treatment.

We are quite certain that this book will be very much useful for research scholars, bioengineers and biomedical scholars, graduate and graduate students in nanotechnology, nanobiotechnology, health, clinical, and pharmaceutical sciences.

Assam, India Hemen Sarma
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About the Editors

Hemen Sarma obtained his Ph.D. in Botany from Gauhati University [2008] and pursued postdoctoral studies at North-Eastern Hill University, Shillong [2009–2010] and the Institute of Advanced Studies in Science and Technology [IASST], Guwahati [2011–2012], India. He is currently senior Assistant Professor at Nanda Nath Saikia College, affiliated with Dibrugarh University, Assam, India [since 2012]. His research focus is on plant–microbiome interactions, biosurfactants, persistent pollutants, sustainable remediation, CRISPR/cas9 gene editing, and nanobiotechnology. Important contributions were made to the bioremediation of emerging contaminants [ECs], endocrine disrupting compounds (EDCs), and persistent organic pollutants (POPs). Dr. Sarma has more than 50 publications to his name in peer-reviewed international journals, including conference papers and book chapters, and patents that have been published or are pending. He is the author of five books by leading international publishers such as John Wiley and Sons, UK; Springer Nature, USA; and Elsevier, USA. Dr. Sarma has contributed to the peer review process of several high-impact journals [ACS, Elsevier, Springer]. He is a review editor of *Frontiers in Microbiology* and the series editor of *Advances in Biotechnology and Bioengineering*, Elsevier. Dr. Sarma has 10 years of teaching experience and completed 04 research projects sponsored by the Department of Biotechnology, the Government of India and the University Grants Commission, New Delhi. He has received a number of awards, distinctions, and fellowships, such as DBT-Overseas Associateship [2015–2016] and DBT-Research Associateship [2011–2012], IISc Research Associateship [2009], and UGC-Dr. DS Kothari Postdoctoral Fellowship Awards [2009–2010]. In 2017–2018, Dr. Sarma joined as an Affiliate in the Department of Chemistry and Biochemistry, University of Texas, El Paso, USA, in a Visitor Professor Fellowship Program. He has received a foreign travel fellowship and has visited many reputed universities for academic purposes, such as Cairo University, Giza, Egypt, in 2011; University of Western Australia, Perth, in 2016; Hamburg University, Germany, in 2016, and University of Texas at El Paso, in 2017–2018.

Sanket Joshi is a Deputy Director, Oil & Gas Research Center, and an Application Specialist, Oil & Gas Science at Sultan Qaboos University, Oman. He holds BSc and MSc degrees from Sardar Patel University, India, and a PhD degree from M.S. University of Baroda, India—all in microbiology. Dr. Joshi has 16 years of academic teaching and research experience and 4 years of industrial R&D experience, in India and Oman. While working in Indian pharma companies, he undertook several turnkey projects (both upstream and downstream) on antibiotics (β-lactams, macrolides, glycopeptides), antidiabetic drug (for type II diabetes), and Co-enzyme Q10. His current research interests encompass energy (in situ/ex situ microbial enhanced light/heavy oil recovery; chemical enhanced oil recovery; biofuels); microbial products (biosurfactants, biopolymers, R&D, and scale-up); and environmental bioremediation (crude oil pollution; analysis, mitigation, and control of souring by sulfate reducing bacteria; HPAM contaminated sites). Those research projects are multidisciplinary, involving both biotechnology and engineering disciplines. Since he joined SQU, his research team has received over 4.13 million USD in research grants and service contracts, and established bioproducts for petroleum and environmental applications. He has about 126 scientific publications in international journals, book chapters, and conference proceedings, and two international books to his credit. He serves as an Academic/Associate Editor for some of the highly reputed journals: *Frontiers in Microbiology*, *PeerJ*, *Ecotoxicology* (Springer), *Petroleum Science and Technology* (Taylor & Francis, UK), *3 Biotech* (Springer), *Applied Biochemistry and Biotechnology* (Springer), and *Open Biotechnology Journal*. Guest editor for *Frontiers in Microbiology*, *Sustainability*, *Scientifica*, and *Open Biotechnology Journal*; and a recognized reviewer for more than 51 international journals (Elsevier, Springer Nature, T&F, Wiley/AOCS, RSC, ACS, Hindawi, DE Gruyter, MDPI, and others). He served as an intermediate guide for 30 undergrad/grad students and 3 PhD students, in India and in Oman. He is also an active member of MEOR research team at SQU since 2009 and established a state-of-the-art research and service laboratory at SQU. Dr. Joshi was 34th in SQU among top 500 authors (based on number of citations 2009–2018, as per SciVal-SCOPUS/Elsevier), with 2376 citations, h-index of 26, and i10 index of 38 Google Scholar).

Ram Prasad is associated with the Department of Botany, Mahatma Gandhi Central University, Motihari, Bihar, India. His research interest includes applied and environmental microbiology, plant–microbe interactions, sustainable agriculture, and nanobiotechnology. Dr. Prasad has more than one hundred seventy-five publications to his credit, including research papers, review articles, and book chapters and five patents issued or pending, and edited or authored several books. Dr. Prasad has 12 years of teaching experience and has been awarded the Young Scientist Award and Prof. J.S. Datta Munshi Gold Medal by the International Society for Ecological Communications; FSAB fellowship by the Society for Applied Biotechnology; the American Cancer Society UICC International Fellowship for Beginning Investigators, USA; Outstanding Scientist Award in the field of Microbiology by Venus International Foundation; BRICPL Science Investigator Award and Research Excellence Award, etc. He has been serving as editorial board members of *Frontiers in Microbiology*, *Frontiers in Nutrition*, *Archives of Phytopathology and Plant Protection*, *Phyton-International Journal of Experimental Botany*; *Academia Journal of Biotechnology*, *Journal of Renewable Materials* including Series editor of Nanotechnology in the Life Sciences, Springer Nature, USA. Previously, Dr. Prasad served as Assistant Professor at Amity University, Uttar Pradesh, India; Visiting Assistant Professor, Whiting School of Engineering, Department of Mechanical Engineering at Johns Hopkins University, Baltimore, United States; and Research Associate Professor at the School of Environmental Science and Engineering, Sun Yat-sen University, Guangzhou, China.

Josef Jampilek completed his Ph.D. degree in Medicinal Chemistry at the Faculty of Pharmacy of Charles University (Czech Republic) in 2004. In 2004–2011, he worked in expert and managerial posts in the R&D Division of the pharmaceutical company Zentiva (Czech Republic). Prof. Jampilek deepened his professional knowledge at the Medicinal Chemistry Institute of Heidelberg University (Germany) and at multiple specialized courses. In 2017, he was designated as a Full Professor of Medicinal Chemistry. At present he works at the Faculty of Natural Sciences, Comenius University, in Bratislava (Slovakia), the Institute of Neuroimmunology of the Slovak Academy of Sciences, and the Regional Centre of Advanced Technologies and Materials, Palacky University in Olomouc (Czech Republic). In addition, he is a visiting professor at the University of Silesia in Katowice (Poland) and Hong Kong Baptist University (Hong Kong SAR, China) and an invited professor/expert at various higher educational institutions. He is an author/coauthor of more than 30 patents/patent applications, more than 220 peer-reviewed scientific publications, 7 university textbooks, more than 35 chapters in monographs, and many invited lectures at international conferences and workshops. He also received several awards for his scientific results, e.g., from Aventis, Elsevier, Willey, Sanofi, and FDA. The research interests of Prof. Jampilek include design, synthesis, and structure–activity relationships of heterocyclic compounds as anti-invasive and anti-inflammatory agents as well as drug delivery nanosystems. He is also interested in ADME, drug bioavailability, and solid-state pharmaceutical analysis.

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Chapter 1
Nanotechnology for Green Applications: How Far on the Anvil of Machine Learning!

Avnish Pareek, Mohd. Zafar, Ramkumar Lakshminarayanan, and Sanket J. Joshi

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1 Introduction

Green applications of technologies are a need of hour for protecting the environment as well as to save the fast depleting finite natural resources by either pushing for quick development of renewable resources and/or by adopting lean processes. For the last two centuries, mankind is working on the developments of processes or products that have robustness, precision, durability, reproducibility, scalability, evolvability, ease of use, and are economic. But the issue of sustainability and environmental safety of these products/processes did not surface up until recently, when more prominent negative effects of human activities started reflecting back. In this scenario, the "Green applications" are proving promising, but one of the biggest challenges here is to meet the population demand and industrial growth while protecting the environment and finite resources.

The idea of green applications has come forward as rescue. It brings everyone's attention toward the importance of protecting, preserving, and sustainably using our environmental resources. It helped in creating a general awareness about environment; not only among different echelons of society but also for researchers, policy makers, and funding bodies. Thence, all the research, policy, funding, and market for any upcoming technology have an obvious orientation toward green application, and relatively new technologies like nanotechnology (Roco and Bainbridge 2001, 2005; Bürgi and Pradeep 2006) and biotechnology (Rigaud 2008) are no exceptions.

Nanotechnology has grown with a rapid pace and has proved itself promising in solving several modern-day problems. Individually, in its own domain, as well as in combination with nanobiotechnology, these technologies have not only shown a rapid progress in R&D but also captured the market in its infancy itself (https://www.transparencymarketresearch.com/nano-biotechnology-market.html. Accessed 8 Jun 2020). Some of the domain-specific and/or combined applications of nanotechnology have brought paradigm shifts in classical S&T fields such as medicine, material sciences, space, construction, food, electronics, pathogen detection, biosurfactant, etc. (De Morais et al. 2014; Bai et al. 2017; Prasad et al. 2017a, b, c). Given the precision, proclivity, and superiority of this technology and its interdisciplinary application, it even appears promising in solving the environment and unsustainability issues of the era.

By far, this nascent field of technology in combination with biotechnology has contributed heavily in medicine and biomaterials R&D sector, but nanomaterials for green applications are still quite away from realization.

There are several issues underlying this delay, and these can be classified into four broad categories: (i) issues intrinsic to bio-nanomaterials; (ii) issues associated with current life-size problems that require "green" solutions on human time scale; (iii) issues associated with sustainable tailor-made production, optimization, scale-up, risk-free maintenance, and disposal of bio-based atomic-scale right-fit assemblies for providing real-time solutions of specific problems at environment scale.

To have further clarity on first category above, the major intrinsic issues of nanomaterials are grouped into six attributes of studies. These are (i) composition, (ii) synthesis, (iii) internal and external properties, (iv) stability, (v) toxicity, and

(vi) life cycle assessment. Although these appear independent attributes but actually they interact to each other and a term “Ensemble Heterogeneity” (h_e) is defined here to understand their interdependence. Machine learning (ML) can provide deeper insights into both visible and hidden levels of these interdependencies. In the present chapter, firstly, these six attributes are reviewed and an understanding is developed that these attributes must be studied for hidden parameters and patterns using ML for producing optimized design solutions for nanomaterials. Secondly, an overview of different types of ML approaches is given that can contribute to the development of optimized design of nanomaterials. Finally, life cycle assessment (LCA) of nanomaterials is discussed. LCA is a tool to assess the environmental impact and sustainability of any technology to be “green.”

Nanomaterials are diverse with their inherent physicochemical and quantum properties they promise great solutions to modern-day life-scale problems in almost all fields of modern science. While understanding nanomaterials and their different facets of forms and functionalities, we come across six major attributes of nanomaterials, which include composition, synthesis, internal and external properties, stability, toxicity, and lifecycle assessment. But despite a large body of research nothing much has been done on prediction and modeling of any of the first four directions except some work has been done using machine learning (ML) on toxicity as described very well by Furxhi and team (Furxhi et al. 2020). Unpredicted and non-modeled design and synthesis of nanomaterial becomes dearer both at cost and time. Moreover, once synthesized, the in vivo studies for functionality, stability, lifecycle, and toxicity do not reflect the real-time behavior of nanomaterial in working environment and hence the likelihood of their failure increases manifold. This failure is attributed to poor understanding of the hidden interactions within and outside the molecular boundary of the nanomaterial. Therefore, a constructionist/emergentist approach is required just not only to predict the hidden patterns of interactions but also to develop a comprehensive mathematical framework that can predict macroscopic life-scale behavior and phenomenon of the nanomaterial in real time (Venkatasubramanian 2019). Such a scenario demands a predictive modeling using ML at each of these six major directions of studies on nanomaterials as mentioned above. This will lead to multiscale model-based informatics platform for the nanomaterials, which will help find more promising processes and most stable and robust products. This phenomenon is not new and called as *Discovery informatics* (Caruthers et al. 2003) for material design. More details on ML and its descriptors of uses with respect to nanomaterials are discussed in the appropriate section of the chapter.

This article is intended broadly in understanding the current challenges associated with nanomaterials and their possible solution using ML. Since ML is data-driven, we have tried to discuss certain aspects of nanomaterials which have variables at core, and hence where the data exist can be further utilized in ML to help understand hidden parameters and patterns of six major directions of studies on nanomaterials, which include composition, synthesis, internal and external properties, stability, toxicity, and lifecycle assessment.

2 Issues Intrinsic to Nanomaterials

Nanotechnology is a field of material science where manipulations are done at cluster level, molecular level, atomic level, or at molecular structural level at nanoscale to obtain novel functionality of the material at life size. So far, since its first conceptual introduction by Erik Drexler in his 1988 book and the potential capabilities of nanotechnology in his subsequent books (Drexler 2006), the magical aptitude of this technology is successfully proved. Rapid pace of nanotechnology has really offered a "technological-leap" (Di Sia 2017) in almost all fields from electronics, telecommunication, ITC, medicine, civil engineering, energy capture and storage, bioremediation, agriculture and food technology, packaging, paper and textile industry, etc. (Hu and Cui 2012; Ratner 2013; Collins and Bell 2014; Fiori et al. 2014; Gonçalves 2015; Mobasser and Firoozi 2016; Lin et al. 2017; McMillin 2017; Prasad et al. 2014, 2017a; Ramos et al. 2017; Beernaert and Fribourg-Blanc 2017; Dasgupta et al. 2017; Abdalla et al. 2018; Han et al. 2018; Hernández-Muñoz et al. 2018; Bajpai et al. 2018; Tripathi et al. 2018; Yildirim and Röcker 2018; Hamad et al. 2018; Ali et al. 2019; He et al. 2019; Šahinagić-Isović et al. 2019; Golovynskyi et al. 2019; Weber et al. 2019; Yaradoddi et al. 2019).

The nanotechnology has practically removed many; if not all, boundaries between different disciplines of classical sciences. The matter responds differently at nanoscale manipulations and so are its functional manifestations. Generally, two approaches are used in the synthesis of nanomaterials, first; top-down approach and second; bottom-up approach (Subramani et al. 2019). In the first approach, materials are synthesized at nano level into devices without much intervention at atomic level. This is a function-oriented approach, wherein which, a specific desired action of material is required at nano level. Goals with high level of precisions are achieved through miniaturization, where conventional technology is not giving the desired results. These types of synthetic materials are unique and are used in a very narrow domain. Any further alterations of such materials for achieving cross-domain functionalities are highly limited. In the second, bottom-up approach, atomic/molecular integration is used first for the synthesis of a specific cluster/material and finally into a functional device. This approach studies and exploits properties at all levels of material organization and thereby can be used for cross-domain functionalities by reinforcement modifications at level of material organization. As compared to top-down approach, bottom-up approach is more systematic but is more complicated.

However synthesized, a nanomaterial must provide consistent performance throughout its operational life time (Lord et al. 2017). Besides the targeted "operational functionality"; mechanical, structural, electrical, and electromagnetic stability is highly desired. The miniaturization at nanoscale has bestowed the highest precision to the material but at the same time, the issues of instability have proved this miniaturization as a blowback. As mentioned previously, while understanding nanomaterials and their different facets of forms and functionalities, we come across six major attributes of nanomaterials, which include composition, synthesis, internal and external properties, stability, toxicity, and lifecycle assessment. In the following sections, each of these six attributes is discussed in detail for the possibility of use of ML for designing a better and "green" nanomaterial.

2.1 Composition

Composition of a nanomaterial is a very important feature. Though, at times, there could be an ambiguity in relating the composition to the physical and/or chemical properties/activities of a substance. For nanomaterials, as Roco (Roco 2011) used "composition", while defining second-generation nanomaterials, it is more related to the chemical activity.

While discussing composition-based classification given by ISO (International Standard Organization), Camboni and others (Camboni et al. 2019) highlight the importance of composition. According to them ISO defines a nanostructure as "Nanostructure is instead defined as a—composition of inter-related constituent parts in which one or more of those parts is a nanoscale region [where] a region is defined by a boundary representing a discontinuity in properties." The ISO technical specification distinguishes between five categories of nanostructured materials:

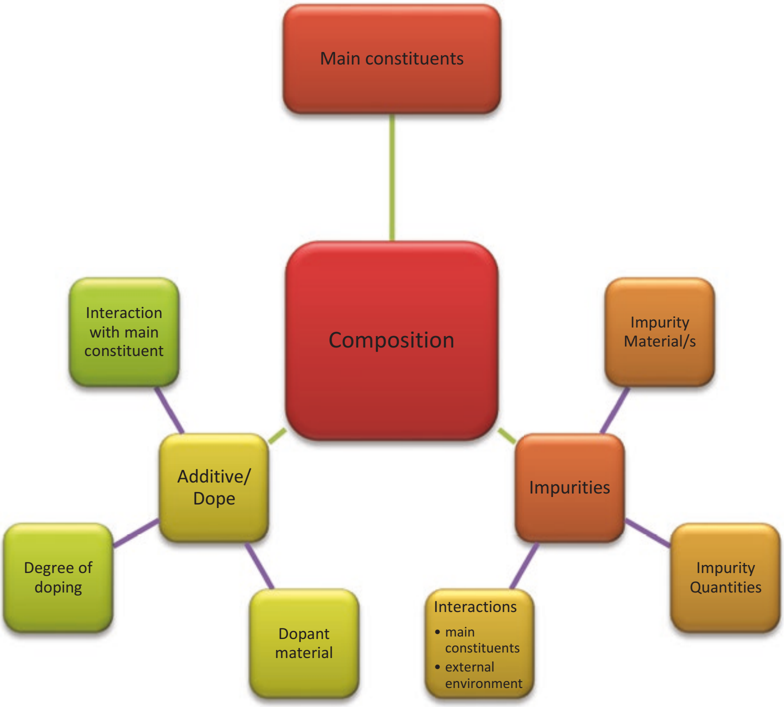

Fig. 1.1 Variables (factors) of composition

nanostructured powders; nanocomposites; solid nanofoam; nanoporous material; and fluid nanodispersion (International Organization for Standardization (ISO) 2010).

A working definition of composition of nanomaterial can be obtained from ECHA guidelines (European Chemicals Agency 2017; ECHA 2019), which defines it as the combination of (1) main constituents, (2) additives, and (3) impurities (Fig. 1.1). With this definition, there can be a change in composition with changes in main constituents, additives, and impurities of the nanomaterial. Such an elaborate understanding of composition explains its dependence upon, purity, synthesis method, process optimization, temperature of synthesis, and time.

Composition is important. It ascertains functionality, fixes stability, elongates operational life, and reduces toxicity. It governs solubility, hydrophobicity, lipophilicity, zeta potential, dispersibility, biological activity, photo-reactivity, and other physiochemical properties of a nanomaterial (Bhatia 2016; Ealias and Saravanakumar 2017; Camboni et al. 2019).

Table 1.1 Different types of nanomaterials

Nanomaterials	Description/Examples	References
Carbon based	Contains primarily carbon only, fullerenes, graphene, carbon nanotubes (CNTs), carbon onions, carbon black, etc.	Gatoo et al. (2014), Bhatia (2016), Ealias and Saravanakumar (2017), Jeevanandam et al. (2018), Camboni et al. (2019), Khan et al. (2019)
Organic	Dendrimers	Abbasi et al. (2014)
Inorganic	Inorganic material, e.g., rare earth-doped nanoparticles (REDN)	Liu et al. (2018)
Composite	Quantum dots/graphene composites	Luo et al. (2015), Tong et al. (2017)
Metallic and metal oxides	Gold nanoparticles, iron oxide nanoparticles	Mody et al. (2010), Gao et al. (2020)
Non-metallic	Solid silica nanoparticles (SiNPs), mesoporous silica nanoparticles (MSNs)	Chen et al. (2013)
Homogenous	Self-assembled Au NPs	Decarolis et al. (2020)
Heterogeneous	Heterogeneous lamella structure, e.g., copper/bronze laminates	Wang et al. (2018), Ma et al. (2019)
Passive	Chemically inert nanoparticles, e.g., carbon nanodots for drug delivery; relatively stable TiO_2 in aqueous environments	Gicheva and Yordanov (2013), Chatzimitakos and Stalikas (2019)
Active	Chemically reactive	Xu et al. (2018)
Biological	From living materials: Naturally occurring such as small polymeric lipoproteins or synthesized using biological systems	Stanley (2014), Saboktakin (2017)

3 Main Constituents in Composition

As such there are different types of nanomaterials classified on various bases. Table 1.1 summarizes some nanomaterials types in literature, based on the main constituents only. Some of the classes in the table are overlapping in nature.

4 Additives in Composition

Additives are the second components of nanomaterial composition. These must not be confused with nano-additives, which are otherwise the physical additions of nanomaterials, to the existing classical materials in use, to improve their physiochemical and/or electromagnetic properties. Additives to nanomaterials are very specific components added to the nanomaterials during synthesis for improving certain fundamental or technical attributes. Unlike impurities, additives are deliberately added during synthesis for a specific output. Technically this addition is called as "doping" and the substance added is known as "dopant." A lot of structured research has been carried out on doping. A detailed study of research work on doping till last decade was summarized by Wei Chen from University of Texas at Arlington, USA in the book series titled as "Doped Nanomaterials and Nanodevices" (Song and Tanner 2010). Doping works good in many functional fields, for example, improvement of optical properties (Bharat et al. 2019), for enhancing water electrolytic properties (Ouyang et al. 2019), for in vivo optical bio-imaging (Tan and Chen 2020), for improved radiosensitizing effects for cancer theranostics (Nakayama et al. 2020). Doping effects are dependent on dopant material, its interaction with main constituent, and degree of doping.

5 Impurities in Composition

Impurities are classed as third component of composition for a nanomaterial. In nanomaterials they affect the physiochemical properties to a larger extent. Although very few individual studies have been done as a sole work on nanomaterial impurities and their effects. Usually, impurities are at ultralow ratios vis-à-vis the total quantity of material under study, but still they have pronounced effect. The miniaturization is mainly responsible; ultralow mass to volume ratio and high surface to mass ratio allows the impurity to interact with the constituents as well as with the external entities. This makes them important at fundamental and technological interests. The effects of impurities are relative, sometimes they are synergistic and improves the properties of the parent nanomaterial and hence become desirable, at other times it may be the reverse case. At other times, these impurities are quite intriguing, and separating them is essential but tedious. Many times the impurities interfere or impede the bare essential tests on functionalities and/or toxicity (Hutchison 2008; Park et al. 2014; Webler et al. 2014; Kakoty et al. 2016; Lord et al. 2017). Some of the main effects of impurities are dependent on impurity material/s, their quantities, and their interactions with main constituents, dopants, and outside environment.

5.1 Synthesis Approach

Nanoparticles are the constituents of nanomaterials. These particles are of different shapes, size, dimension, and surface morphologies ranging up to 100 nm. They can be solid or hollow, homogeneous, or heterogeneous in their composition, may be chemically active or passive in their surroundings, or have any other nature or property as given in Table 1.1. All the nanoparticles are synthesized by either top-down or bottom-up approach (Ealias and Saravanakumar 2017). The method of synthesis has a profound effect on the macroscopic behavior of the nanoparticles and thereby on nanomaterials. Therefore, it is imperative to understand the factors and/or variables of synthesis method that affect the behavior of the final product. Table 1.2 summarizes some of the common methods of synthesis and the regular factors/variables their-in. This table is populated here from the perspective of understanding the opportunity that these factors can be used to capture the nonlinear data generated during synthesis that can be used in ML. Besides these regular variables of synthesis methods key steps in the self-assembly of nanoparticles using different methodologies (Decarolis et al. 2020) can also give valuable inputs to ML modeling.

5.2 Intrinsic and Extrinsic Properties

Intrinsic properties of nanoparticles are dependent on size, density, volume, mass, surface area, quantum properties, crystal structure, quantities of impurity and/or dopant, etc. Studies have already shown far-reaching effect of particle size and mass of nanoparticles on nano-(eco) toxicology (Aşik et al. 2016; Guo et al. 2016; Perde-Schrepler et al. 2019). To rapidly identify, characterize, and quantify nanoparticles in serum and environmental water samples (Zhou et al. 2017) used EMSD (Elemental mass size distribution) that measures mass, size, and composition of traces of nanoparticles in complex samples. This proves that these intrinsic properties of nanoparticles are fundamental and particle specific and remain constant throughout the different levels of organization from atoms to crystal structures via molecules. Therefore, it is obvious that these properties must be interfering and affecting composition, synthesis, internal and external properties, stability, toxicity, and lifecycle assessment of nanomaterials. Such unique signature properties can be used to predict variations and subsequently can give inputs to ML. However, in the existing scenario, many labs are doing redundant studies to optimize the preparation of

Table 1.2 Factors affecting nanoparticle synthesis in some common synthesis methods

Synthesis approach	Common factors affecting each method	References
Top-down methods		
Laser ablation, e.g., laser ablation synthesis in liquid solution (LASiS)	Material parameters (bulk target, solvent and solutes, system temperature, and pressure) and laser parameters (wavelength, duration, energy, repetition rate, number of laser pulses, and the spot area on the target).	Amendola and Meneghetti (2013)
Mechanical milling	Mill type, milling speed, ball size distribution, process kinetics, energy transferred, milling type, milling temperature, milling duration ball mass, ball density, ball velocity	Prasad Yadav et al. (2012), Bello et al. (2015)
Chemical etching	Influence of the doping level, HF–oxidant molar ratio (χ), solvent concentration, metal catalyst amount	Geyer et al. (2015), Vinzons et al. (2017), Shiao et al. (2018)
Sputtering	Thickness of the layer, temperature and duration of annealing, substrate type, etc.	Tan et al. (2018)
Electro-explosion	Input power, current density, medium temperature and wire diameter, metal properties, interaction of metal with the medium	Ahmadi et al. (2018)
Bottom-up methods		
Spinning/electro-spinning	Solution parameters (concentration of the polymer solution, molecular weight, viscosity, surface tension, solvents, conductivity/surface charge density) and processing parameters (voltage, collector/needle distance, flow rate, diameter of the syringe), ambient temperature, and humidity	Kadavil et al. (2019)
Template-support synthesis	Nature of template-synthetic/natural, type of template-hard versus soft template, methods in template preparation, method adopted for nanomaterial synthesis (hydrothermal method, precipitation, or solgel method) method of template removal (e.g., dissolution, sintering, and etching)	Xie et al. (2016)
Plasma or flame spraying synthesis	Properties of plasma torch, injection, fixture, feedstock, and substrate	Unabia et al. (2018)
Laser pyrolysis	Laser power, reactor pressure, gas flow rate, and residual precursor	Belchi et al. (2019)
Chemical vapor deposition (CVD)	Technique used, gases used, source material, substrate and their interaction, and temperature regime	Park et al. (2014), Kadavil et al. (2019)
Atomic or molecular condensation	Nature of the metal used, nature of its interaction with gas, temperature regime	Nentwich (2011)
Biological synthesis via bacteria, yeast, fungi, algae, plants, etc.	Several factors, mainly dependent on material–organism interaction and cellular response	Iravani (2011), Cheeseman et al. (2020); Prasad et al. (2016); Srivastava et al. (2021)

(continued)

Table 1.2 (continued)

Synthesis approach	Common factors affecting each method	References
Physical vapor deposition (PVD)	Technique used, evaporation of solid, vapor phase transport to the substrate, vapor condensation, electromagnetic properties of substrate and its interaction	Yap and Zhang (2015)
Supercritical fluid synthesis	Density, dielectric constant, solubilizing capacity of supercritical fluid, temperature and pressure regime, interaction of base material with SCF	Kate et al. (2019)
Sol-gel process	Metal solvent interaction, pH, temperature, reaction time, residence time, sol state, gel state	Ramesh (2013), Parashar et al. (2020)
Aerosol-based process	Coagulation and sintering properties, process-specific characteristics	Pratsinis (2012)

nanomaterials for their uses and to evaluate and compare functionality, stability, and toxicity. This is because of lack of information on fundamental properties of nanoparticles and standardized protocols to test and verify (Renero-Lecuna et al. 2019). This makes use of ML more necessary with nanomaterials.

Extrinsic properties of nanomaterials are also equally important. Usually, structure activity relations (SARs) are studied for nanomaterials, in particular quantitative structure activity relations (QSARs) are studied in computational models for toxicology and are specifically used in safety manuals (European Chemicals Agency 2017). Solubility, dustiness, hydrophobicity, zeta potential, dispersibility, etc., are some of the extrinsic properties of nanoparticles, which are important for determining its external behaviors such as bioactivity, redox potential, radical formation, photo-reactivity, dissolution, interaction with natural organic material (NOM), adsorption, desorption, sedimentation, photochemical/biodegradation, etc. (ECHA 2019). Application of QSAR models requires precisely calculated diverse physicochemical (PChem) descriptors for small molecules like nanoparticles. For toxicological studies, some of these descriptors were made available through the study of behavior of external properties, i.e., indirect relationship was used to define the descriptors. But for design, synthesis, functionality, stability, etc., the QSAR models cannot be directly applied as PChem descriptors are not available and this limit the applicability of QSAR models to the nanomaterials (Wang et al. 2017). Despite all these limitations, most of the nano-combinatorial models available as on date are QSAR based, but are far from the realistic environments of nanomaterials (Bai et al. 2017). A classical study of deviation of behavior of nanoparticles in realistic environments; from the expected behavior based on initial design was reported in a study on cerium oxide nanoparticles (CeO_2 NPs) (Casals et al. 2017). The CeO_2 NPs were designed to show anti-inflammatory effects by scavenging reactive oxygen species but instead this particle started to show pro-inflammatory effect at times in between. Authors noted that there were several unstudied hidden parameters, such as aggregation size, degree of impurity, etc. have interactions with their immediate environment that are responsible for this alteration of behavior. Further, they found that aggression size is more prominent variable than composition or original size of the particle. Therefore, it is obvious here that the design must take into account all the intrinsic, extrinsic properties along with their environmental interactions. Also, the weightage of each of the variables should be taken into design consideration for effective functionality.

Thence, unsupervised ML can be used here with the given variables to obtain data and develop pattern recognition models, and reinforcement learning can be used to understand interaction with the environment. More details of the same have been discussed elsewhere.

5.3 Toxicity

Toxicity of nanoparticles is of great concern for public health, consumer safety, health and safety of workers, as well as of environmental safety (Starón et al. 2020). The miniaturization and the alteration of PChem properties are mainly responsible for this toxicity. Many studies have been done previously on toxicity of different nanoparticles (Gatoo et al. 2014; Ramsden 2016; Ramos et al. 2017; Wu et al. 2017; Jeevanandam et al. 2018; Khan et al. 2019). It is one of the most studied fields for nanoparticles because of its widespread concern. ML application is already being used in toxicology studies of nanomaterials (Bai et al. 2017; Adir et al. 2019; To et al. 2019; Afantitis et al. 2020; Brown et al. 2020; Furxhi et al. 2020; Prasad 2019) and hence we are not discussing it here.

5.4 Stability

Nanoparticles have high volume to mass ratio and therefore have high surface area energies. Hence, they show high reactivity and are used in many applications. Most of the current studies focus on this high reactivity attribute of nanoparticles not only to obtain the desired functionality but also for detection and characterization of nanoparticle itself. But the flip side of this high surface energy of nanoparticle is its reduced stability. The concept of stability of nanoparticle is about their life for a specific short time period given the fact that the nanoparticles are thermodynamically unstable as compared to the parent bulk (Phan and Haes 2019). Definitely, these particles will not perish immediately after their synthesis, but a balance of stability to reactivity should be much sought after direction of their synthesis design, because in most cases, nanoparticles are highly unstable and react to their microenvironment immediately to reach stability. Such cases were reported by many authors (Casals et al. 2017; Parra-Robert et al. 2019; Yokel et al. 2019). The concept of balance between stability and reactivity is not straightforward. Instability must be observed at minimum three levels: at the levels of structure, interaction, and application. All the three levels of instabilities have their own manifestations in positive and negative aspects of initial design. Besides affecting the objectivity of design, these levels of instabilities may even cause toxicity (Gicheva and Yordanov 2013) because they affect the extrinsic properties such as aggregation/dispersion and thermal stability. Therefore, size-dependent characteristic retention is desired for a finite time (Phan and Haes 2019). At the levels of interaction Xu et al. (2018) have described four types of stability—dispersion stability, thermal stability, structural stability, and chemical stability.

In bio-nano-interactions, in particular with the proteins at cellular or subcellular level, colloidal stability is of primary importance. A design defined interaction of the given nanoparticle is only possible if the nanoparticle has colloidal stability, and that is why, in nano-biomedicines at times a protein core is used, that increases its colloidal stability (Kopp et al. 2017).

When it comes to ecotoxicity of nano-wastes, this reactivity to stability issue becomes more compelling to be addressed beyond the targeted objectivity of the design. In aqueous environments, their stability depends on the interactions of the PChem parameters of the environment and the nanoparticles characteristics (Gicheva and Yordanov 2013). Hydrophobic particles will make aggregates and settle, and do not directly impact the aqueous environment and life immediately. However, the hydrophilic particles remain suspended for longer period of time in the aqueous environment and may have more pronounced effect. Such particles or their degradation products may show bioaccumulation and food chain intoxication in longer runs (Rienzie and Adassooriya 2018). It is understood, from the above that ML-based studies and development of nanoparticles is a need of hour and must be taken up before even designing of the desired particle.

6 Efficacy of Nanomaterial (E_{nm}) and Ensemble Heterogeneity (h_{e})—Defining and Analyzing

Any given nanomaterial has to be assessed on many parameters and their interactions as depicted in Fig. 1.2. These parameters are inclusive, dependent, and interactive. These must be studied and monitored throughout the life time of a nanomaterial. Such a constant monitoring will ensure improved design, more stability, and less toxicity of existing and future nanomaterials.

If the operational functionality is represented as f_{o} and operational life is presented as l_{o}, and can be seen from Fig. 1.2.

$$\begin{aligned} f_{\text{o}} l_{\text{o}} &= \text{Product of } f\text{actors of } (\text{composition}) \\ &\times (\text{synthesis approach}) \times (\text{intrinsic property}) \\ &\times (\text{extrinsic property}) \times (s\text{tability}) \times (t\text{oxicity}) \\ &= \text{Factor of net internal interaction } I_i \end{aligned} \tag{1.1}$$

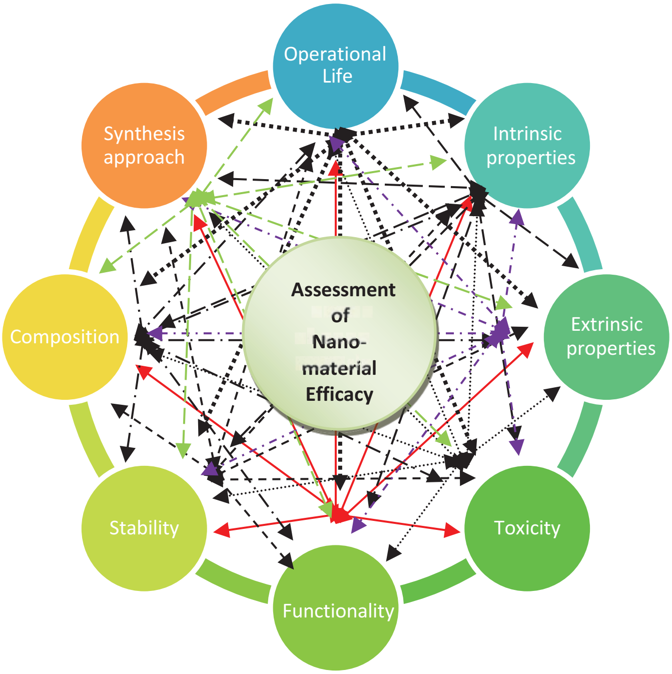

Fig. 1.2 Interactions of different factors "Ensembles" of nanomaterials for assessment of "Efficacy"

Since environmental factors will also affect functionality and operational life of the nanomaterial, and if we denote it as environmental interaction; i.e., I_e

$$f_o l_o = I_i x I_e \tag{1.2}$$

Since different internal factors do not affect the overall performance equally, and besides directly affecting the performance, these factors have their own effect on other factors also—so say a factor x_1 directly affects the nanoparticle by some quantity say; a_{x1} and have its interaction with other factors in different permutation combinations, as x_1x_2, x_1x_3, x_1x_4, x_1x_5, $x_1x_2x_3$, $\mathrm{x_1x_2x_4}$, $\mathrm{x_1x_2x_5}$, $\mathrm{x_1x_2x_6}$, $\mathrm{x_1x_3x_4}$, $\mathrm{x_1x_3x_5}$, $\mathrm{x_1x_3x_6}$, and so on. So the net effect (ε_{x1}) of $\mathrm{x_1}$ on a nanoparticle can be given by following equation

$$\begin{gathered}\varepsilon_{x1} = a_{x1} + x_1x_2 + x_1x_3 + x_1x_4 + x_1x_5 + x_1x_6 + x_1x_2x_3 + x_1x_2x_4 + x_1x_2x_5 + x_1x_2x_6 \\ + x_1x_3x_4 + x_1x_3x_5 + x_1x_3x_6 \ldots\end{gathered} \tag{1.3}$$

Similarly, the effects of other factors can be given by ε_{x2}, ε_{x3}, ε_{x4}, ε_{x5}, ε_{x6}, and so on, therefore

$$f_o l_o = I_i x I_e = \left(\varepsilon_{x2} + \varepsilon_{x3} + \varepsilon_{x4} + \varepsilon_{x5} + \varepsilon_{x6} + \ldots\right) x I_e \tag{1.4}$$

The interaction of these effects is representatively assumed here as additive but it could be of any nature and that makes the overall internal interactions I_i further complicated.

As far as environmental interactions I_e are considered, innumerable sub-factors are present that make drawing a "universal normal" for I_e nearly impossible. So, for a given environment, interactions need to be understood almost on the similar lines that of I_i, and then a product of $I_i \times I_e = f_o l_o$ can be determined. This final product of Functionality and Operational Life can be called as *Efficacy of Nanomaterial (E_{nm})*, should be maximum with all the given sub-factors as described above. If all the factors are synergistically supporting each other than the maximum value of E_{nm} will come as 1 for the given nanomaterial, but if any there is an antagonistic factor is present, this will cause heterogeneity in the complete "Ensemble" of factors for the given nanomaterial and subsequently its interaction with other factors described above will bring down this value of E_{nm} to less than 1. Thence, causing an increase in system entropy for the given nanomaterial. This increase in system entropy can be called as "*Ensemble Heterogeneity*" *(h_e)*. Therefore:

$$E_{nm} \propto \frac{1}{h_e} \tag{1.5}$$

7 Machine Learning and Nanomaterials

Machine learning, a subfield of artificial intelligence (AI), is widely used in the applications of nanotechnology in the field animal sciences, agricultural sciences, nutrition industry, water treatment, pharmaceutical and medical sciences, catalysis, and energy saving (Wang et al. 2019). In classical programming, the paradigm of symbolic AI, human input rules (a program), and data to be processed according to these rules, and outcome answers (Fig. 1.3).

With machine learning, humans input data as well as the answers expected from the data and outcome the rules (Fig. 1.4). These rules can then be applied to new data to produce the original solution (Chollet 2017).

Machine learning rules are derived based on the algorithms and the mathematical model. Based on the rules, computers with a training set of data can produce a prediction on a specific task. In the machine learning approach, the steps involved are classifying data, identify the correlations among the data, predicting the impact of associations in the new data. By minimizing the mathematical error function, the

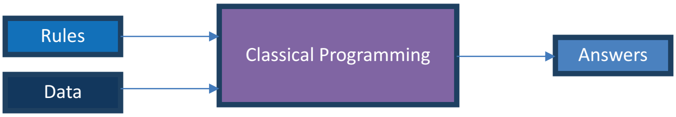

Fig. 1.3 Classical programming scheme

Fig. 1.4 Machine learning scheme

data accuracy is refined for the accuracy of the predictions. As learning is dependent on the experience of past learning, the regression approach is the basic approach. Based on the type of data available, the outcome of the learning model provides accuracy. Machine learning approaches are commonly used to discover new nanomaterials as well as to predict nanomaterials properties, such as toxicity, activity, energy difference, defect state, and morphology (Kalinin et al. 2015). According to the learning approach, the categories are supervised learning, unsupervised learning, semi-supervised learning, and reinforcement learning.

7.1 Machine Learning Applications

Supervised learning requires labeled data for training, the commonly performed tasks of supervised machine learning are prediction and classification. For example, to do classification (a supervised learning task), first label the data for training the model to classify data into the labeled groups. Supervised learning is required at sub-factors levels, where, known inputs are related to unknown outputs by finding the unknown functions using standard fitting procedure. This will generate patterns in labeled training data, and the desired results of unknown functions can be estimated by extrapolating these patterns (Valencia-Zapata et al. 2017).

The physical and chemical properties like roughness, dimension, permittivity, resistivity, and Young's modulus are used as used input parameters for training model in machine learning. Other than this, for the visualization of the morphology and structure of nanomaterials, high-resolution imagine techniques viz., AFM (atomic force microscopy), Cryo-EM (cryo-electron microscopy), and STEM (scanning transmission electron microscopy) are the inputs for the training the model in nanomaterials design. The physical and chemical behavior of the quantum mechanical properties of the small organic molecules, the inputs of the raw molecular graph to the model with the mathematical algorithm and characterization technique for enhanced prediction (Brown et al. 2020). Given the type of variables available and the enormous unique data generated from nanomaterial assemblies, all four types of ML are required at different levels for deciphering and curating different degrees of ensemble heterogeneity (h_e) affecting nanomaterial synthesis, functionality, stability, lifecycle, and toxicity. The first type of learning required here is supervised learning, as the objectivity here is to develop a nanomaterial in order to achieve highest Efficacy (E_{nm}) as described in Eq. (5). In the given premises of different factors and their sub-factors (Ensembles); the ML has to map the process to the given desired outputs. The second type of learning required here is unsupervised learning. It is required at the clustering of samples and classifying them in some or the other order. This will help finding patterns in unlabeled data and will assist in predicting future inputs and decision-making (Ghahramani 2004). The third type of ML required here is the reinforcement learning. It is required at the interfaces of factors, where, the different factors are interacting within I_i and I_e and also at the interface of I_i and I_e. This type of ML is good at finding the optimal value at an interaction situation to maximize the endpoint (reward)(Morales and Zaragoza 2011; Sutton and Barto 2018). Reinforcement learning takes us to decision optimization and process control in synthesis or functioning of the given nanomaterial. Finally, semi-supervised learning makes the fourth type of learning required here to understand and learn representations. In this approach, algorithm is provided with both labeled and unlabeled data (Grandvalet and Bengio 2005). Techniques in this category are useful where data are incomplete or altogether unavailable in nanomaterial synthesis and functioning. The unavailability of the data is a prominent case with nanomaterials, where, below 50 nm size the physical, optical, electromechanical properties go into quantum regime form the physical regime of the larger quantities of the same material (Lauterwasser 2014).

Algorithms are written to produce solution to classes of problems. Within a given class and with a given set of data; algorithms are trained to respond. In different types of learning as mentioned in previous paragraphs, different types of dataset combinations are provided to algorithms. The data here are either labeled or unlabeled. The choice of dataset combination depends on the type of data availability, data quantity, and variance. Machine learning techniques employed are selected on these basic rules.

Most preferred type of learning is supervised learning (Sammut and Webb 2017), but from the given understanding of the extent of nanomaterials data, it needs to be restricted to the domains at sub-factors or similar levels only. As such, supervised learning is excellent. It allows a very specific definition of labels; thereby, it facilitates setting boundary condition. This quality further helps to set up classes and class intervals. Since input and output data are more restricted in boundary conditions, they are more reliable as compared to any other types of ML techniques. Since the classes are known, the algorithm and analysis output will also be known and predictive. That is how it is also called sometimes as active learning and is compared with some fields of Operations Research, such as Bandit problems, Optimal Experimental design, Decision theory, and Information computation (Sammut and Webb 2010). But this type of learning has its own challenges (Valencia-Zapata et al. 2017). The known labels are the backbones in this learning but if the labels are noisy then the output data may have error. The bias-variance tradeoff is another issue. If the algorithm is restricted and has high bias, the model produced will be simpler and most of the boundary conditions are not considered. In otherwise case, if, the algorithm has high variance the produced model is complex and can very well capture the minor details for better representation of training dataset. However, this can over fit the model and may be representing the data in high dimensional space. High variance model may be good at smaller range and class of data and can render a good fit for experimental design but a more complex learning setup will get skewed-up results. Hence, a large number of dataset is required to reduce the variance bias and incorrect classification (Geman et al. 1992). Moreover, at times, the supervised learning may be complex as compared to unsupervised learning as each data have to be well understood and labeled upfront. Another issue with supervised learning is that it is not real time and uses off-line analysis. This restricts the user to study the process activity when it is happening. A lot of computational time is also required for supervised learning. A dynamically big and continually growing in-line data also cannot be handled smoothly using supervised learning because of difficulty in having predefined labels and boundary. But at the same time, supervised learning is the first choice for anomaly detection (Görnitz et al. 2013). Type of algorithm used also has its pros and cons. Some common algorithms used in Supervised learning are Decision Trees (Quinlan 1986), Linear Discriminant Analysis (Tharwat et al. 2017), Gradient boosting (Dorogush et al. 2018), K Nearest Neighbors (Zhang et al. 2017), Linear Regression (Atkeson et al. 1997), Linear SVC (Support vector Classifier) (Winters-Hilt and Merat 2007), Logistic Regression (Lee 2019), Naive Bayes (Berrar 2018), Neural Networks (Konar 2005), Regression Trees (e.g. Random Forest) (Louppe 2014), Support Vector Regression (SVR) (Awad and Khanna 2015), etc.

Nanomaterial machine learning application widely uses Support Vector Machine, Artificial Neural Network, Decision Tree Algorithm, Random Forest Algorithm, and Convolutional neural networks.

7.1.1 Support Vector Machine

Support vector machine (SVM) models are used to perform linear and nonlinear classification, regression, and outlier detection. SVM performs well with small- and medium-sized datasets (Kavitha et al. 2016).

7.1.2 Artificial Neural Network (ANN)

Application of neural network is numerous, and it is the base of the deep learning, a subfield of machine learning—the algorithms designed with the inspiration by the structure of the human brain to solve complex data-driven problems. The neural network takes in data, train themselves to recognize the patterns in this data, and then predict the outputs for a new set of similar data. When input data are fed to the neural network, the data are processed via layers of perceptron to produce the desired output (Géron 2017). The workflow of the ANN is to collect data, create the network, configure the network, initialize the weights and biases, train the network, validate the network, and use the network.

7.1.3 Decision Tree Algorithms

The decision tree is a type of supervised learning algorithm mostly used in classification problems. Tree has influenced in wide area of machine learning covering both classification and regression. A decision tree is a flowchart-like structure where each internal node denotes a test on an attribute, each branch represents an outcome of a test and each leaf or terminal node holds a class label. The topmost node in a tree is the root node. In decision analysis, a decision tree can be used to visually and explicitly represent decisions and decision-making. Nonlinear relationships between parameters do not affect the performance (Géron 2017).

7.1.4 Random Forest Algorithms

Random Forest Method develops a lot of decision tree based on the random selection of data and random selection of variables. It provides the class of dependent variable based on many trees. As the trees are based on the random selection of data as well as variables, these are the random tree. Many such random trees lead to a random forest. Most of the tree can provide correct predication of class for the most part of the data as well as the tree may mistake in a different place. By conduct voting for each of the observation and then decide about the class of the observation based on the poll result, it is expected to be more close to the correct classification (Ao et al. 2019).

7.1.5 Convolutional Neural Network (CNN)

Convolutional neural network (CNN) is a multilayer neural network of the deep learning framework. CNN is commonly used in image classification and recognition problems. CNN has hidden layers called convolutional layers.

Table 1.3 Some recent applications of ML approaches in manufactured nanomaterials (MNMs)

S. No.	Process related to MNMs	ML approaches/ algorithm	Findings	Reference
1.	Mathematical modeling of nano-Y_2O_3 dispersed ferritic alloys	ML-based integrated artificial neural network-genetic algorithm (ANN-GA) model	– An integrated ANN-GA model was developed for some physical (e.g., density and porosity) and mechanical (e.g., hardness, Young's modulus, and compressive strength) properties of alloy and used for optimization of process of nano-Y_2O_3 dispersed ferritic alloys synthesis.	Karak et al. (2015)

(continued)

Table 1.3 (continued)

S. No.	Process related to MNMs	ML approaches/ algorithm	Findings	Reference
2.	Analysis of the catalytic efficiency of platinum nanoparticles	ML-based artificial neural networks (ANNs) and binary decision tree models	– ML models were developed to map the catalytic efficiency of Pt nanocrystals to some structural features such as nanoparticle diameter, surface area, and sphericity. – The models were efficiently predicted the functional properties of hypothetical nanomaterials at a resolution on which both the computation and experimental methods failed.	Fernandez et al. (2017)
3.	Biomedical effects of MNMs	Naive Bayes and k-means clustering algorithm	– Data mining revealed that the polymer nanomaterial is promising material in research, but with a decreasing trend, however, the metallic and carbon-based nanomaterials grown with increasing trend.	Li et al. (2019)
4.	Multivariate modeling of engineered nanomaterial (ENMs) features	ML-based model based on random forests (RF) algorithm	– Several features of ENMs such as surface area, shape, and polydispersity associated with developmental toxicity were modeled and identified by ML approach.	To et al. (2019)
5.	Morphological engineering of nanoscale metal-organic frameworks (nMOFs)	ML-based labelme software and a Python script Github (https://github.com/zmzeng/Mask_RCNN).	– ML-associated deep learning modeled nanoscale metal-organic frameworks (nMOFs) from Hf-oxo clusters and linear dicarboxylate ligands and revealed a new opportunity of ML to guide the morphological engineering of MNMs.	Chen et al. (2020)
6.	Prediction of protein corona on nanomaterials	ML based in silico prediction model using random forest (RF) algorithm	– ML-based prediction model revealed the better performance of fluorescence change (FCs) as the engineered nanomaterial descriptors (ENMs) than the conventional descriptors in terms of ENM size and surface charge, in the prediction of corona formation.	Duan et al. (2020)
7.	Nanomaterial-based gas sensing system	ML-based support vector machine	– ML-based SVM perfectly classified the multi-sensor chips based gas sensing system with good estimation of tested gaseous concentration.	Thai et al. (2020)

(continued)

Table 1.3 (continued)

S. No.	Process related to MNMs	ML approaches/algorithm	Findings	Reference
8.	Mathematical models for zinc oxide (ZnO) nanostructures	ML-based kernel ridge regression (KRR) and artificial neural network (ANN)	– ML-based mathematical models which simulate the zinc oxide (ZnO) nanostructures-based synthesis of ZnO-based devices and applications were developed. – The developed models were efficiently – Predicted the optical band gap energy of ZnO and – Also capable of automated prediction of its semiconductor properties.	Regonia et al. (2020)
9.	Optimization of thin-film nanocomposite (TFN) membranes	ML-based gradient boosting tree model	– ML-based-gradient boosted tree model was used to understand the TFN membranes through optimization of nanoparticle parameters such as porosity, size, hydrophilicity, and loading rates.	Yeo et al. (2020)
10.	Electrochemical nanozyme sensor with MoS_2/MWCNTs porous nanohybrid network	ML-based artificial neural network approach	– ML-ANN-based intelligent analysis of carbendazim (CBZ) using electrochemical nanozyme sensor was developed and discussed in comparison with regression analysis.	Zhu et al. (2020)

Convolutional layer receives the input transforms the input in some pattern and then outputs the transform input to the next layer. In convolutional layer, this transformation is a convolution operation. The networks can handle patterns and images more precisely. With each convolutional layer, it is required to specify the number of filters for the layers. Filters are used to detect the patterns. In an image their multiple edges, shapes, and textures, for example, one filter will be edge detector and some detect corners. In deep layers, it becomes more sophisticated and able to detect specific objects (Xin and Wang 2019) (Table 1.3).

Supervised learning models are widely used in nanomachine learning applications, still the usage of unsupervised, reinforcement and semi-supervised has limited application.

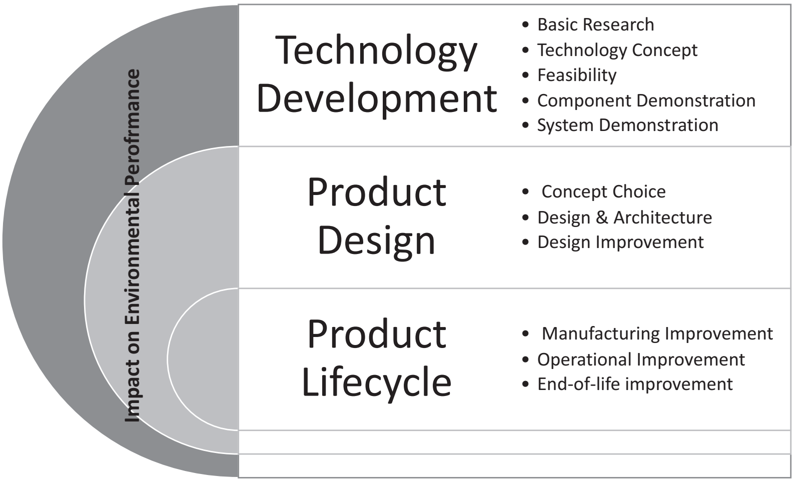

Fig. 1.5 Framework of impact of future environmental impact of an emerging technology related to different stage of product development (adapted from Moni et al. (2020))

8 Life Cycle Assessment (LCA) of Nanomaterials

8.1 Essentiality and Challenges

The innovative technology in the area of manufactured nanomaterials (MNMs) has a large potential of economic and environmental impact as a commercially available technology. The decisions regarding product design, technology development, and product life cycle can change the environmental burden of novel materials including MNMs (Fig. 1.5). Nowadays, the MNMs which contain about 50% or more of the particles in the size range of 1–100 nm are extensively utilized in various industrial applications and consumer products (Salieri et al. 2018). These MNMs can be used in different fields with wider applications as high-performance materials, energy storage and conservation materials, surface coating agents, and in textile (Cucurachi and Blanco Rocha 2019). These MNMs are usually produced through different processes including physical and chemical vapor deposition, liquid-phase synthesis, and self-assembly materials which are subjected to material and energy exchanges with emission of soil, air, and water pollutants along with material losses.

The evaluation of environmental impacts is related to the life cycle of MNMs, which can be a holistic approach of life cycle assessment (LCA) and risk assessment (RA). LCA is a systematic method which utilizes the concept of life cycle thinking for evaluation of potential environmental impacts of products, services, and processes throughout their life spans (Salieri et al. 2018). It is recognized as a significant tool for the evaluation of potential environmental impacts at a system level during the early stages of emerging technologies related to nanomaterials. However, the LCA of MNMs is facing many challenges, and the LCA communities

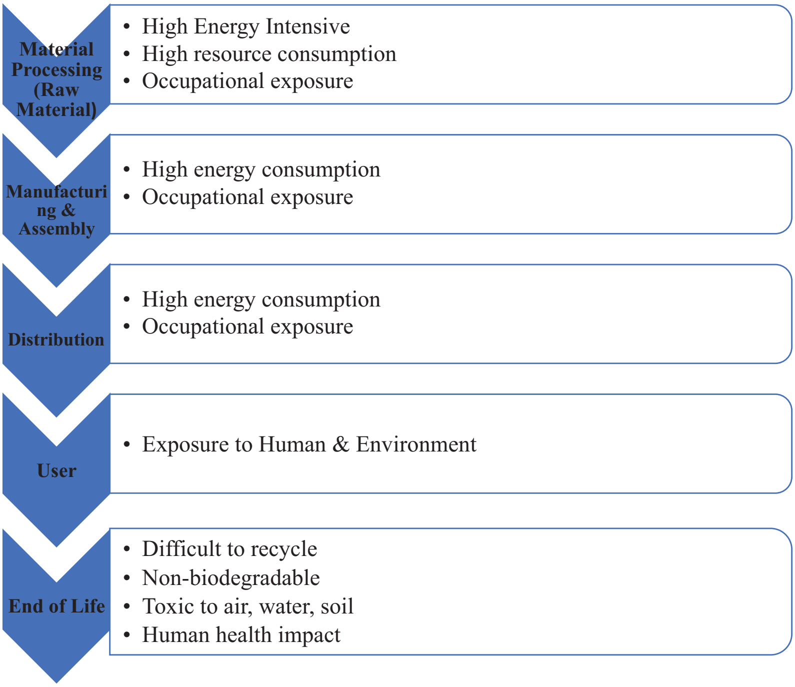

Fig. 1.6 Environmental concerns associated with different stages of product manufacturing

are closely following the rapid development and progress in the LCA methodologies (van der Giesen et al. 2020). The application of LCA to emerging technologies/materials (e.g., MNMs) has opened several new avenues for the development of methodologies that can potentially benefit the technology developer and can also help in policymaking through taking decision on product based on the potential environmental impact of the technology (Cucurachi and Blanco Rocha 2019). One of the major challenges related to LCA of MNMs is related to a limited understanding of the environmental fate of MNMs such as volatilization, degradation, solubilization, and adsorption in the abiotic environment. Another challenge is related to the immature products, i.e., the processes related to MNMs production are in an infant stage of technological development. In the early state, there are many aspects related to raw materials, and magnitude of the future production process along with the future handling is existing (Arvidsson 2015). The major environmental concerns associated with different stages of product (e.g., nanomaterial) manufacturing are illustrated in Fig. 1.6.

The functional unit is the basis of evaluation in the LCA processes; however, it is difficult to define in case of MNMs (Moni et al. 2020). Although it includes a unique functionality that can make a comparison of MNMs with the existing technologies for the assessment of different environmental impacts. It is also noteworthy that the poor quality of data is related to lack of transparency and variations during data processing which further affecting the reliability of LCA of MNMs (Moni et al. 2020). The variation in data lies in inconsistent functional units and system boundaries which can provide conflicts in LCA results of MNMs. The overestimation of environmental impacts is another challenge, when LCA is based on lab-scale data since the process yield and efficiency are not the same at production level. Thus, it is necessary to use scale-up framework and make assumptions related to the large-scale production, when compared to an established industrial technology (Moni et al. 2020). The understanding of uncertainty in the LCA process of MNMs is also important with its proper implication for making the proper decision by policy maker. The LCA results are widespread used by policy maker, marketing analysts, and financing bodies. Thus, communication related to uncertainty is critical to ensure transparency and credibility of LCA studies.

In view of above-mentioned challenges, several developments have been reported in the conventional LCA approaches (Katelhön et al. 2016; Cucurachi et al. 2018; van der Giesen et al. 2020). The conventional LCAs are guided by the International Organization for Standardization (ISO) 14044-14044 standards), which are available in many literatures (Baumann and Tillmann 2004; Curran 2012). These manuals have guided the application of modeling and assessment of environmental impact ex-post, i.e., after commercialization of products and retrospective in nature (Moni et al. 2020). However, several ISO standards (e.g., ISO and methodologies are also available, when LCA used in ex-ante, i.e., before a product/technology is deployed at commercial level for emerging technologies such as MNMs (Gavankar et al. 2015; van der Giesen et al. 2020).

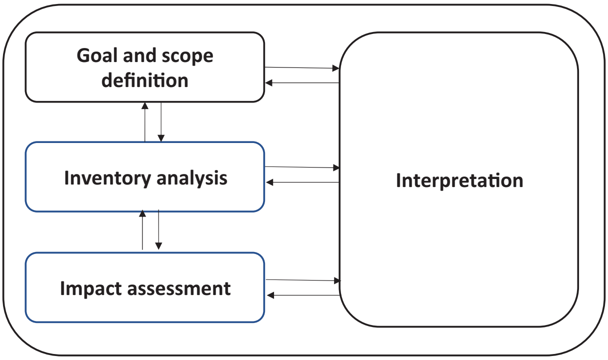

Fig. 1.7 Framework life cycle assessment (LCA) as per ISO 1997/2006

8.2 Basic Life Cycle Analysis (LCA) Framework and Improvement for Emerging Technology

As per the ISO 14040, the basic framework of LCA methodology includes: (i) Goal and scope definition, (ii) life cycle inventory (LCI) analysis, (iii) life cycle impact assessment (LCIA), and (iv) interpretation (Fig. 1.7). The goal and scope definition includes defining the system boundary which details the product and process with a functional unit of study. The functional unit can describe the function of the product to which all environmental impacts are related (Arvidsson 2015). Inventory analysis includes the compilation of inventory related to energy and material inputs and environmental release. This step releases a list of emission and resources uses with respect to input parameters. The emissions are related to functional units and summarized for all processes with product lifecycle. The impact assessment evaluated the potential environmental impacts that arise from emission and resource uses. During this step, the impacts are categories into global warming potential, acidification potential, eutrophication potential, ozone depletion, human toxicity potential, ecotoxicity potential, energy use, and water use (Arvidsson 2015). The interpretation of results helps in the decision-making for implementation related to product (Curran 2012).

It is noteworthy that the LCA is use and end-of-life, but in case of MNMs, LCA is often conducted with a system boundary that included the manufacturing of nanoproducts to the factory gate only. It is reported that the LCAs for nanoparticles are often missing several points at which nanoparticles are release during the complete life cycle; thus, lacking the assessment by ecological relevance (Windsor et al. 2018). In order to overcome the limitation of conventional LCA approach, several studies have been reported where LCA applied to new, emerging, and future technologies and product development (Villares et al. 2016; Salieri et al. 2018; van der Giesen et al. 2020). These selected LCA approaches are consequential LCA, lifecycle sustainability analysis (LCSA), dynamic LCA, anticipatory LCA, prospective LCA, and ex-ante LCA (van der Giesen et al. 2020). Consequential LCA mainly focused on the quantification of potential environmental impacts that accomplished a policy change. In LCSA approach, the dimensions of sustainability are included along with the environmental impact to introduce a new technology on economic and societal scale. Dynamic LCA focuses on inclusion of dynamics of parameters that are expected to change over time (Alfaro et al. 2010). Anticipatory LCA takes a forward look rather than retrospective assessment and involves uncertainty analysis through critical modeling decision to stakeholders (Wender et al. 2014). Perspective and ex-ante LCAs are focusing on emerging technology, which is in the early stage of development.

The challenges associated with ex-ante LCA are associated with all stages of LCA framework. Goal and scope definition under ex-ante approach are challenging, w.r.t. well-established technologies and mainly rely on temporal and geographical scope (e.g., technological performance and market situation), functional unit and alternatives, and choice of impact categories. Unavailability of LCI inventory is a major hurdle which can be overcome by using secondary data in combination of sensitivity analysis. The ex-ante LCA also realized that the potential environmental impact cannot be completely covered under the existing impacts categories in ex-post LCA studies. The unavailability of suitable impact categories and specific characterization factors may hinder the environmental evaluation of an emerging technology associated with MNMs (van der Giesen et al. 2020). The outcome interpretation of ex-ante LCA study is covered under suitable assumptions and high uncertainty surrounding the modeling choice with possible implications of technology.

In order to overcome the challenges associated with the ex-ante LCA, the following improvement in methodology, techniques, and approaches has been suggested (van der Giesen et al. 2020).

(a) Modeling consistent future foreground system—Modeling the future incumbent and new technologies for future LCI data and potential market share.
(b) Modeling consistent future background systems.
(c) Dealing the uncertainty in ex-ante LCA—covering uncertainty around future incumbent and new technologies and dealing "unknown," w.r.t. impact categories.

The modeling is the choice for comparison including the background system, when a new technology is expected to be adopted commercially. Gavankar et al. (2015) have reported the role of technology maturity in LCA and introduced the concept of technology readiness level (TRL) and manufacturing readiness levels (MRL) to the LCA approach. The MRL level 5–10 suited well for ex-post LCA approaches with better management of risk and uncertainty with associated features to deal strong cause–effect, quantitative analysis, and probability. However, with MRL 1–5, ex-ante LCA suited well with comparative poor management of risk and management with associated features to deal weak cause–effect, qualitative evaluation, and deep uncertainty (van der Giesen et al. 2020).

Coupling the LCA methodology with artificial intelligence-based optimization, modeling and simulation tools can overcome the limitation related to variability and uncertainty analysis (López-Andrés et al. 2018). Process simulation using Monte Carlo (MC) simulation allows quantification of inputs and output of the process/product with possible quantification and propagation of variability and uncertainty into the LCA results. The artificial intelligence-based multi-optimization model can be used to generate alternative of optimal process parameters with reduced environmental impacts of the system/product per functional unit (López-Andrés et al. 2018). Several studies which included MC simulation, genetic algorithm (GA), and neural network (NN) to LCA to simulate, optimize, and model for evaluation and reduction of impacts have been reported (Ozbilen et al. 2013; Elhami et al. 2017;

Table 1.4 Some recent applications of LCA methodology for evaluation of environmental impacts of manufactured nanomaterials (MNMs)

S. No.	Type of MNMs	LCA methodologies/ tools	Findings and suggestion	References
1.	Biostimulator—methanogenic bacteria	LCA—GaBi software 6.0	– A significant reduction in greenhouse gas emission by co-nanoparticles was observed. – Lowest acidification, human toxicity potential, and eutrophication impacts were delivered by co-NPs. Lowest resource and ozone layer depletion were delivered by Ni-NPs.	Hijazi et al. (2020)
2.	Lignin nanoparticle biorefinery	LCA—Gabi software (cradle-to-gate approach)	– A suitable decision support system for early-stage lignin nanoparticle production technology under the perspective of environmental impact was developed. – A better understanding of environmental impacts associated with innovative production of lignin nanoparticles is provided.	Koch et al. (2020)
3.	Silver nanoparticles (AgNPs)	LCA—SimaPro 8.5.2 (cradle-to-gate approach)	– Industrial-scale synthesis of AgNPs (MNMs) was modeled with the projection of future LCI using three different scale-up factors. – Scaling up reduced the environmental emissions up to 90% and 83% at globally and industrial sectors, respectively. – Significant variation in global environmental impact of AgNPs was observed as a function of different synthesis method, scale, and desired product application.	Temizel-Sekeryan and Hicks (2020)

(continued)

Table 1.4 (continued)

S. No.	Type of MNMs	LCA methodologies/ tools	Findings and suggestion	References
4.	TiO_2 nanoparticles in mortars	LCA—based on ISO14040/14044 (cradle-to-gate approach)	– With the addition of 0.5% of nano-TiO_2, the global warming potential (GWP) of mortars was significantly reduced with the RA and environmental impact. – Despite the apparent harmful effect of nano-TiO_2 using a cradle-to-gate approach, the environmental performance of TiO_2 nanoparticles was significantly enhanced due to their effects on service life.	Moro et al. (2020)
5.	Gold nanoparticles (AuNPs)	Anticipatory LCA	– Significant improvement in environmental impact and production costs was reported with the adoption of continuous-flow production in place of the batch system. – The environmental impacts in terms of human toxicity freshwater–ecotoxicity and depletion of gold resources were reported.	Grimaldi et al. (2020)
6.	Biodiesel/diesel blends (B5) with carbon nanoparticles	SimaPro software with Ecoinvent database	– Waste-oriented carbon nanoparticles served as an excellent eco-friendly fuel additive in biodiesel/ diesel blends with the enhancement of the environmental impacts.	Hosseinzadeh-Bandbafha et al. (2020)

(continued)

Table 1.4 (continued)

S. No.	Type of MNMs	LCA methodologies/ tools	Findings and suggestion	References
7.	Silver nanoparticles (AgNPs)	LCA—GaBi 6.0 software	– The synthesis of AgNPs with glucose and corn starch as reducing stabilizing agents, respectively, in a microwave-assisted reaction system were evaluated for environmental impacts. – Both glucose and starch showed negligible environmental impacts and reported as “environmental-benign materials” for the production of AgNPs.	Bafana et al. (2018)
8.	Composite polyvinylidene fluoride (PVDF) nanomaterials—algal membrane photoreactor (A-MPR) system	LCA-Simapro 8.4. (cradle-to-gate approach)	– The fabrication of silver/ graphene oxide—polyvinylidene fluoride (Ag/GO-PVDF) membrane reported a higher environmental impact than the fabrication of neat PVDF membrane fabrication, because of the addition of Ag/GO nanohybrids. – A better environmental footprint was reported by A-MPR system using Ag/GO-PVDF than membrane than neat PVDF membrane.	Chong et al. (2018)
9.	Fe_3O_4 nanoparticles	LCA-GaBi software	– Significant improvement in environmental impacts of Fe_3O_4-based magnetic nanoparticles synthesized by a novel eco-friendly method using glutathione as a reductant and stabilizer was reported. – It is reported that the coating of free and reactive –SH groups on nanoparticles performs environmental remediation and helps in reduction of environmental impacts.	Marimón-Bolívar and González (2018)

(continued)

Table 1.4 (continued)

S. No.	Type of MNMs	LCA methodologies/ tools	Findings and suggestion	References
10.	Silver, copper, and zinc nanoparticles	SimaPro 7.3 software with Ecoinvent v2.2 database	– The environmental impact analysis based on life cycle indicator reported that the weight fraction of these nanoparticles determined their energy input needs and environmental footprint.	Slotte and Zevenhoven (2017)

Hou et al. 2020). Machine learning-based models including k-nearest neighbors (KNN), support vector machine (SVM), neural networks (NN), random forest (RF), adaptive boosting (AdaBoost), and gradient boosting machine (GBM) have been used to determine the ecotoxicity characteristics of different chemicals in LCA (Hou et al. 2020). Thus, it can be concluded that the ML model can explore the complex process associated with MNMs and reveal the pattern associated with the prediction of environmental impact (e.g., ecotoxicity) for LCA.

8.3 Recent Development in the Application of LCA for Nanomaterials

The application of LCA to the nanomaterials getting advancement day-by-day through addressing the challenges described in the previous section. Several efforts have been taken to determine the nanoparticle emission from MNMs using different modeling approaches at inventory level (Cucurachi and Blanco Rocha 2019). Besides, several studies related to some important development in the implications of immaturity of MNMs, characterization factors for MNMs emission, incorporation of upscaling factor in emerging nanotechnologies, and risk assessment of MNMs are summarized in Table 1.4.

9 Conclusion

Nanomaterials are diverse, with their inherent physicochemical and quantum properties they promise great solutions to modern-day life scale problems in almost all fields of modern science. While understanding nanomaterials and their different facets of forms and functionalities, we come across six major attributes of nanomaterials, which include composition, synthesis, internal and external properties, stability, toxicity, and lifecycle assessment. But despite a large body of research nothing much has been done on prediction and modeling of any of the first four directions except some work has been done using machine learning (ML) on toxicity and LCA. Unpredicted and non-modeled design and synthesis of nanomaterial become dearer both at cost and time. Moreover, once synthesized, the in vivo studies for functionality, stability, lifecycle, and toxicity do not reflect the real-time behavior of nanomaterial in working environment and hence the likelihood of their failure increases manifold. This failure is attributed to poor understanding of the hidden interactions within and outside the molecular boundary of the nanomaterial. Therefore, a constructionist/emergentist approach is required just not only to predict the hidden patterns of interactions but also to develop a comprehensive mathematical framework that can predict macroscopic life-scale behavior and phenomenon of the nanomaterial in real time. Such a scenario demands a predictive modeling using ML at each of these six major directions of studies on nanomaterials as discussed in the chapter. This will lead to multiscale model-based informatics platform for the nanomaterials, which will help find more promising processes and most stable and robust products.

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Part I

Nanotechnology for Green Applications

Chapter 2
Copper- and Iron-Based Bio-Nanocomposites for Green Applications

Revathi Kottappara, Suresh C. Pillai, and Baiju Kizhakkekilikoodayil Vijayan

Contents

1 Introduction

The term bio-composites refer to those composites which are the combination of a naturally occurring polymer and an inorganic component. Such composites become bio-nanocomposites when one of its dimensions comes under the nanoscale range (Darder et al. 2007). The different methods by which bio-nanocomposites can be prepared include template assisted methods, solution intercalation, melt intercalation, and in situ intercalative polymerization (Pande and Sanklecha 2017). Among

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the naturally occurring polysaccharides, cellulose and chitin are the most promising biopolymers for several applications. The production of cellulose and chitin was estimated to be 10^{11} tons per year. One of the most abundant natural polymers is cellulose and it contains monomers joined together by glycosidic oxygen bridges. Cellobiose, a dimer of glucose is identified as the repeating unit in cellulose. The advantages of this fibrous biopolymer include biocompatibility, significantly reduced toxicity, and high availability. Cellulose (polymer of β-(1 → 4)-linked D-glucopyranose) and chitin (polymer of β-(1 → 4)-linked 2-acetamido-2-deoxy-D-glucopyranose are almost identical in structure except that in the C-2 position, chitin possesses an acetamido group while cellulose possesses a hydroxyl group (Kurita 2006). It consists of three hydroxyl groups per anhydroglucose unit (AGU). The water insoluble property of cellulose arises due to the extended intra- and intermolecular hydrogen bonds within the subunits. Since cellulose is highly rich in hydroxyl groups, several functional groups can be attached to it by various chemical transformations. If the hydroxyl group is chemically modified into $-NH_2$, $-NRH$, and $-NR_1R_2$ amine groups, in an aqueous solution, these amine groups can be protonated to positively charged $-NH_3^+$, $-NRH_2^+$, and $-NR_1R_2H^+$ groups which can easily capture the negatively charges toxic anions like F^-, AsO_2^-, AsO_4^{3-} through electrostatic interaction (Mandal and Mayadevi 2008; Ammavasi and Mariappan 2018).

Chitosan is a polysaccharide biopolymer derived from the deacetylation of chitin. Its chemical structure consists of (1 → 4)-2-amino-2-deoxy-β-D-glucan units (Abdou et al. 2008). Chitin and its deacetylated form chitosan have found different applications in the biological field due to its advantageous properties including nontoxicity, ability to absorb metal ions, fiber forming capacity, and so on (Uragami 2001). The chemical structures of cellulose and chitin were shown in Fig. 2.1. One of the interesting areas of researchers is in the use of biopolymers for antibacterial applications. The biopolymers can be used itself or in the composite form. Generally, two approaches are employed for this, first is the chemical approach which involves the chemical modification of the biopolymer with antibacterial materials like quaternary ammonium or phosphonium salts (Konwar et al. 2016). Such a method is generally time-consuming process and sometimes causes loss of cross-linking property of the polymer (Peng et al. 2010). The second approach is the development of biopolymer-based composites in the form of films or gels.

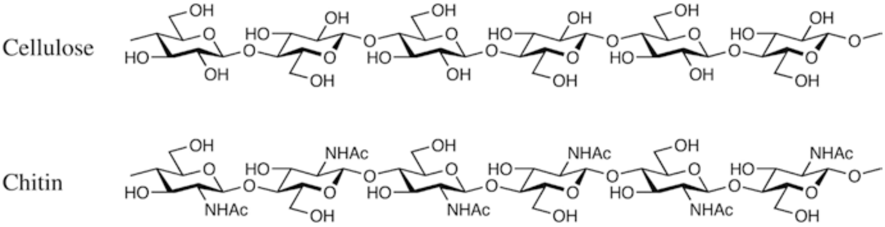


Fig. 2.1 Chemical structures of cellulose and chitin. Reproduced with permission from reference Kurita (2006). Copyright © 2006, Springer Nature

Since the past few years, the researchers' interest was concentrated on the introduction of metal nanoparticle-based bio-nanocomposite toward a number of applications such as wound dressings, veterinary, disposable health care products, biodefense, protective suits, and so on (Tessier et al. 2005; Li et al. 2006; Durán et al. 2007; Kwakye-Awuah et al. 2008; Molloy et al. 2008). The conventionally exploited metallic nanoparticles for diverse applications include silver, gold, palladium, zinc, and titanium oxide (Vigneshwaran et al. 2006; Yadav et al. 2006; Chen and Chiang 2008; Singh et al. 2008; Mary et al. 2009). Since ancient times, silver has been widely used as an antibacterial agent. Among different forms of metallic nanoparticles, nanostructures of copper stand out due to its extraordinary antimicrobial properties against pathogenic microorganisms, such as *Salmonella typhimurium* and *Listeria monocytogenes* as well as catalytic property, optical and magnetic properties (Gould et al. 2009; Yao et al. 2011; O'gorman and Humphreys 2012; Umer et al. 2014; Yadav et al. 2017; Srivastava et al. 2021)). Reduced cost, reduced toxicity, and high availability make metallic copper- and copper-based materials to be widely used material compared to silver, gold, or palladium for several applications. Besides copper, magnetic iron-based nanostructures also attract researchers interest due to its potential applications in diverse fields including drug delivery (Kohler et al. 2005), magnetic resonance imaging (MRI) (Lee and Hyeon 2012), bio-separation (Lee et al. 2010), catalysis (Zhang et al. 2005), and wastewater treatment (Giraldo et al. 2013). Among the metallic nanoscale materials, zerovalent iron has received significant attention in the field of environmental remediation due to its potential in degrading a large spectrum of water pollutants such as organic pollutants, hexavalent chromium, and toxic heavy metals (Mueller et al. 2012; Fu et al. 2014; Thakare et al. 2021).

2 Application of Copper and Iron-Based Bio-Nanocomposites

2.1 Antibacterial Applications

Previous literature reports indicate that the emergence of new strains of bacteria having higher resistance capacity is merely due to the overuse of conventional antibiotics. In this context, the development of potential antibacterial products is worth attracting for solving this problem. As a step toward cheap and safe antibacterial materials, copper- and iron-based nanoparticles incorporated with natural polymers offer better results. For the past few decades, cost-effective antimicrobial nanocomposites have received increasing attention in the industrial field especially in biomedical, drug delivery, and pharmaceutical applications (Govindaraju et al. 2016; Meenakshi et al. 2016; Prasad et al. 2017). The biopolymer-based metal nanocomposites have advantages such as high aspect ratio, low density, and also economically feasible.

2.1.1 Antibacterial Application of Copper-Based Bio-Nanocomposites

Copper is one of the 26 essential natural elements present in plant and animal tissues. Besides the metallic copper, its different forms including copper oxides, ionic copper, and copper containing molecular complexes also found to possess some degree of antibacterial property (Cady et al. 2011). Among several metallic nanoparticles, copper stands out due to its effective antibacterial properties against several bacterial strains and has grabbed researchers' attention recently (Gould et al. 2009; Zhu et al. 2012). Copper is an important metal present in plant and animal tissues for serving various roles. Since the use of mere copper nanoparticles is highly prone to aggregation it will lead to deterioration of its chemical properties and hence reduces the antibacterial potential. Then the use of proper supporting material like cellulose and chitosan for the deposition of the copper nanoparticle can retain its antibacterial property by delaying the releasing time of metal ions (Toshikazu 1999). Pinto et al. developed copper nanofillers in different cellulose matrices (vegetable and bacterial) and investigated its antibacterial activity by choosing *Staphylococcus aureus* and *Klebsiella pneumonia* as pathogens (Pinto et al. 2013). Their results suggest that the antibacterial effect of the developed nanocomposite proportionally increases with the copper content in the sample and among which the effective substrate material is vegetal cellulose fibers. Their study also indicates that the morphological variations in the samples also alter the antibacterial capacity of resulting materials.

Cellulose can be either bacterial cellulose or vegetable-based cellulose. Bacterial cellulose (BC) is formed by culturing the strain of aerobic Gram-positive bacteria (Iguchi et al. 2000). Since bacterial cellulose is devoid of lignin and hemicelluloses, its purity is much higher compared to vegetable cellulose. Besides, bacterial cellulose possess several advantages compared to vegetable cellulose and includes: (1) hundred times lower in dimension compared to vegetable cellulose which makes it highly porous in nature, (2) biodegradable, biocompatible, nontoxic, and nonallergenic polymer, (3) high mechanical stability, high crystallinity (70–80%), high degree of polymerization and excellent water retention capacity (Araújo et al. 2018). Bacterial cellulose has found its space in different areas like medical applications, textile, and packaging industry (Andrade et al. 2010). The hydroxyl functional groups present over the surface of bacterial cellulose makes the incorporation of copper nanoparticles adsorbed much easier. Pinto et al. also found that although the structural formula of vegetable and bacterial cellulose is identical, the comparatively closed structured bacterial cellulose reduces the oxidation susceptibility of copper nanoparticles adsorbed over the surface to a greater extent (Pinto et al. 2012). The antibacterial potential of copper—cellulose bio-composite was also studied by Cady et al. against resistant *pathogen A. baumannii* (Cady et al. 2011). Another report by Araújo et al. investigated the antibacterial effectiveness of bacterial cellulose–copper bio-nanocomposite developed by the hydrothermal method (Araújo et al. 2018).

Xie et al. developed bacterial cellulose–graphene oxide–CuO bio-nanocomposite films possessing good antibacterial capacity (Xie et al. 2020). The bio-nanocomposite prepared by the homogeneous blending of the graphene oxide (GO)–CuO nanohybrids on the surface of the bacterial cellulose matrix were found to be more efficient in destroying Gram-positive bacteria than Gram-negative bacteria. The antibacterial property of the bio-composite material can be due to combinational effects of several actions including the direct interaction of the CuO nanorods and two-dimensional graphene nanosheets with the membranes of the microorganism causing unfavorable variations in the permeability of membranes and distracting the integrity of the bacterial membrane by surface deterioration, cellular deformation, and roughness. Besides, a higher concentration of intercellular reactive oxygen species (ROS) may significantly enhance the destruction of bacteria by oxidative damage of lipid membrane DNA and proteins (Kumar and Anthony 2016; Aziz et al. 2015, 2016, 2019). They found that the number of reactive oxygen species in the 5 mg/mL bacterial cellulose–graphene oxide–CuO bio-nanocomposite-treated bacteria were 1.72 times more than that in the control group. In the future, such a nanocomposite will find its space to be utilized for biomedical applications and potential packaging materials.

Reports indicate that there is a significant enhancement in the antimicrobial activity when chitosan is incorporated with other nanomaterials especially with metallic nanoparticles like copper. Such enhancement may be due to the dominating effect of metal nanoparticles which can intercalate with the nucleic acid strands of DNA and destructing biochemical mechanisms. Besides, the ability of copper nanomaterials to deactivate the enzymes upon entering through the cell wall also inhibits bacterial growth and is found to be due to the formation of hydrogen peroxide (Zain et al. 2014; Yadav et al. 2017). The formation of copper–chitosan nanocomposites can be carried out by the dissolution of copper precursor in acidified chitosan solution leading to the chelate linkage between the copper ions with the amino groups of the polymer. This coordination follows the coupled oxidation of hydroxyl groups of the chitosan chain and the reduction of the copper ions (Wei and Qian 2008; Tran et al. 2010). The stability of the resulting copper–chitosan composite is due to the strong chemical interaction between the electron rich nitrogen and positively charges copper ions. A research report by Manikandan and Sathiyabama demonstrated the copper–chitosan nanoparticles having efficient antibacterial property synthesized by green method (Manikandan and Sathiyabama 2015). Here, the chitosan biopolymer serves a dual role as a capping agent and reducing agent. The most accepted mechanism on the antimicrobial effect of chitosan suggests the electrostatic interaction between the positive charges of chitosan with the negative charged microbial cell membrane. The resulting impermeable layer developed around the cell wall blocks the transfer of necessary minerals toward the cell leading to the damage of microbes (Chen et al. 2002; Morsi et al. 2017). Besides, the chelating capacity of chitosan units with the nutrients also takes part in disrupting the growth of bacteria.

Copper oxide-based chitosan nanocomposite hydrogel beads exhibited potential antibacterial capacity against both Gram-positive and Gram-negative bacteria (Farhoudian et al. 2016). Jayaramudu et al. also studied the antibacterial activity of chitosan capped copper/copper oxide synthesized by chemical reduction method and obtained excellent results against *E. coli* and Bacillus (Jayaramudu et al. 2019) and explored its potential in utilizing for wound healing applications. They found that the chitosan capped CuO nanoparticles and chitosan–CuO–chitosan nanocomposite possess higher antibacterial efficiency compared to the corresponding copper nanoparticle counterparts. The nanocomposite formed by the incorporation of chitosan with Montmorillonite (MMT) is also of interest to antibacterial researchers. There are reports on the noticeable enhancement in the permeability and strength of even by the incorporation of 1–5 wt% MMT (Giannakas et al. 2014). However, mere montmorillonite does not possess an antibacterial capacity. Hence the application of MMT–chitosan composite in antibacterial applications such as food packaging requires additional incorporation of copper or copper oxide. Here the use of MMT is of particular advantage since the bio-nanocomposite containing only copper and chitosan causes burst release of copper ions and destroys the food material (Drelich et al. 2011; Martucci and Ruseckaite 2017). The combination of copper ions with exchangeable positively charged ions such as Na^+, K^+, Mg^{2+}, and Ca^{2+} in high cation exchange clay MMT, successfully prevents such loss of copper ions. A recent study by Nouri et al. demonstrated the antibacterial activity of MMT–CuO bio-nanocomposite against 2 g negative bacterium *E. coli* (PTCC 1270), *P. aeruginosa* (PTCC 1430), and two Gram-positive bacterium (*S. aureus* (PTCC 1112) *B. cereus* (PTCC-1015) with 99% mortality (Nouri et al. 2018).

2.1.2 Antibacterial Activity of Iron-Based Bio-Nanocomposites

Among the metal oxides, iron oxides are one of the widely studied antimicrobial materials (Behera et al. 2012; Hajipour et al. 2012). Konwar et al. reported the efficiency of chitosan–iron oxide-coated graphene oxide nanocomposite hydrogel toward antibacterial applications (Konwar et al. 2016). Although graphene oxide is cytotoxic at relatively higher concentrations, at lower concentrations, it is favorable for antibacterial applications. The antibacterial effects of graphene oxide-based materials take place by the physical damage to the cell membrane upon direct contact bacteria using sharp edges of graphene sheets. Konwar et al. fabricated chitosan–iron oxide-coated graphene oxide nanocomposite hydrogel by a two-step process. This involves, the initial preparation of iron oxide-coated graphene oxide (GIO) nanostructure by a coprecipitation method. This followed by the incorporation of the GIO nanomaterials within the chitosan hydrogel. The interaction between the chitosan and GIO nanomaterials was accomplished by the secondary interactions like hydrogen bonding as well as the electrostatic interaction between the nanomaterials and the matrix phase. Their study well demonstrated the potential antibacterial activity of the resulting chitosan–iron oxide-coated graphene oxide nanocomposite hydrogel toward different toxic microorganisms including *C. albicans*, *S. aureus*, *E. coli*, and *MRSA* which covers both Gram-negative and Gram-positive bacterial strain. This indicates that such a biofilm could find its place in the biomedical and food packaging industry.

2.2 Antifungal Applications

One of the serious problems faced by human society for the past few decades is the potential antimicrobial agents. The harmful effect of microbes is more pronounced in the agricultural field. The conventional pesticides are mostly highly toxic and cause serious health problems for human health and deteriorate the soil. From the eighteenth century itself, copper-based compounds were used as biocides (Tokoro et al. 1988). However, the usage of such compounds also raises the same adverse problems. Chitosan is proved to possess excellent defense capacity against bacteria, fungi, and viruses in their different stages of growth (Xu et al. 2007). The antifungal activity of chitosan relies on several components like the extent of acetylation, concentration, method of use, molecular weight, as well as the target substrate (Rubina et al. 2017). Several research reports demonstrate the antibacterial and antifungal activity of copper–chitosan bio-nanocomposite successfully (Saharan et al. 2013, 2015; Arjunan et al. 2017). For the first time, Rubina et al. reported copper–chitosan bio-nanocomposite having efficient antifungal activity against two sclerotium-forming plant pathogenic fungi *Sclerotiumrolfsii* (*S. rolfsii*) and *Rhizoctoniasolani* (*R. solani*) AG-4 in vitro by physicochemical methods (Rubina et al. 2017). They adopted a metal–vapor synthesis method for the synthesis of copper nanoparticles which is later used for the copper–chitosan bio-nanocomposite by impregnation of chitosan in acetone or toluene as an organic solvent. They observed that the higher concentration of copper–chitosan bio-nanocomposite synthesized using acetone as solvent showed significantly enhanced inhibition property and was supposed to be due to the destruction of the integrity of cytoplasm by loss of content, cytoplasmic coagulation, alternations in the shape of mycelia, or destruction of the hyphae.

2.3 Application in Medical Field

2.3.1 Medical Application of Copper-Based Bio-Nanocomposites

A work by Cady et al. developed copper nanoparticle–cotton bio-composite comprising of a chemically modified cotton substrate having a layer of sub-5 nm copper-based nanoparticles (Cady et al. 2011). The copper–cotton nanocomposite prepared by layer-by-layer electrostatic assembly process was found to exhibit potential in destroying multidrug resistant bacteria pathogen, wound-associated bacterium, *Acinetobacter baumannii* (*A. baumannii*). The advantage of using the layer-by-layer method is that it imparts a negative charge on the surface of the cotton substrate for chelating with the copper ions. The mechanism of antibacterial activity was reported to be due to a contact killing process and not simply due to the enhanced release of the copper ions. They also investigated the biocompatibility of the developed copper–cotton bio-nanocomposite toward embryonic fibroblast stem cells in vitro and explored its capacity in wound care.

Cisplatin is well known for its application in chemotherapy. However, it is applicable only to a narrow spectrum of tumors and also causes serious side effects (Ho et al. 2003). There are reports on the anticancer activity of chitosan oligomers that depends on the chemical nature of chitosan, molecular weight as well as charge properties (Kim and Rajapakse 2005; Huang et al. 2006; Wang et al. 2009). The Schiff-base complex of Cu $^{2+}$ derived from 4-hydroxysalicylaldehyde and amino acid also exhibits potential anticancer activity against Ehrlich ascites carcinoma (EAC) (Zishen et al. 1993). Wang et al. developed a nano-chitosan salicylaldehyde Schiff-base–copper complex (NCS–Sal–Cu) which is having efficient inhibition potential against the growth of the liver cancer cell lines SMMC-7721 in vitro (Wang et al. 2009). The nano-chitosan Schiff-base copper complex was formed by the interaction of nano-chitosan, Schiff-base, and copper through both covalent and coordinate bonds. The developed bio-nanocomposite possesses several advantages, namely, (1) the high solubility of nano-chitosan facilitates the solubility of Schiff-base without affecting the anticancer activity of chitosan; and (2) the toxic effect of Schiff-base complex was reduced using natural chitosan as the supporting material. The anticancer properties of any drug material depend on its ability to bind with the cellular receptor DNA. The antitumor properties of drug chemicals were exerted to DNA through binding thereby altering the replication of DNA and destructing the growth of the tumor cell (Wang et al. 2004). The binding between the copper complex and DNA takes place through both electrostatic interaction and intercalation modes. Wang et al. demonstrated that the nano-chitosan Schiff-base Cu complexes can be used as promising alternatives to *cis*-platin in the case of liver-cancer treatment (Kato et al. 2001; Wang et al. 2009). The investigation on the mechanism of the interaction between the nano-chitosan Schiff-base Cu complexes with the cell suggests an electrostatic interaction between the chitosan polymer having an excess of positive charge with the negatively charged cell surface leading to adsorptive endocytosis and membrane instability (Lee et al. 1998). The boosting of anticancer performance is on account of the destruction of tumor cells as well as improvement in the lymphokines production (Tokoro et al. 1988) (Fig. 2.2). Their investigations suggest that the enhanced anticancer activity of the nano-chitosan salicylaldehyde

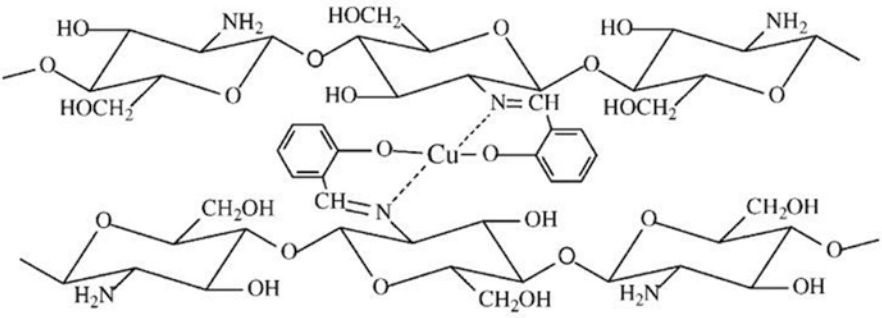


Fig. 2.2 The supposed structure of NCS–Sal–Cu. Reproduced with permission from reference Wang et al. (2009). Copyright © 2008 John Wiley & Sons, Ltd

Schiff-base–copper complex was due to the synergistic activity of the chitosan matrix and the planar construction of the copper complex which destructs the secondary structure of DNA.

2.3.2 Medical Application of Iron-Based Bio-Nanocomposites

Primarily, chitosan has used in different applications such as in wound dressing, slimming and tissue engineering, and also in drug delivery (Ali and Ahmed 2018). The potential antibacterial performance and reduced immunogenicity in combination with promising biocompatibility and biodegradability offer chitosan outstanding opportunities in diverse applications (Ali and Ahmed 2018). The occurrence of primary amine functional group in the polymer chain imparts chitosan significant biological properties like controlled drug delivery, mucoadhesion, transfection, in situ gelation, permeation enhancement, colon targeting, and efflux pump inhibition (Bravo-Osuna et al. 2007; Dünnhaupt et al. 2012; Ali and Ahmed 2018). In addition, in areas of orthopedics, dentistry, ophthalmology, and surgical measures, the property of the bio adhesiveness makes the chitosan material to adhere soft/hard tissues (Needleman et al. 1997; Magetsari et al. 2014). The exceptional hemostatic, bacteriostatic, anti-cholestermic, anticarcinogenic, and fungistatic properties of chitosan make chitosan extensively exploited in drug delivery applications (Saikia et al. 2015).

The advancements in the drug delivery field focus on maximizing the concentration of chemotherapeutic agents directly to the tumor cells thereby increasing its efficiency. Recent development follows the selective transport of antitumor molecules to the targeted site by external stimuli such as acidic pH, temperature, magnetic gradients, or enzymatic systems or through ligand- or receptor-mediated targeting mechanisms (Meers 2001; Needham and Dewhirst 2001; Rapoport 2004). Such targeted distribution significantly reduces the nonspecific distribution of the drug to the nontarget organs, leading to lower systemic toxicity. Arias et al. demonstrated a coacervation methodology for the fabrication of magnetic/chitosan core-shell nanocomposite having excellent responsiveness to magnetic gradients which can be utilized for the intravenous delivery of the antitumor agent gemcitabine to the cancer tissue (Arias et al. 2012). The developed Fe_3O_4 nuclei encapsulated into the chitosan nanocomposite offers improved drug loading and reduced drug release properties. In addition, due to the specific polymer dissolution in acidic environments, Fe_3O_4/chitosan nanocomposite also possesses a pH stimulated release of gemcitabine that could be advantageous for intracellular drug delivery (Arias et al. 2012).

There are also reports on the applicability of iron oxide–chitosan nanocomposite for the effective oral delivery of insulin (Kebede et al. 2013). The iron oxide–chitosan nanocomposite incorporated with insulin has reported possessing the inherent capacity to reduce blood glucose level to over 51% in diabetic rats (Kebede et al. 2013). The phosphoramide compounds are shown to possess anticancer prodrug properties and also efficient insecticide and pesticide properties (Miyamoto et al. 1999; Jiang and Hu 2007; Jiang et al. 2009). Antibacterial efficiency of chitosan/

phosphoramide/1–5% Fe_3O_4 NPs was demonstrated by Shariatinia et al. (Shariatinia and Nikfar 2013). In vitro antibacterial analysis suggests that the developed chitosan/phosphoramide/1–5% Fe_3O_4 NPs showed the greater antibacterial property of the film for Gram-positive bacteria including *Staphylococcus aureus* (*S. aureus*), *Bacillus cereus* (*B. cereus*). The potential of iron–chitosan bio-nanocomposite in drug delivery is also reported well by Lin et al. (2015). They developed multifunctional and biocompatible polyethylene glycol–chitosan–iron oxide nanocomposite with near-infrared fluorescent cyanin dye (MTX-PEG-CS-IONPs-Cy5.5). The developed bio-nanocomposites possess significant fluorescence and magnetic resonance imaging (MRI) capacity. The combination of superparamagnetic, targeting, fluorescent, and anticancer properties offers of the iron–chitosan bio-composite self-targeted curative drug delivery.

2.4 Packaging Applications

2.4.1 Packaging Applications of Copper-Based Bio-Nanocomposites

The packaging industry mostly depends on petroleum-based plastics (more than 300 million tons per year) due to their high accessibility and reduced cost, promising mechanical properties as well as a good protection barrier to gases (Shankar et al. 2014). The ever increasing use of nonbiodegradable polymers always creates serious environmental challenges. Such nonbiodegradable synthetic polymers are generally derived from petroleum resources. Hence to conserve nonrenewable petroleum sources and to reduce adverse environmental problems, it is strictly necessary to switch toward renewable biodegradable polymers. There are several reports on the fabrication of composites based on biodegradable polymers like polypropylene carbonate, polylactic acid, chitosan, and so on. The major bottleneck in utilizing biopolymer-based nanocomposite in the packaging industry is poor mechanical as well as processing properties (Tunç and Duman 2011). Although chitosan was found to possess higher antibacterial capacity, the low mechanical strength, thermal stability, and also higher permeability to water and air restricts its industrial applications especially for the food packaging industry (Shahbazi et al. 2017). Chitosan–Clay (cloisite 20A) nanocomposite was developed to enhance the functional performance and scanning electron microscopy (SEM) and atomic function microscopy (AFM) analyses indicate that the electron beam irradiation enhanced the chitosan/clay film owing to the clay intercalation process.

The conventional methods adopted for such modifications are mixing with other polymers and cross-linkers and the addition of filler materials into the chitosan matrix (Campos et al. 2009; Sanuja et al. 2015; Hu et al. 2016). Among such methods, the fabrication of chitosan-based nanocomposite is of particular interest due to enhanced antibacterial property, high surface to volume ratio (Rathore et al. 2014). Hence in order to apply for food packaging applications, it is essential to modify the physicochemical properties of chitosan. The widely accepted material that has been used for the past few decades for the preparation of chitosan nanocomposite is montmorillonite (MMT). This layered silicate material is well known for its high abundance, reduced cost, high aspect ratios (100–1500), and high surface-to-volume ratio (700–800 m^2/g). Packaging materials possessing efficient antibacterial activity is one of the attractive features of the packaging industry since an increased shelf life of food devoicing the growth of pathogenic microorganisms is essential (Rhim 2013; Shankar et al. 2014). Compared to the bulk bio-composites, the effective antibacterial action of bio-nanocomposite is attributed to the significantly improved surface area, high surface to volume ratio, and high specificity (Shankar et al. 2014). Copper-based bio-composites are particularly attracting the interest of researchers because of its reduced sensitivity to animal tissue and the increased sensitivity to micropathogens (Hostynek and Maibach 2004). Shankar et al. developed agar–copper nanoparticles bio-nanocomposite films having strong antimicrobial activity against both Gram-positive and Gram-negative foodborne pathogens (Shankar et al. 2014). The agar–Cu nanoparticle bio-nanocomposite possessing strong UV barrier property has the potential to be utilized for the packaging of UV sensitive food products like a potato. However, cellulose and chitosan were of particular interest due to their bulk availability and low cost. In 2016, Sadanand et al. synthesized cellulose–Cu nanoparticle bio-nanocomposite in situ using wet regenerated cellulose films, *Ocimum sanctum* leaf extract, and copper precursor (Sadanand et al. 2016). They found that the tensile strength of the developed bio-composite was higher than the conventional polymers like polyethylene and polypropylene used for packaging applications and hence can be an effective candidate in the packaging industry.

2.4.2 Packaging Application of Iron-Based Bio-Nanocomposite

Magnetic cellulose bio-nanocomposites have gained the attention of researchers for several applications including security paper, electromagnetic shielding, and magnetic filtering due to its peculiar properties of cellulose fibers as well as magnetic materials (Morsi et al. 2017). Wu et al. reported the fabrication of a magnetic paper sheet using magnetic cellulose fiber $Fe_3O_4@SiO_2$ composite (Wu et al. 2011). They used vacuum–lumen-loading method for the development of magnetic bio-nanocomposite. $Fe_3O_4@SiO_2$ nanoparticles bearing positive charge allows easy dispersion in water suspension which can be further deposited on the exterior, in the pores, and especially in the lumens of fibers. They used polyethylenimine (PEI) as retention aid in the process. Several factors such as pulp beating, modification of the Fe_3O_4 using silica shell, PEI dosing, and vacuum application facilitates the loading of nanoparticles into the lumens of fibers. They found that there is a chance for a slight decrease in the physical strength of fabricated paper due to the deposition of nanoparticles on the exterior of fibers which will sometimes lead to stop up the generation of the hydrogen bond between the fibers. Their findings regarding the fabrication of magnetic paper having tiny remnant magnetization and coercivity open up new concepts in the paper industry, packaging, and information storage (Wu et al. 2011).

2.5 Catalysis

2.5.1 Catalysis Application of Copper-Based Bio-Nanocomposites

The utilization of bio-nanocomposite for catalytic reactions will hopefully introduce the development of green protocols in the industry. Maleki et al. demonstrated the use of cellulose matrix embedded copper decorated magnetic bio-nanocomposite, γ-Fe_2O_3/Cu@cellulose, as an efficient green catalyst for the synthesis of 1,4-dihydropyridines and polyhydroquinolines (Maleki et al. 2019). The developed nanocatalyst offers several advantages such as solvent-free conditions, room temperature reaction, reduced reaction time, high yield, and high atom economy. The methylene blue reduction capacity of in situ-generated chitosan/fluorescein–copper was reported by Saldías et al. (Saldías et al. 2018). The efficient catalytic activity of copper nanoparticles stabilized chitosan/poly (vinyl alcohol) based film toward a reduction of aromatic nitro compounds to aromatic amines was reported by Souza et al.. The developed nanocatalyst can be a potential alternative to noble metal-based catalyst and offers advantages including remarkable recyclability at least up to six cycles, allows simple handling of the catalyst, high uptake capacity, and stimuli-responsive properties (de Souza et al. 2017).

2.5.2 Catalysis Applications of Iron-Based Bio-Nanocomposites

Multicomponent nanocomposites are of special interest due to its widespread application (Carlsson et al. 2012). Magnetic iron and iron oxide (Fe_3O_4 and g-Fe_2O_3) nanomaterials are attracting the interest of the researchers due to its profound applications including magnetic resonance imaging, catalysis, and bio-separation (Lee et al. 2010; Lee and Hyeon 2012; Kucheryavy et al. 2013). The major requirement in utilizing magnetic nanostructures in any application is the proper supporting system which restricts the agglomeration of the magnetic nanomaterials. In 2013, Xiong et al. used nanofibrillated cellulose as a support material for the facile synthesis of Fe_3O_4–Ag nanocomposite (Xiong et al. 2013). Here the nanofibrillated cellulose (NFC) plays a dual role by acting both as biocompatible support for the Fe_3O_4–Ag nanoparticles and reducing the silver ions. The electronic features of hydroxyl and ether groups make it favorable for the reduction of silver ions (Hirai et al. 1979; Benaissi et al. 2010). They also suggest that Fe_3O_4/Ag@NFC nanocomposite can be effectively tuned from highly porous flexible aerogels to solid and stiff films. Their investigations also demonstrate that Fe_3O_4/Ag@NFC nanocomposite aerogel possesses efficient catalytic hydrogenation potential for the reduction of para nitrophenol to para aminophenol. The Fe_3O_4 nanospheres anchored on carboxyl cellulose nanospheres were reported as excellent nanocatalysts in the Fenton-like system for the rapid removal of textile dye navy blue from aqueous solution (Qin et al. 2015). The carboxyl cellulose nanospheres act as a stabilizer of Fe_3O_4

nanoparticles thereby controlling the particle agglomeration and at the same time, it also controls the structure and morphology of the Fe_3O_4 nanospheres.

The widely accepted method for the synthesis of 1, 2, 3-triazoles is the Huisgen 1,3-dipolar cycloaddition of alkynes and azides (Huisgen et al. 1986). The conventional reaction generally requires a relatively higher temperature and results in providing a mixture of 1, 4- and 1,5-disubstituted 1,2,3-triazoles (Fig. 2.6). Cu catalyzed azide–alkyne cycloaddition (CuAAC) reaction leading resulting in the efficient synthesis of 1,4-disubstituted 1,2,3-triazoles has found potential applications in a variety of fields including chemical and combinatorial synthesis, bioconjugation, and biology to materials science (Moses and Moorhouse 2007; Meldal and Tornøe 2008; Jewett and Bertozzi 2010; Qin et al. 2010; Chuprakov et al. 2013). The bio-nanocomposites of iron and copper with chitosan (CS–Fe_3O_4–Cu) are reported to be efficient catalysts for azide–alkyne cycloaddition (Chetia et al. 2015). The developed magnetically recoverable heterogeneous bio-nanocomposite offers excellent results with various azides and alkynes (including internal alkynes) and provides very high regioselectivity, with only the 1,4- disubstituted 1,2,3-triazole regioisomer being formed.

Benzimidazole and benzodiazepine derivatives have significant importance in the material science (Boydston et al. 2006; Lim et al. 2012) and medical field due to its extensive applications in several diseases including HIV infections (Merluzzi et al. 1990), cardiovascular problems (Werner et al. 1990). Maleki et al. demonstrated the potential of chitosan supported iron oxide nanoparticles in catalyzing selective syntheses of 1,2-disubstituted benzimidazole and 1,5-benzodiazepine derivatives using 1,2-diamines and aldehydes or ketones in ethanol at ambient temperature (Maleki et al. 2014) (Fig. 2.3). The recyclable and eco-friendly bio-nanocomposite catalysts promise the high yield synthesis of biologically and pharmaceutically relevant benzimidazole and benzodiazepine derivatives.

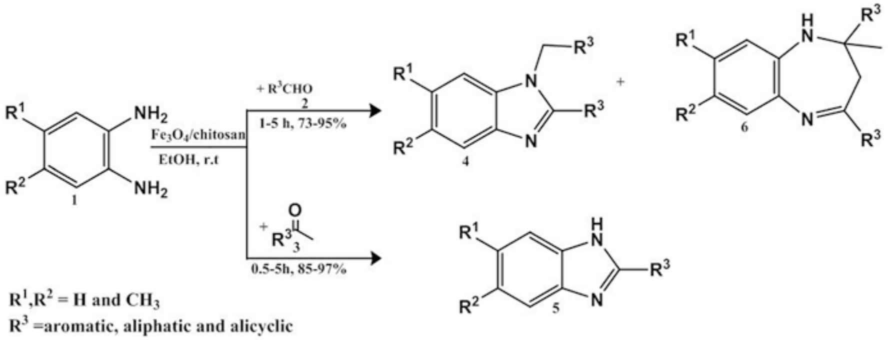


Fig. 2.3 Synthesis of benzimidazole and benzodiazepine derivatives in the presence of Fe_3O_4–chitosan nanocatalyst (Maleki et al. 2014)

2.6 Water Purification

For the past few decades, the increasing environmental pollution caused by the effluents from several industries including textile, plastic, leather, planting, and so on, is very alarming. Even at low concentrations, the water bodies were contaminated by toxic pollutants such as coloring agents and heavy metals. Removal of such pollutants from the industrial effluents before entering into the environment is strictly necessary (Ardejani et al. 2007). Several methods are available for the removal of such contaminants from effluents using reverse osmosis (Yüksel et al. 2013), ion exchange (Constantin et al. 2013), chemical precipitation (Benatti et al. 2009), and adsorption (Peláez-Cid et al. 2013). Among the several methods available for the removal of contaminants from effluents, adsorption using natural polymer-based materials is found superior due to its cost-effectiveness, reduced energy consumption, and also it does not generate harmful sludge (Saber-Samandari Saber-Samandari et al. 2014). Chitosan is known to effective for adsorbing anionic of reactive dye. However, it has poor sorption capacity for basic dyes. The sorption capacity of chitosan can be made possible by modifying chitosan with different functional groups including carboxylate, sulfonate, and phosphate (Huang et al. 2011).

2.6.1 Water Purification Using Copper-Based Bio-Nanocomposite

Samadi et al. reported the application of Cu–TiO_2/chitosan nanocomposite thin film for the removal of lead (Pb^{2+}) and chromium (Cr^{6+}) from an aquatic medium by photocatalytic process (Samadi et al. 2014). The copper–chitosan-based bio-nanocomposite thin film containing Cu^{2+} as the dopant synthesized by the solgel method on a polycarbonate substrate will be a reliable and inexpensive material for the water treatment process. Khan et al. also revealed the catalytic efficiency of copper and silver nanoparticles supported on the surface of cellulose acetate (CA)–CuO bio-composite toward the hydrogenation reduction of para nitrophenol to para aminophenol using sodium borohydride as the reducing agent (Khan Khan et al. 2017). The enhanced catalytic performance of zerovalent Cu–Ag nanoparticle–CA–CuO bio-nanocomposite (Cu^0–Ag^0/CA–CuO) was found to be due to the fast hydride ion transfer from sodium borohydride to Cu^0–Ag^0/CA–CuO. This happens because of the strong chemical interaction between Cu^0–Ag^0/CA–CuO and sodium borohydride (Khan Khan et al. 2017). Dankovich et al. reported the efficient in situ incorporation of copper nanoparticles in cellulosic fibers which can be utilized for water purification purposes. Their analysis suggests that the developed copper nanoparticle papers possess an increased bacteria reduction of log 8.8 for *E. coli* (Dankovich and Smith 2014).

2.6.2 Water Purification Based on Iron-Based Bio-Nanocomposites

Cellulose beads are considered to be a potential adsorbent due to its peculiar properties such as high surface area, porosity, and hydrophilic nature (Guo and Chen 2005). Cellulose beads and cellulose derived beads have found widespread applications ion exchangers, packing materials for chromatography, adsorbents for heavy metal ions and proteins, ingredients in cosmetic materials, and carriers for immobilization of biocatalysts (Stamberg and Peska 1983; Boeden et al. 1991; Wolf 1997). Saber-Samandari et al. reported the efficiency of chitosan/Fe-substituted hydroxyapatite composite beads for removal of basic dye (methyl orange) and heavy metal (Pb^{2+}) from aqueous solution (Saber-Samandari Saber-Samandari et al. 2014). The incorporation of hydroxyapatite in the bio-nanocomposite beads offers the capacity to remove heavy metal ions like Pb^{2+}, Cr^{2+}, Zn^{2+}, Cu^{2+}, Cd^{2+}, Co^{2+}, V^{5+}, Ni^{2+}, and Sb^{3+} from waters (Corami et al. 2007). Further, Jiang et al. also reported the efficiency of magnetic maghemite (c-Fe_2O_3)/chitosan nanocomposite films developed by the solution casting process for removal of methyl orange from aqueous solution (Jiang et al. 2012). The heavy metal lead, Pb^{2+} is also critically dangerous to the environment even in small quantities and their removal is still a challenging problem regarding environmental safety. A magnetic chitosan and clinctopile bio-nanocomposite for the effective removal of lead from water bodies was demonstrated by Javanbakht et al. (Javanbakht et al. 2016). The adsorption capacity of the nanocomposite depends on different parameters such as pH, temperature contact time, and Pb^{2+} concentration in solution. The spontaneous ($\Delta G < 0$) and exothermic ($\Delta H < 0$) adsorption process was found to follow pseudo second-order kinetics with a maximum theoretical adsorption capacity of 136.99 mg/g. The magnetic nanocomposite possesses a saturation magnetization value of 9.50 emu/g offers an efficient separation of the adsorbent material from the system by a simple and fast magnetic separation method.

Bio-nanocomposite of iron in the form of a hydrogel is a promising adsorbent for the removal of several oxianions such as phosphate (Fagundes et al. 2001), arsenate (dos Santos et al. 2011), and chromium (Zimmermann et al. 2010). Several researchers attempt to explain the mechanism of removal of chromium (VI) using chitosan–Fe bio-composites. Zimmermann et al. demonstrated that the mechanism of $HCrO_4^-$ adsorption by chitosan–Fe nanocomposite follows a ligand exchange reaction between the coordinated nitrate and $HCrO_4^-$ ions (Zimmermann et al. 2010). There is also a suggestion for the partial reduction of Cr (VI) bound to chitosan to less toxic Cr (III). Yu et al. demonstrated the mechanism of chromium (VI) removal using a magnetic–chitosan bio-nanocomposite. The adsorption of Cr (VI) onto magnetic–chitosan bio-nanocomposite was an endothermic and spontaneous process. In the pH range 2 to 5, Cr (VI) exists as $HCrO_4^-$ which can chelate with Fe (III) on chitosan–Fe bio-composites via the ligand-exchange mechanism (Zimmermann et al. 2010). However, at a pH value higher than 5, the concentration of CrO_4^{2-} drastically increases, which cannot be adsorbed by the magnetic chitosan–Fe bio-composites. Moreover, at higher pH, there will be competition between OH− and Cr (VI) species upon chelation with Fe (III) leading to a decrease in the final pH of the solution (Yu et al. 2013a, b). Hence, the optimum pH value selected for the adsorption experiments was pH 3. Yu et al. proposed a possible mechanism for the adsorption process of Cr (VI) on chitosan–Fe bio-composites and is shown in (Yu et al. 2013a, b). They found that at optimum pH, the predominating form of Cr (VI) is negatively charged $HCrO_4^-$ which can be adsorbed by the positively charged chitosan–Fe bio-composites through electrostatic attraction and ion-exchange interaction. The controlling mechanism among these for the removal of Cr (VI) is the ion exchange mechanism (Yu et al. 2013a, b).

The major advantage of using iron-based nanomaterials for cleaning purposes is high adsorption capacity toward toxic metals and organic pollutants and the easy separation from the reaction medium (Zhong et al. 2006). The agglomeration of the magnetic nanomaterials occurs due to interparticle dipolar forces causing a decrease in the intrinsic magnetism and also decreases the surface area (Olsson et al. 2010). Xiong et al. developed cellulose @ultrasmall iron oxide nanospheres (cellulose@γ-Fe_2O_3) by a simple coprecipitation method (Xiong et al. 2014). They used 1-butyl-3-methylimidazolium chloride (Bmim)Cl as the cosolvent for both cellulose and iron salt. Their study suggests that superparamagnetic bio-nanocomposite possesses excellent adsorption efficiency for Pb^{2+} with an adsorption capacity of 21.5 mg/g and methylene blue with an adsorption capacity of 40.5 mg/g showing its potential to be utilized as an efficient nanoadsorbent in water treatment methods.

The toxic carcinogenic chemical arsenic exists as arsenite and arsenate depending on the redox conditions (Mercer and Tobiason 2008). According to the World Health Organization (WHO), the maximum permissible concentration of arsenic in drinking water is 10 ppb (Jing et al. 2012). The conventional methods employed for the removal of arsenic from water bodies include oxidation (Martin et al. 2007) coagulation (Moreno-Casillas et al. 2007), membrane separation (Iqbal et al. 2007), ion exchange (Anirudhan and Unnithan 2007), chemical Precipitation (Mercer and Tobiason 2008), and adsorption (Maji et al. 2007). Among these, the most efficient method in terms of reduced cost, high concentration efficiency, and environmentally friendly nature is the adsorption method (Gu et al. 2005; O'Connell et al. 2008). Yu et al. demonstrated the potential of magnetic bio-composites of cellulose@iron oxide nanoparticles for efficient removal of arsenic (Yu et al. 2013a, b). The sensitive magnetic induced behavior shown by the resulting cellulose@Fe_2O_3 nanoparticles offers easy separation of the materials to form the aqueous solution using an external magnetic field. The Langmuir adsorption capacities for the removal of arsenite and arsenate using cellulose@iron oxide nanoparticles were found to be 23.16 and 32.11 mg g^1, respectively. Besides, Zhou et al. reported the efficiency of magnetic composites of cellulose@nanoscale-zero-valent iron for the removal of arsenic from water (Zhou et al. 2014). The developed cellulose@zerovalent iron composites could be used to treat solutions in the pH range of 6–9. The presence of SO_4^{2-}, HCO_3^-, and SiO_3^{2-} (up to 40 mg L^{-1}) did not affect the removal rates (> 97%) of As(III) by formed nanocomposites. They also found that the rate of removal As(III) does not show noticeable change when phosphate concentrations were less than 20 mg L^{-1}.

2.7 Sensor

In this era of increasing environmental pollution, the development of proper environmental gas sensing is in increasing demand. Among the common air pollutants, nitrogen dioxide (NO_2) is particularly harmful due to its severity in causing critical respiratory problems and acid rain. The most required features of an ideal sensor cover rapid sensitivity, fast response, high reversibility, low cost, simple structure, simple in handling, and capability of being integrated with a variety of substrates specifically at room temperature (Sadasivuni et al. 2014a; Wang et al. 2015). The noticeable advantages of recently developed conducting polymer nanocomposite sensors include reduced power consumption, room temperature operability, and enhanced performance (Sadasivuni et al. 2014b).

2.7.1 Copper-Based Bio-Nanocomposite in Sensor Application

The reliable monitoring of the humidity content in the environment is of particular importance in several industrial fields such as agriculture, especially in areas prone to landslides (Hadi and Hashim 2017). Chemical gas purification, ovens, laundry, film desiccation, textile, and paper industry are some of the areas where the humidity sensor can offer a better development (Chen and Lu 2005). The major requirements of a humidity sensor include high sensitivity, fast response as well as recovery, good thermal and mechanical stability, negligible hysteresis over periods of usage, and a large operating range for both humidity and temperature. Hadi and Hashim (2017) reported the potential of using a carboxymethyl cellulose–starch–CuO bio-nanocomposite as a humidity sensor which can offer a higher sensitivity in the humidity range (60–90) RH% (Hadi and Hashim 2017). The electrical and optical measurements of the developed bio-nanocomposite suggest that the DC conductivity as well as absorbance of the nanocomposite blend increases whereas the energy band gap decreases with an increase in the concentration of copper oxide nanoparticles. A smart and professional cellulose acetate–copper oxide (CA–CuO) nanocomposite-based sensor was fabricated by Chani et al. (2016). They found that the developed film and pellet type sensor shows a sensing range from 0 to 90% relative humidity (RH) and the mechanism behind sensing is based on the change in resistance as well as a capacitance with a change in humidity. The fabricated bio-nanocomposite-based sensor shows the decrease in resistance by 1093 times and an increase in capacitance by 127 times with a relative humidity change from 0 to 90%. An average change in resistance and capacitance is up to 3.8 MΩ/% RH and 19.2 pF/% RH, respectively.

2.7.2 Iron-Based Bio-Nanocomposite in Sensor Application

Sadasivuni et al. reported the potential of utilizing biofriendly cellulose nanocrystal/iron oxide nanocomposite as a flexible NO_2 sensor (Sadasivuni et al. 2016) (Fig. 2.4). Cellulose nanocrystals (CNC) are the crystalline particles obtained by the acid hydrolysis of cellulose fibers. The CNCs with high crystallinity, stability, and excellent mechanical properties can be obtained using concentrate sulfuric acid (Khoshkava and Kamal 2013; Wei et al. 2014). Cellulose nanocrystals are generally rigid in shape and anisometric in nature. Cellulose nanocrystal/iron oxide nanocomposite sensor is capable of detecting the gas as low as parts-per-million in a short time. The synergistic effect of the large surface to volume ratio in combination with characteristic physical and electrical properties of iron oxide and cellulose nanocrystals makes the resulting composite an ultrasensitive sensor having high sensor response, flexibility, room temperature operation, low power consumption, durability, and low production cost.

For the past few years, the development of electrochemical biosensors for the detection of different pesticides is also an interesting area for researchers (Aragay et al. 2012). Compared to conventional sensing techniques, biosensors offer significant advantages including high sensitivity, high specificity at a reduced cost (Jeyapragasam and Saraswathi 2014). The commonly used electrochemical biosensors work by inhibiting the enzyme acetylcholinesterase (AChE) (Periasamy et al. 2009; Pundir and Chauhan 2012). The principle behind an electrochemical AChE biosensor is shown in Fig. 2.5. At constant potential at the electrode, acetylcholinesterase undergoes an oxidative enzymatic reaction to form thiocholine. The monitoring of the rate of inhibition is carried out using amperometric/voltammetric detection of thiocholine. Jeyapragasam and Saraswathi (2014) reported the potential of using iron oxide–chitosan nanocomposite-based electrochemical biosensor for the detection of carbofuran (Jeyapragasam and Saraswathi 2014).

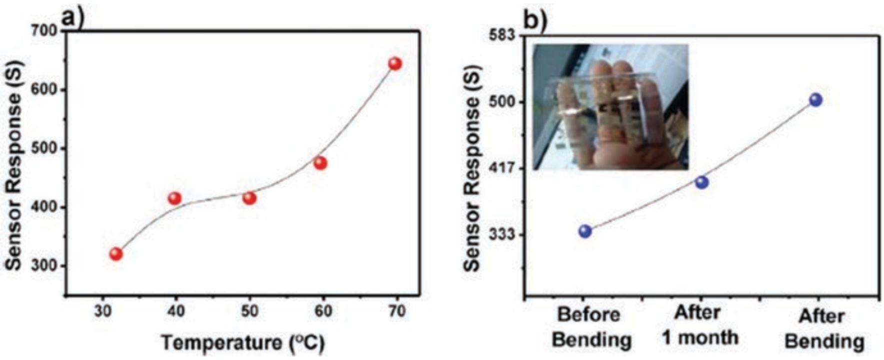
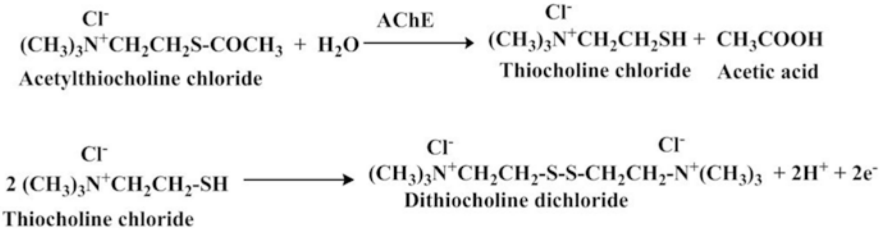


Fig. 2.4 (**a**) Temperature and (**b**) flexibility effect on the relative resistance change of CNC/iron oxide nanocomposite in the presence of NO_2 gas at 500 ppm. Reproduced with permission from ref. (Sadasivuni et al. 2016). Copyright© 2016 Elsevier B.V. All rights reserved



$$\underset{\text{Acetylthiocholine chloride}}{\overset{Cl^-}{(CH_3)_3N^+CH_2CH_2S\text{-}COCH_3}} + H_2O \xrightarrow{\text{AChE}} \underset{\text{Thiocholine chloride}}{\overset{Cl^-}{(CH_3)_3N^+CH_2CH_2SH}} + \underset{\text{Acetic acid}}{CH_3COOH}$$

$$2\,\underset{\text{Thiocholine chloride}}{\overset{Cl^-}{(CH_3)_3N^+CH_2CH_2\text{-}SH}} \longrightarrow \underset{\text{Dithiocholine dichloride}}{\overset{Cl^-}{(CH_3)_3N^+CH_2CH_2}\text{-}S\text{-}S\text{-}\overset{Cl^-}{CH_2CH_2\text{-}N^+(CH_3)_3}} + 2H^+ + 2e^-$$

Fig. 2.5 The principle of an electrochemical AChE biosensor (Jeyapragasam and Saraswathi 2014)

The good biocompatibility, reduced toxicity, high adsorption capacity, and fast electron transfer capacity make Fe_3O_4 nanoparticles favorable to act as an electrode matrix in enzyme biosensors (Rossi et al. 2004). Besides, the outstanding film-forming capacity, excellent adhesion property, biocompatibility, and high mechanical strength of chitosan material to act as an efficient carrier material for enzyme immobilization (Krajewska 2004). In the magnetic Fe_3O_4–chitosan nanocomposite, the presence of chitosan inhibits the agglomeration of the Fe_3O_4 nanoparticles and at the same time prevents the loss of the AChE enzyme molecules by providing a favorable biocompatible microenvironment to takes place the enzyme function property (Jeyapragasam and Saraswathi 2014).

Tiwari et al. demonstrated the possibility of using graphene oxide modified iron oxide–chitosan hybrid as an electrochemical geno-sensor for the detection of pathogens (Tiwari et al. 2015). Using electrochemical impedance spectroscopic analysis, they observed that the as prepared bio-composite bio-nanocomposite can detect *E. coli* in the range of 10^{-6} to 10^{-14} M. It is also worth significant that the fabricated bio-nanosensor is highly effective in terms of selectivity, sensitivity, and even after six repeated cycles, it retains 90% of its initial activity. Kaushik et al. reported the efficiency of iron oxide nanoparticles chitosan composite for glucose sensing material (Kaushik et al. 2008) (Fig. 2.6). Their fabricated glucose oxidase/chitosan–Fe_3O_4/ITO bio-nanocomposite bioelectrode shows a fast response time (5 s), linearity as 10–400 mg dL^{-1} of glucose, sensitivity as 9.3_A/(mg dLcm^2), and a shelf life of 8 weeks under cooling conditions.

A comprehensive table of the application of copper and iron based for different applications is given below (Table 1):

3 Conclusions

The current chapter presents the use of copper- and iron-based bio-nanocomposites with cellulose and chitosan for different applications including antibacterial, medical, packaging, and sensors. The effective surface chemical modifications provided by cellulose and chitosan in combination with magnetic iron and copper have been widely explored. There are wide varieties of bioresources to implement physical,

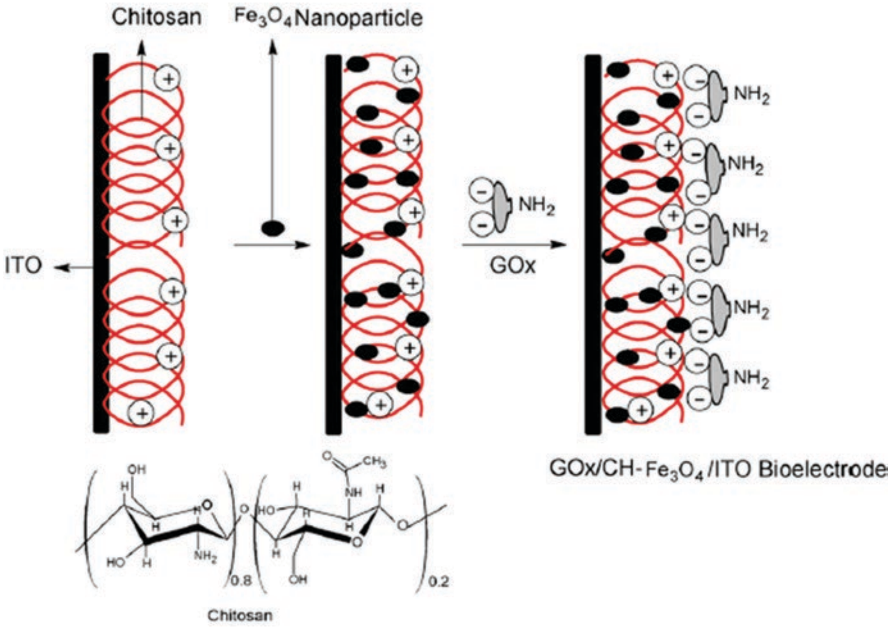


Fig. 2.6 The mechanism of development of chitosan–Fe_3O_4 bio-nanocomposite and shattering of glucose oxidase on the formed matrix. Reproduced with permission from reference Kaushik et al. (2008). Copyright © 2008 Published by Elsevier BV

chemical as well as mechanical properties of copper/iron-based bio-nanocomposite to make them beneficial for a variety of applications. Both cellulose and chitosan offer the promising potential for long lasting economic development due to its favorable characteristics such as biodegradability, biocompatibility, and their flexibility to adjust with various physical and chemical transformations. The possibility to utilize copper/iron-based bio-nanocomposite in different applications will be an environmentally friendly platform for eliminating the problems aroused by the non-eco-friendly composites.

Table 2.1 Summary of copper and iron based bio-nanocomposites for different applications

Sl. No	Bio-nanocomposite	Application	Highlight	Reference
1	Copper nanofillers in cellulose	Antibacterial activity	Vegetal cellulose fibers act as an effective substrate	Pinto et al. (2013)
2	Bacterial cellulose–Cu	Antimicrobial activity	Varying hydrothermal synthesis time results in composites with a varying copper content	Araújo et al. (2018)
3	GO–CuO–bacterial cellulose	Antibacterial activity	Superior activity against Gram-positive bacteria and biocompatibility toward mice fibroblast cells.	Xie et al. (2020)
4	Cu NPs–cotton composite	Antibacterial activity	Layer-by-layer electrostatic assembly process was used to prepare sub-5 nm Cu NP coatings on cotton	Cady et al. (2011)
5	Cellulose–copper–γ-Fe_2O_3 composite	Catalytic synthesis of Hantzsch 1,4-dihydropyridine and polyhydroquinoline derivatives	Excellent thermal stability and leaching free nature	Maleki et al. 2019
6	Chitosan–Cu NPs	Catalytic reduction of aromatic nitrocompounds	Low energy of activation along with good recyclability up to six cycles	de Souza et al. (2017)
7	Chitosan–copper–iron oxide	Catalyst for azide–alkyne cycloaddition reactions	Magnetically recoverable and effective for the synthesis of a wide range of 1,2,3-triazoles	Chetia et al. (2015)
8	Chitosan–GO–Cu	Detection and catalytic reduction of paranitrophenol	A high sensitivity of 1.729 ± 0.027 μAmM^{-1} cm^{-2} and a detection limit of 3.5 mM toward 4-NP	Khan et al. (2019)
9	Cu NPs sputtered bacterial cellulose	Enhanced mechanical, thermal, and conduction properties.	High conductivity (0.026 S m^{-1}), good mechanical properties (41.4 Mpa), and excellent EMI shielding (55 dB).	Lv et al. (2016)
10	Carboxymethyl cellulose–starch–CuO	Humidity sensor	High sensitivity in the humidity range (60–90) RH%.	Hadi and Hashim (2017)
11	Chitosan–CuO–neem seed	Biomedical application	Highest cytotoxicity (IC_{50}: 16.33 μg/mL) against human breast cancer (MCF-7) cell line was found	Revathi and Thambidurai (2019)

(continued)

Table 2.1 (continued)

Sl. No	Bio-nanocomposite	Application	Highlight	Reference
12	Sodium alginate (SA) and cellulose nano whisker (CNW)–CuO NPs	Food packaging	Metal–polymeric film offers promising antimicrobial and antioxidant activity	Saravanakumar et al. (2020)
13	Chitosan–CuO	Antibacterial and dye degradation	Comparatively good inhibition effects on Gram-negative bacteria than Gram-positive bacteria.	Sathiyavimal et al. (2020)
14	Magnetic chitosan glyoxal/fly ash/ Fe_3O_4	Removal of anionic azo dye	The adsorption process follows pseudo second-order kinetic, and Freundlich isotherm models.	Malek et al. (2020)
15	Cu NPs@ Fe_3O_4–chitosan	Catalyst for the synthesis of amino- and *N*-sulfonyl tetrazoles	Magnetic removal of the catalyst and reusability	Motahharifar et al. (2020)
16	Cu@cotton cellulosic nanocomposite	H_2 production and catalytic reduction of 4-nitrophenol	Efficient for the reduction of 4-nitrophenol in real samples like milk and juice	Khan (2020)
17	Copper oxide/ chitosan nanocomposite	Sensing and catalysis	Enhanced tensile strength and flexibility	Aslam et al. (2020)
18	Chitosan functionalized iron nanosheet	Removal of As(III) and Sb(III)	Removal mechanism follows surface complexation and hydrogen bonding	Zeng et al. (2020)
19	Magnetic Fe_3O_4-functionalized chitosan	Catalytic synthesis of polyhydroquinoline, 1,4-dyhdropyridine and 1,8-dioxo-decahydroacridine derivatives	Average size of magnetic NPs was 30 nm	Asgharnasl et al. (2020)
20	Copper-hydroxyapatite/ chitosan/ polyvinyl pyrrolidone	Bone tissue engineering	Blood compatible with the hemolytic ratio of <2%	Narayanan et al. (2020)
21	Fe_3O_4–cellulose nanocrystals–copper	Electrochemical sensing of venlafaxine	The linear dynamic range for venlafaxine by the modified electrode was 0.05–600.0 μM and limit of detection was 0.01 μM	Khalilzadeh et al. (2020)

(continued)

Table 2.1 (continued)

Sl. No	Bio-nanocomposite	Application	Highlight	Reference
22	Ag/cu cellulose	Colorimetric detection of Hg(II), photocatalysis, and antimicrobial	Effective for detoxification of toxic pollutants	Kokilavani et al. (2020)
23	Fe–Cu–cellulose nanocrystals	Antibacterial activity and Pb^{2+} removal	Composite has an antibacterial ratio of 95.9–99.9% and retain 80.41% Pb^{2+} removal efficiency after six cycles	Chen et al. (2020a)
24	$CuFe_2O_4$–chitosan	Electrochemical sensor	Possess nanomolar detection limit toward biomarker	Chen et al. (2020b)
25	Chitosan–CuO	H_2S gas sensor	Allows H_2S detection at 40 °C with a fast response time of 14 s	Ali et al. (2020)
26	Fe_3O_4–chitosan	Magnetic drug delivery	High drug loading and low burst release	Arias et al. (2012)
27	Cellulose nanocrystals–magnetite	Glucose sensing	Dermal and oral blood glucose monitoring	Tracey et al. (2020)
28	A-Fe_2O_3 encapsulated chitosan grafted polyaniline	Electrochemical sensing of paracetamol	Efficient sensing properties with sensing range 5.0–100.0 μM, sensitivity 1.1 $mV \cdot \mu M^{-1} \cdot cm^{-2}$, response time 50s, recovery time 20s, limit of detection 5.7 μM, and stability for 40 days	Kushwaha and Shukla (2020)
29	Copper–cobalt–nickel ferrite/graphene oxide/polyaniline tri-composite	Absorbing agent in cotton fabric	Microwave absorption capacity of composite could achieve to −33 Db at 10.8 GHz	Sun et al. (2020)
30	Polypyyrole–chitosan–Fe_3O_4	Nonenzymatic glucose biosensor	The developed sensor has selective detection of glucose with a limit of detection of 234 μM	Abdul Amir Al-Mokaram et al. (2016)

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Chapter 3
Current Aspects of Nanotechnology: Applications in Agriculture

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Contents

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1 Introduction

Nanotechnology is an emerging field that has the potential to revolutionize the agriculture sector in the current century (Prasad et al. 2017). It is a multidisciplinary field where biology, chemistry, physics, material science, and engineering play a role in technological developments (Bayda et al. 2020). Nanotechnology has made a significant impact on the society, environment, industries, and daily life of human beings (Gupta and Xie 2018; Thangadurai et al. 2020a, b). The nanomaterial has a size reduction to the nanometer scale (10^{-9}) and modifies the biological, physical, and chemical properties of the materials (Jeevanandam et al. 2018). The reduced size and changes in properties of materials find novel and innovative applications in various sectors (Nile et al. 2020). The size varies from 1 to 100 nm with a large surface area that gives the unique features to nanomaterials and this property offers enormous applications in various fields (Khan et al. 2019). Several countries are depending on agriculture and they started using nanotechnology to improve crop productivity, processing of foods, and improving food security (Ditta 2012; Sekhon 2014; Marchiol 2018; Prasad et al. 2017a, b). Agriculture is the backbone for many countries with the majority of the population dependent on it for their livelihood (Kanianska 2016). The interventions related to nanotechnology applied to the agriculture field are very important in developing countries like India (Mukhopadhyay 2014; Shang et al. 2019). The products that are developed using nanotechnology for application in the agriculture sector depend on several factors that include cost of the product, effectiveness of the product, acceptance by the agriculture community, risk assessment, market demand, effectiveness in the environment, and profit margins (Singh et al. 2015a; b; Kah et al. 2019; Kah and Kookana 2020; Sangeetha et al. 2017a). In the coming years, the agriculture sector will face a lot of challenges with increasing population, reduced land area, investments related to fertilizers and pesticides, environmental issues, and pest management (Wield et al. 2013; Pingali et al. 2019; Sangeetha et al. 2017b, c). These issues can be overcome by introducing nanotechnology to improve the crop productivity and nutritional value of the crops (Manjunatha et al. 2016). The nanomaterials play a vital role in the agriculture field at various stages starting from water storage to delivery of nutrients and fertilizers in a predetermined manner (Usman et al. 2020). The nanoporous membranes, nanocapsules, nanofibers, nanocarriers, nanosensors, and nanoemulsions reduce the chemical usage such that the damage to plants as well as the ecosystem will be maintained (Robles-Garcia et al. 2016; He et al. 2019). In the following sections, we address the types of nanomaterials, potential applications of nanomaterials in the agriculture field, and future prospects of nanotechnology in the agriculture sector.

2 Sources of Nanomaterials

According to the European Commission, the nanomaterial is defined as a material that is natural, incidental, or manufactured material consisting of nanoparticles (Boverhof et al. 2015). The nanomaterials are smaller than one micrometer in one or more dimensions (Jeevanandam et al. 2018). The materials are derived from different sources such as natural, incidental, and engineered nanomaterials (Hochella et al. 2019).

2.1 Natural Nanomaterials

The nanomaterials naturally exist in nature in the form of forest fires (Jeevanandam et al. 2018), volcanoes ash (Griffin et al. 2018), dust storms (Jeevanandam et al. 2018), ocean spray, radioactive decay of radon gas (Lewis and Kannan 2014), mineral springs (Griffin et al. 2018), acid mine drainage sites (Crane and Sapsford 2018), and metal-containing rocks (Sharma et al. 2015). The living organisms also function as natural nanomaterials which include viral capsid proteins (Koudelka et al. 2015), waxy crystals of lotus plant (Barthlott et al. 2017), spider silk (Das et al. 2017), natural colloids (Coman 2018), horny materials (Wani et al. 2011), bird's feathers (Jeevanandam et al. 2018), hair (Fulekar and Pathak 2017), and claws (Griffin et al. 2018). Nature provides both macro and micro nanoparticles such as plant extracts, microbial extracts, redox active secondary metabolites (Siddiqi et al. 2018), milk, proteins, and peptides (Marslin et al. 2018). Now the emerging field of nanotechnology related to agriculture is phytonanotechnology (Saxena 2019). The phytonanotechnology employs the compounds and substances isolated from plants are modified or coated to form nanoparticles (Lewis Oscar et al. 2016). The modified nanoparticles have biological activity that plays a role in both agriculture and medical fields (Skonieczna and Hudy 2018). The biomass produced as byproducts from plant materials is used as feedstocks for the growth of fungi and bacteria to generate nanoparticles in in vivo conditions (Kuppusamy et al. 2016). The plant-based microalgae is well suited for the synthesis of good nanomaterials (Sharma et al. 2016). The phytonanotechnology provides numerous benefits including waste minimization, conversion of byproducts to value-added nanomaterials, bio reductive formation of metal salts, natural product coating for stability, activity, and reduced toxicity (Ghosh et al. 2017). This is the new field where research and scientific development are essential for transforming the biomass waste into useful nanomaterials (Zamani et al. 2019).

2.2 Incidental Nanomaterials

The nanomaterials are produced by industrial processes and mechanical processes (Jeevanandam et al. 2018). The sources of nanomaterials produced in this category are vehicle exhausts, combustion processes, and welding fumes (Rai and Biswas 2018). The best examples under this category are burning gas, candle, and biomass

(John et al. 2017). The nanomaterials produced are ultrafine particles that contribute to air pollution (Stone et al. 2017).

2.3 Engineered Nanomaterials

The nanomaterials are engineered and manufactured by scientists and researchers to cater to the needs of the scientific domain as well as the required properties (Jeevanandam et al. 2018). The nanomaterials that come under this category are carbon nanotubes, metal and metal oxide nanoparticles, and quantum dots (Tebaldi et al. 2016). The engineered nanomaterials size varies from 1 to 100 nm with at least one dimension. The materials have more advantages due to their unique physical and chemical properties (Khan et al. 2019; Srivastava et al. 2021). The engineered nanomaterials have novel properties due to its surface area, particle size, surface reactivity, presence of coatings, and surface charge (Prasad et al. 2016). Previous studies reported that the plant species when exposed to engineered nanomaterials for long duration results in physiological, morphological, and genetic changes. These changes may affect the nutritional status of the plant, plant growth, and crop yield. Furthermore, the nanomaterials enter the food chain through the soil to various parts of the plant (Prasad 2019a, b). Different classes of engineered nanomaterials and their impact on plant growth and crop yield are shown in Table 3.1.

3 Different Forms of Nanomaterials Applied in Agriculture

Nanomaterials are small in scale and exhibit different novel properties due to their size, shape, surface area. The nanomaterials are available in different nanoformulations such as nanocarriers, nanotubes, nanoclays, nanocomposites, nanosensors, nanofibers, and nanocapsules (Fig. 3.1).

3.1 Nanocarriers

Nanocarriers are one form of nanomaterials used as a carrier for the transport of substances (Patra et al. 2018). There are various types of nanocarriers which include polymers, carbon-based nonmaterial, micelles, and liposomes (Yan et al. 2018). The nanomaterials act as carrier systems for the delivery of agrochemicals in the form of capsules (Vega-Vásquez et al. 2020). The encapsulated materials deliver chemicals, growth regulators, and micronutrients in encapsulated form (Shang et al. 2019). The study by Santo Pereira et al. (2019) evaluated the effects of seed priming using chitosan/alginate-based and chitosan/tripolyphosphate based encapsulated material for delivering gibberellic acid GA3 on growth and productivity of *S. lycopersicum*. The

Table 3.1 Engineered nanomaterials and their applications in the agriculture field

S. No.	Engineered nanomaterials (ENM)	Property	Agriculture application	Reference
I.	**Inorganic nanomaterials**			
a.	*Metals*			
	Al	Nanofertilizer	Seed growth	Machado et al. (2015)
	Ag	Plant growth regulators	Seed germination; stimulates plant growth; antimicrobial activity	Mahakham et al. (2017), Huang et al. (2020)
	Cu	Nanofertilizer pesticides, bactericidal	Foliar application; promote plant growth; controls pests; suppresses the bacterial growth	Lopez-Vargas et al. (2018), Kasana et al. (2016), El-Saadony et al. (2020)
	Zn	Nanofertilizer	Micronutrient for metabolic activity, management of oxidative stress, promotes plant growth, seed germination, root growth	Chen (2018), Kolencik et al. (2019), Kasana et al. (2016)
	Fe	Nanofertilizer	Promote plant growth	Boutchuen et al. (2019), Duhan et al. (2017)
	Mo	Nanofertilizer	Promotes plant growth	Mushinskiy and Aminova (2019), Sanzari et al. (2019)
	Mn	Nanofertilizer	Promote plant growth	Dimkpa et al. (2018)
	Si	Nanofertilizer	Regulates plant metabolic activities	Rastogi et al. (2019)
b.	*Metal oxides*			
	CuO	Nano insecticidal	Controls insects	Dimkpa et al. (2018)
	Fe_2O_3	Plant growth promote materials	Seed germination	Rui et al. (2016), Boutchuen et al. (2019), Palchoudhury et al. (2018)
	Fe_3O_4	Nanofertilizer	Promotes plant growth	Jeyasubramanian et al. (2016)
	ZnO	Nanofertilizer	Seed germination	Prasad et al. (2012)
	Al_2O_3	Bactericidal	Antimicrobial activity against soil microorganisms	Fajardo et al. (2014)
	TiO_2	Bactericidal	Bacterial spot disease	Mattiello and Marchiol (2017)
	MgO	Pesticide	Nano priming agent for seed germination; Controls plant pests	Raliya et al. (2017)
	SiO_2	Nanofertilizer	Mitigating salt stress	Rastogi et al. (2019)
c.	*Quantum dots*			

(continued)

Table 3.1 (continued)

S. No.	Engineered nanomaterials (ENM)	Property	Agriculture application	Reference
	CdSe	Pesticide detection	Detection of Triazophos using quantum dot nanobeads	Liao et al. (2019)
	Silicon quantum dots	Photosynthesis	Water soluble silicon quantum dots enhance photosynthesis in lettuce plants	Li et al. (2020a, b)
	Carbon dots	Plant growth regulators	Improves the plant growth	Li et al. (2020a, b)
II.	**Organic nanomatreials**			
	Fullerenes	Water retention capacity	C_{60} enhances water retention capacity, biomass, and fruit yield.	Husen and Siddiqi (2014)
	Nanotubes	Carbon nanotubes	Water retention capacity, biomass, and fruit yield.	Husen and Siddiqi (2014)
	Electrospun nanofibers	Insecticidal property	Effectively release sex pheromones to attract male insects and controls the insects	Noruzi (2016)
III.	**Hybrid nanomaterials**			
	Inorganics–inorganics	Metal–metal oxides	Detection and separation of heavy metal ions	Yang et al. (2019)
	Organics–inorganics	Magnetite–carbon nanocomposites	Extracted fungicide Triazole residue from fruit sample	Meroni and Ardizzone (2018)
	Organics–organics	Urea–hydroxyapatite nanomaterials	Slow release of nitrogen	Kottegoda et al. (2017)

results found that a fourfold increase in productivity using nano AlG/Cs-GA3. Silicon nanoparticles (Si-NPs) are used as carrier agents for the delivery of proteins, nucleotides, nutrients, and chemicals in plants. The silicon nanoparticles are directly applied or used as carrier systems to release pesticides, insecticides on pests and larvae of insects. The activity of Si-NPs is due to the dehydration properties of silica that result in impairment of the digestive tract of insects (Rastogi et al. 2019). Not only play a role in pesticide/insect management, but the silicon nanocarriers deliver herbicides and fertilizers to improve productivity (Caceres et al. 2019). In another study, Janmohammadi et al. (2016) reported the use of silicon dioxide nanoparticles as delivery vehicles for fertilizers to improve plant productivity. Nanocarrier systems have also been explored for the transfer of plant growth regulators (Camara et al. 2019). These nanoparticulate systems have shown increased biological activity and reduced the concentrations of herbicides, fungicides, and insecticides in the environment (Pereira et al. 2019). The nanocarriers deliver the substance in

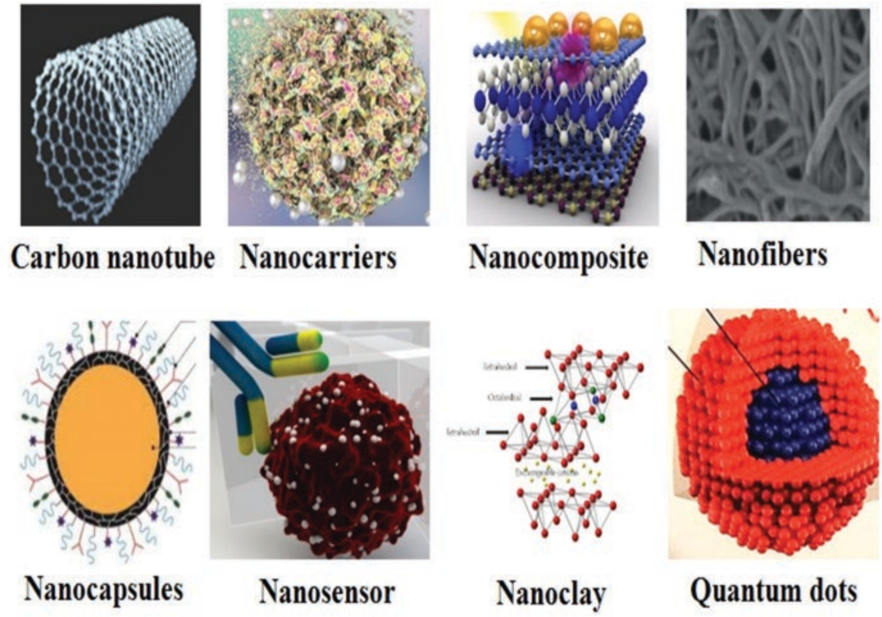

Fig. 3.1 Different forms of nanomaterials used in agriculture
Source: https://www.britannica.com/science/carbon-nanotube; https://www.news-medical.net/life-sciences/Nanocarriers-for-Drug-Delivery.aspx; https://www.azonano.com/article.aspx?ArticleID=4117; https://en.wikipedia.org/wiki/Nanofiber, https://www.sciencedirect.com/science/article/abs/pii/S0001868616301117; https://light.utoronto.ca/research-3/nanobiosensors; https://www.edn.com/quantum-dots-explained; Guo et al. 2018

sustained release at a predetermined rate to maintain a constant concentration of active substances for a specific period (Huang et al. 2018). The advantages of this carrier system are protected against degradation, improvement in the solubility of substances, and prolonged release of active ingredients with optimum concentration maintenance (Wang and Liu 2019).

3.2 Nanotubes

Nanotubes are made up of carbon, which are cylindrical molecules with rolled-up sheets of single-layer carbon atoms. The carbon nanotubes are large molecules, 1–3 nm in diameter, and thousands of nm long (Saifuddin et al. 2013). The carbon nanotubes are stronger compared with steel. The carbon nanotubes are extensively utilized in agriculture along with other fields of application. In the agriculture field, the carbon nanotubes have mixed effects on plants. The CN tubes improve the plant biomass by regulating plant growth (Shang et al. 2019). However, studies reported the acute toxicity and alterations at the genetic level in many plants (Verma et al.

2019). Carbon nanotubes (CNTs) are of two types which include single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs) (Saifuddin et al. 2013). The carbon nanotubes have various properties, they are—nano size, large surface volume ratio, water solubility, electric properties, mechanical strength, biocompatibility, higher immobilization efficiency, and strong photoluminescence (He et al. 2013). Due to various physical, chemical, biological, and mechanical properties, these carbon nanotubes have potential applications in various fields (Ibrahim 2013). In agriculture, the use of CNTs increases germination through the penetration of moisture into the seeds. The carbon nanotubes act as vehicles to deliver desired molecules into seeds and protect the seeds from diseases. The CNTs have not shown any adverse effect on plants (Pourkhaloee et al. 2011). The CNTs with their microtubular structure and physical properties play a role in biotechnological applications. The CNTs act as transporters, which transport chemicals/genes into the plant cells (Zaytseva and Neumann 2016). The impact of CNTs in agriculture results in seed germination, root growth, and biomass enhancement (Pandey et al. 2018). The carbon nanotubes induce phytotoxicity in plant cells which results in a change in gene expression in plant cells (Verma et al. 2019). Several studies have been done to explore the effect of CNTs on different plants such as rice, onion, tomato, corn, soyabean, broccoli, radish, and switchgrass. The required concentration for seed germination is a 50–100 mg/L concentration of CNTs (Patel et al. 2020). The CNTs enhance the germination rate, plant growth rate, and also biomass (Pandey et al. 2018). The factors that influence are shape, size, solubility, concentration, and functional groups. The functionalized carbon nanotubes alter seed germination and plant growth rate (Patel et al. 2020). The application of carbon nanotubes on different plants and their biological effects are represented in Table 3.2.

3.3 *3.3 Nanosensors*

The nanosensors consist of bio receptor molecules used as selective agents for targeting the analyte molecule (Nikhil et al. 2016). The nanosensors applied to agriculture for the detection of crop health and crop harvest and determine microbial or chemical contamination of the crop (Misra et al. 2013). The nanosensors diagnose the disease caused by plant infecting viruses, bacteria, and fungi (Khan and Rizvi 2014). Generally, the soilborne microorganisms infect the plants and cause diseases. The nanosensors are used for the detection of soilborne contaminants and also monitor environmental contaminants (Sekhon 2014). Apart from disease identification, the nanosensors are used for monitoring soil conditions such as soil pH, moisture, and environmental contaminants. In the soil environment, the pollutants are detected by nanosensors which include pesticides, insecticides, herbicides, fertilizers, pathogens, and crop growth (Singh et al. 2015a; b). Not only the detection mechanism, but the nanosensors are also used in smart delivery systems for efficient use for monitoring water resources, nutrients concentration, and chemical concentration

Table 3.2 Applications of carbon nanotubes on different plants and their biological effects

S. No.	Type of carbon nanotube	Plant	Biological effect	References
1	MWCNT'S	Tomato seeds	Seed germination	Srinivasan and Saraswathi (2010)
2	MWCNT'S	Broccoli	Enhanced growth and water uptake.	Martínez-Ballesta et al. (2016)
3	CNT'S	Rice	Enhanced plant growth and yield	Joshi et al. (2020)
4	MWCNT'S	Tomato plant	Fruit metabolome effected	McGehee et al. (2017)
5	MWCNT'S	Mustard seeds	Mustard seed germination and growth enhancement	Subagio et al. (2019)
6	CNT's	Maize	Enhancement of plant growth, nutrient, and water uptake.	Tiwari et al. (2014)

through precision farming (Kaushal and Wani 2017). The nanosensors facilitate real-time monitoring of crop and field conditions, plant diseases, plant growth, pest/insect attacks, and environmental stressors. This real-time monitoring prevents the excessive use of chemicals, pesticides, fertilizers, herbicides, insecticides in the environment and helps in the reduction of contaminants in the environment (Prasad et al. 2014). The nanodetectors detect the chemicals at a nanogram level or lesser which results in producing reliable, stable, and quick responses (Noah and Ndangili 2019). In another study, Yola and Atar (2017) identified atrazine using platinum nanoparticles/carbon nitride nanotubes with molecularly imprinted polymers. The methyl parathion was detected with enzyme acetylcholinesterase immobilized on multi walled carbon nanotube. The methyl parathion was detected based on the inhibitory activity of acetylcholinesterase (Dhull et al. 2013). Using gold nanoparticles as biosensors, the acetamiprid in soil was detected as the acetamiprid binding aptamer. This nanosensor detected acetamiprid was in the concentration range of 75 nm–7.5 μm (Shi et al. 2013). Furthermore, glyphosate, a herbicide in the soil was detected using a novel hollow fiber pencil graphite modified electrode (Gholivand et al. 2018). Currently, the aptamer based nanosensors are used for detecting pesticides, insecticides, and herbicides (Willner and Vikesland 2018). Not only the chemical organic compounds, but the metals such as Cu^{2+}, As^{3+}, and mercury in the soil environment are also detected by using nanosensors (Verdian 2018). The nanosensors are used to detect various types of chemicals based on different sensing mechanisms (Table 3.3).

The nanosensors are also used for detecting the soilborne pathogens using synthetic oligonucleotides, DNA probes, enzymes, and antibodies represented in Table 3.4 (Koedrith et al. 2015). A recent study by Guilger et al. (2017) reported that the biogenic silver nanoparticle coated with *Trichoderma harzianum* was used for controlling the disease caused by the fungus *Sclerotonia sclerotiorum*.

Table 3.3 Detection of chemical compounds using nanosensors

S. No	Name of the chemical compound	Nanosensor	Reference
1	Malathion	Nonenzymatic electrochemical sensing (Au-NPs/chitosan hybrid composite)	Bolat and Abaci (2018)
2	Methyl parathion	Electrochemical sensor (silver particles supported grapheme nanoribbons)	Govindasamy et al. (2017)
3	Parathion	Nonenzymatic electrochemical sensor (nickel oxide modified screen printed electrode)	Khairy et al. (2018)
4	Chlorpyrifos	Electrochemical immunosensing (gold nanopartciles)	Talan et al. (2018)
5	Acetamiprid	Aptamer based nanosensor (optical/electrochemical)	Verdian (2018)
6	N-methyl carbamate	Colorimetric sensor	Qian and Lin (2015)
7	Carbofuran	Carbon-based electrode (Butyryl cholinesterase inhibition)	Dey et al. (2015)
8	Trizophos	Electrochemiluminiscence sensor	Li et al. (2019)
9	Atrazine	Magnetoelastic biosensor	Sang et al. (2018)
10	Aldicarb	Immunochromatographic test strip-colorimetric sensor (monoclonal antibody specific for aldicarb)	Liu et al. (2017)
11	Cypermethrin	Colorimetric sensor based on silver nanoparticles	Kodir et al. (2016)

Table 3.4 Plant pathogens detected using nanosensors

S. No	Plant pathogens	Nanosensors detection	References
1	Cucumber mosaic virus	Electrochemical DNA sensor	Zulkifli et al. (2016)
2	Maize chlorotic mottle virus	Unmodified gold nanoparticles	Liu et al. (2015)
3	Watermelon silver mottle virus	Nano-inspired biosensors	Kumar and Arora (2020)
4	Banana bunchy top virus	Gold nanoparticle based immunobinding assay	Majumder and Johari (2018)
5	*Pseudomonas syringae*	Colloidal gold nanoparticles	Lau et al. (2017)
6	*Xanthomonas campestris*	Gold nanoparticles by chimeric phages	Peng and Chen (2018)
7	*Agrobacterium tumefaciens*	Gold nanoparticles—lateral flow assay	Fuller et al. (2017)
8	*Ralstonia Solanacearum*	Gold nanoparticles functionalized with oligonucleotides	Khaledian et al. (2017)
9	*Botrytis cinerea*	Nanobiosensor	Bilkiss et al. (2019)
10	*Fusarium graminearum*	Nanobiosensor	Khiyami et al. (2014)

3.4 Nanocapsules

Nanocapsules are the widely used delivery systems for the transport of bioactive compounds. Nanocapsules consist of an external polymeric membrane and the inner part consists of a liquid or polymeric matrix (Deng et al. 2020). The inner matrix consists of bioactive compounds such as chemicals, genes, and herbicides that target particular parts of a plant to release their content (Martinez-Ballesta et al. 2018). The herbicides are effectively penetrated the tissues and cuticles of the plant, allowing the slow and consistent release of the compound. The nanocapsules are synthesized by coacervation or pregelation (Kumar et al. 2015). In this process cross-linking of polyelectrolytes in the presence of counter ion will take place to form nanocapsules. The nanocapsules are also produced by the polymerization of monomers. The optimized process for the preparation of nanocapsules gives higher performance results (Deng et al. 2020). The polymer materials used for the preparation of nanocapsules are chitosan, zein, casein, alginate, and sodium tripolyphosphate (Grillo et al. 2014). Using these nanocapsules, the plant protection products are delivered into the parts of a plant. The micronutrient fertilizers are delivered into the plant to enhance the plant growth and crop yield. The plant protection products are delivered into the plant in order to protect from plant associated diseases (Predoi et al. 2020). The study by Oliveira et al. (2015a, b) used poly (epsilon–caprolactone) (PCL) nanocapsules to deliver the atrazine at a concentration of 7.5×10^{12} particles/mL into the mustard plant *Brassica Juncea*. The polymeric nanoparticles, that is, poly (epsilon–caprolactone) have good physicochemical properties, enhanced bioavailability and biocompatibility. The nanocapsules release the herbicide slowly in a controlled manner and reduce the impact on the environment (Bombo et al. 2019). In another study by Petosa et al. (2017) demonstrated the delivery of pesticides into the root zone of a plant using nanocapsules. This increased the crop yield by protecting the plants from pests. They found that the nanocapsule consists of pyrethroid bifenthrin could be a promising candidate for the delivery of pesticides for plant protection.

3.5 Nanoclays

The nanoclays are natural materials consisting of mineral particles. The clay particles consist of silicates present in the form of layers. The nanoclays are composed of elements such as silicon, oxygen, and other elements (Awasthi et al. 2019). The nanoclays are formed as multilayers with corner linked silicate SiO_4 tetrahedron (Guo et al. 2018). The layers absorb or dissipate water due to a lack of bond between the layers, which causes swelling or shrinkage of the clay materials. Examples of nanoclays are talc, mica, kaolin seprhite, mount morillonite, and serpentine. The nanoclays have water holding capacity and slow release of nutrients (Cecilia et al. 2018). In drought conditions, these nanoclays can be applied to convert the desert sand into fertile soil. The natural bentonite clays are used for water retention and swelling capacity that plays a role in agriculture (Jacinto et al. 2016). The natural nanoclay materials are used for the slow release of fertilizers such as N, P, and K into the plants compared with conventional fertilizers (Guo et al. 2018). The natural clay polymer materials are used for sequestration of metals like Cu, Zn, Pb, U, and Cd from contaminated environments. The nanoclays remove metals and ions from the environment and also enrich the ecological health of the environment (Sen et al. 2015).

3.6 Nanocomposites

Nanocomposites are the materials consist of nanosized particles into a matrix of solid material. The nanocomposites are polymers with biocompatible and biodegradable features that make an ideal system for the delivery of micronutrients for crop protection (Guha et al. 2020). Nanocomposites are classified into different types. They are:

(a) Polymer matrix nanocomposites: The polymer matrix nanocomposites are polymer/carbon nanotube, polyester/TiO_2, and thermoplastic/thermosetting (Bhattacharya 2016).
(b) Ceramic matrix nanocomposites: The ceramic matrix nanocomposites are Al_2O_3/TiO_2 , SiO_2/Ni, Al_2O_3/CNT, and Al_2O_3/SiO_2
(c) Metal matrix nanocomposites: The metal matrix nanocomposites are Ni/Al_2O_3, Fe/MgO, Al/CNT, Co/Cr, Fe-Cr/Al_2O_3, and Mg/CNT (Malaki et al. 2019).

The nanocomposites have antibacterial effects such as disruption of the bacterial cell membrane, penetrate the cell, and interact with DNA/proteins (Wang et al. 2017). The nanocomposites have potential applications in agriculture which include plant growth, antibacterial effect, pest management, and alters the soil microbial community (Usman et al. 2020). The polymeric nanocomposites enhance the utility of genetic engineering tools in the plant system (Ashfaq et al. 2019).

3.7 Nanofibers

Nanofibers are fiber materials made up of polymers both inorganic and organic. The nanofibers are nanometre range in diameter with unique properties such as high mass transport, high surface area, and high nanoporosity (Lim 2017). For the preparation of nanofibers, electrospinning is the technique used to make them suitable to be used in various fields. The electrospun nanofibers usage in agriculture is at an infancy stage and it is novel compared to the conventional methods (Noruzi 2016). The nanofibers are used in agriculture for the protection of the plants and also improve the crop yield. The nanofibers are made from acrylic, fluoropolymers, nylon, polycarbonate, and polysulfones. The biological polymers are chitosan, polylactic acid, and glycolic acid (Xue et al. 2019).

The carbon nanofibers can penetrate the seed coat and also have translocation ability. The carbon nanofibers translocate from root to shoot to leaves within the plant system. The carbon nanofibers slowly release metal nanoparticles into the plant and act as carrier systems for the delivery of micronutrients (Ashfaq et al. 2017). They increase the germination rate, water retention capacity, and growth stimulants in plants. The carbon nanofibers are the new generation fertilizers that increase nutrient uptake and acts as defense regulators. They protect the plants from pests, insects, and disease-causing microorganisms (Mohamed et al. 2018). In the case of plant protection, pheromone-based nanofibers are used for the protection of plants. The sex pheromones are loaded into the nanofibers and these nanofibers are widely used to control the plant pathogens (Oliveira et al. 2015a, b). *Trichoderma* is used as a biocontrol agent. The *Trichoderma* is mixed with an electrospinning solution and made into nanofibers. These encapsulated nanofibers showed antifungal activity against *Alternaria* and *Fusarium* species (Stojanov and Berlec 2020). The encapsulated nanofibers also deliver the pesticide molecules in a predetermined manner. The plant growth promoting bacteria are encapsulated in the nanofibers and are applied to the plant for enhancement of plant growth (De Gregorio et al. 2017).

4 Applications of Nanotechnology in Agriculture

Nanotechnology has more impact in various fields particularly in agriculture and its allied fields. In agriculture, the nanomaterials are used for crop protection, disease identification, pest control, water management in the field, nanofertilizer release, and plant protection (Prasad et al. 2017a; Abd-Elsalam et al. 2019) (Fig. 3.2). Various applications of nanotechnology are represented in Table 3.5.

4.1 Precision Agriculture

Precision agriculture is also called as precision farming. Precision farming utilizes information technology to get maximum output such as crop yield and reducing inputs (fertilizers, herbicides, insecticides, fungicides, and pesticides) (Shang et al. 2019). In precision agriculture, the environment variables are monitored and the nutrients are released in a controlled manner. The environmental parameters are monitored using a geosynchronous positioning system (GPS), remote sensing (RS), and geographical information system (GIS) (Finger et al. 2019). Using information technology, the soil and crops receive nutrients and chemicals exactly what they need for optimum health, yield, and ecological balance (Saiz-Rubio and Rovira-Más 2020). The remote sensing technology collects the correct data and analyzes it effectively for precision agriculture (Shafi et al. 2019). The remote sensing technology divides the agriculture farm into different management zones. The requirements for each zone vary and the needs are satisfied using GPS and GIS technology

(Georgi et al. 2018). The zones are divided based on the soil type, pest infestation, soil pH, nutrient availability, moisture content, weather predictions, fertility requirements, hybrid responses, and crop characteristics (Vallentin et al. 2019). The land information can be accessed using land records. The land records provide the data related to characteristics of crops, cropping practices of the regions, soil survey maps, field boundaries, irrigation system, and nearby roads (Georgi et al. 2018). The GIS and GPS together provide real-time data that farmers can use devices to increase the resources as well as its efficiency (Oshunsanya and Aliku 2016). Precision farming utilizes exact resources in required quantities to the soil as well as the plant (Andreo 2013). Precision farming reduces contaminants, pollutants, and agricultural waste in the environment. Thus, this technology is an environmentally friendly and sustainable practice (Shafi et al. 2019).

4.2 Smart Farming

The nanomaterials particularly nanosensors play a role in real-time monitoring of crop yield and plant growth. The application of nanosensors in the agriculture field converts conventional methods into a smart farming system which encompasses

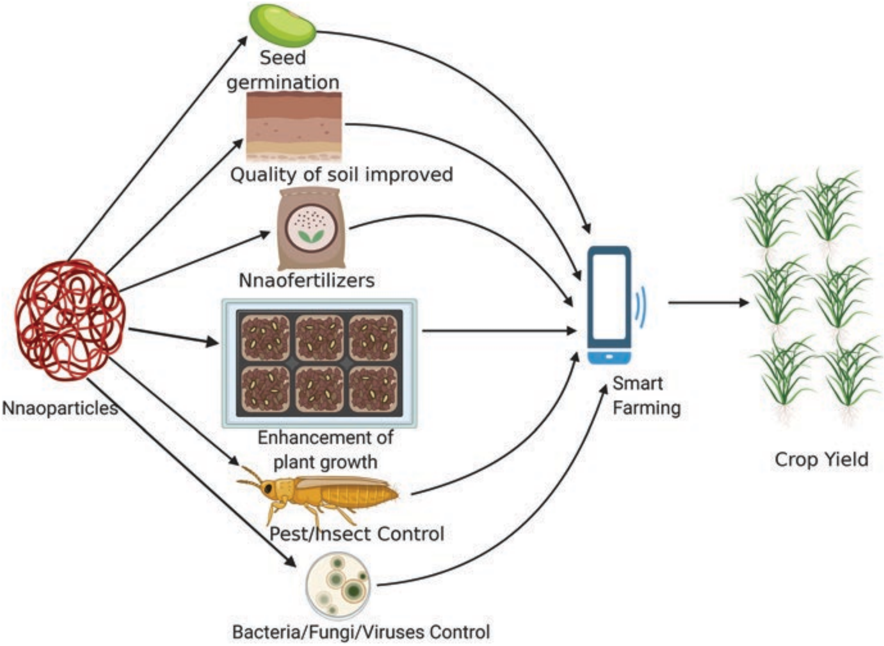

Fig. 3.2 Effect of nanoparticles on plant growth and crop yield. (The figure was drawn using Biorender.com)

Table 3.5 Various applications of nanotechnology in agriculture

S. No	Agriculture applications	References
1	Micronutrient supply	Predoi et al. (2020)
2	Water management	Dasgupta et al. (2017)
3	Improve the quality of the soil	Bandala and Berli (2018)
4	Delivery of fertilizers	Solanki et al. (2015)
5	Smart monitoring	Giraldo et al. (2019)
6	Analysis of gene expression and regulation	Chun et al. (2018)
7	Application of plant growth regulators	Fincheira et al. (2020)
8	Plant disease detection	Younas et al. (2020)
9	Application of fungicides/herbicides/insecticides	Mehrazar et al. (2015)
10	Pest/insect management	Sabry and Ragaei (2018)
11	Precision farming	Anjum and Pradhan (2018)
12	Stimulates seed germination, root and shoot length	Mahakham et al. (2017)
13	Stimulates plant growth	Sanzari et al. (2019)
14	Enhancement of nutrients and their value	Marzouk et al. (2019)
15	Development of stress-resistant plants	Zhao et al. (2020), Saxena et al. (2016), Das and Das (2019)
16	Increase plant productivity/crop yield	Vuong (2019), Shang et al. (2019)
16	Fortification of plant nutrients	Elemike et al. (2019)
17	Post-harvest technology	Sandeep et al. (2016), Ruffo Roberto et al. (2019)

environment friendly approaches and energy efficient practices for sustainable agriculture (Pramanik et al. 2020). In smart farming the practices involved are:

(a) Nanosensors are used to detect soil pH, humidity, nutrients requirement, pests identification, and pesticide residues. The nanosensors detect the chemicals in very low concentrations and high sensitivity making them more useful for smart farming (Shang et al. 2019).
(b) Nanoclay hybrid is used as a smart delivery system to deliver the fertilizers like nitrogen (N), phosphorus (P), and potassium (K). The nanoclay systems slowly release the fertilizers compared to conventional fertilizers (Duhan et al. 2017).
(c) Nanocomposites have emerged as promising tools for the delivery of fertilizers and agrochemicals into the plants that facilitate the slow and controlled release of nutrients into the plant system (Guha et al. 2020).

Thus, the smart sensors linked with precision farming provide correct and accurate information to the farmers to make a better decision for farming that will enhance the productivity in the agriculture produce (Saiz-Rubio and Rovira-Más 2020).

4.3 Delivery of Chemicals, Pesticides, Herbicides, Fertilizers, and Plant Growth Regulators Using Nanotechnology

Nanoformulations such as nanocarriers, nanocapsules, nanofibers, nanocomposites, nanogels, and nanoemulsions are used for the delivery of various compounds into the various parts of the plant system (Martinez-Ballesta et al. 2018). The nanomaterials have unique properties like specific nanoscale size, surface to volume ratio, biocompatibility, and biodegradability that makes the materials to store and deliver the compounds in a controlled manner in order to increase the plant growth, crop yield, plant protection, and minimizing the environmental contaminants (Iavicoli et al. 2017). The nanoscale delivery vehicles used in nanoformulations have improved stability, biocompatibility, and biodegradability nature that make them environmentally friendly technology (Patra et al. 2018; Prasad et al. 2019).

4.4 Crop Condition and Environmental Stress can be Monitored Using Field Sensing System

The nanotechnology uses real-time monitoring of plant growth and yield using nanosensors and filed sensing mechanism. The sensors monitor the real-time monitoring of in situ parameters which includes, soil pH, moisture level, soil humidity, soil fertility, plant growth, nutrients availability, insects, pests, weeds, disease causing microbes, and environment temperature (Saiz-Rubio and Rovira-Más 2020). The wireless nanosensors located across the field provides the real-time data to minimize the usage of pesticides, herbicides, insecticides and maximizes the crop yield. The required quantities are released in a controlled manner based on signals linked with information technology (Shang et al. 2019).

4.5 Detection of Plant Pathogens and Control Mechanisms

The nanomaterials coated with biological recognition elements (DNA/antibody/proteins/enzymes) are used for the detection of plant pathogens. The nanosensors play an important role in the detection of disease-causing microorganisms from plant and soil ecosystem (Kumar and Arora 2020). The nanomaterials made up of metals are used for controlling plant pathogens, pests, and insects (Abd-Elsalam and Prasad 2018, 2019). The silver and copper nanoparticles showed antimicrobial activity against plant pathogens (Ramezani et al. 2019).

4.6 Environmental Stress Resistant and Disease Resistant Traits can be Improved by Nanotechnology

Currently, the research is focused on the development of disease resistant and environmental stress resistant varieties using recombinant DNA technology (Parmar et al. 2017). The nanodelivery vehicles such as carbon nanotubes, nanocarriers, nanofiber materials deliver genes into various parts of the plant in order to develop new traits that can tolerate the disease and stress imposed by the environment (Jeevanandam et al. 2018).

5 Future Prospects of Nanotechnology in Agriculture

The nanomaterials with unique properties are developed as vehicles such as nanocarriers, nanocomposites, nanotubes, nanofibers, and nanoclays for the delivery of fertilizers and biochemical compounds into the plant system (Kalia et al. 2020). The process will be monitored using nanosensor based real-time monitoring and wireless sensing system that makes them an ideal system for precision farming (Shafi et al. 2019). Apart from the delivery of chemicals, detection system, nanotechnology has solutions for degrading the persistent chemicals into the environment as useful chemicals. Thus, nanotechnology has potential scope in near future to increase crop yield and sustainable nature of the environment (Shang et al. 2019).

6 Conclusions

The modern nanotechnology applications in the areas such as precision agriculture, nanosensor detection, and smart farming can reform the agriculture arena using smart gadgets. The broad range of applications of nanotechnology in the agriculture field are fertilizer delivery, pesticide reduction, herbicides reduction, delivery of the compounds using carriers, plant pathogen detection, and pathogen control. In precision agriculture, the nutrients are delivered in a controlled manner using nanosensor based mechanisms. The nanosensors detect the plant pathogens in the field itself and release the nanomaterials to control the pathogens in in situ mode. The smart farming system provides the data related to the requirements of the agriculture field according to the crop needs and in turn, the nanosensors release the chemicals to the plant system. Thus, nanotechnology would play a vital role in the near future in precision agriculture and smart farming to enhance plant growth, biomass, and crop yield.

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Chapter 4
Magnetic Nanoparticles from Bacteria

Anoop R. Markande, Kruti Mistry, Shraddha Undaviya, and Anamika Jha

Contents

1 Introduction

In the environment, there exist certain organisms that demonstrate geomagnetism-assisted navigation—which helps them to locate a specific area utilizing the magnetic field. In the animal kingdom, many birds, insects, reptiles, fishes, and mammals use this unique technique for recognizing the migratory route previously visited. The highly studied magnetotactic bacteria (MTB) show magnetoreception using magnetic minerals as internal magnets (magnetite, Fe_3O_4, or greigite Fe_3S_4). The MTB was isolated, characterized, and first reported from various water samples in 1963 (Jacob and Suthindhiran 2016).

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2 Magnetotactic Bacteria (MTB)

Magnetotactic bacteria are a unique ecophysiological group that differs in morphology, physiology, and phylogeny but is characterized by the geomagnetism based movement called magnetotaxis. MTB has been consistently reported from aquatic habitats (marine, estuarine and freshwater) especially sediments but rarely from topsoil that exhibits a vertical gradient of chemical concentration. This is due to their preferential habitation in oxic–anoxic interface (OAI) in the natural environment, which is seldom seen in the uppermost strata of environmental sediments (Jacob and Suthindhiran 2016; Monteil et al. 2020; Qin et al. 2020).

The diversity of MTB includes vibrio, rods, spirilla, ovoid, coccoid, as well as large and multicellular organisms. Most of the reported MTB belong to phylum proteobacteria (α, γ, and δ) and in particular Nitrospirae group, candidatus division OP3 as a part of subphylum Planctomycetes, Verrucomicrobia, and Chlamydia. All the members are characterized by dark intracellular inclusions with different types of magnetosome crystals (Fig. 4.1) (Faivre and Schüler 2008; Lower and Bazylinski 2013; Alphandéry 2020).

They move downward toward accumulated sulfur and move upward to oxidize stored sulfur in the presence of oxygen. Magnetotactic bacteria showing polar magneto-aerotaxis falls into two different internal redox states: in the oxic zones, cells can uptake a large amount of stored sulfur as an electron donor and oxidized. In this state, cells swim toward the deeper region by utilizing the locomotion apparatus (flagella) and stored the electron donor in the form of sulfide, where they finally enter into a reduced state (due to accumulated sulfide) and start migrating to find oxygen as electron acceptor (Lower and Bazylinski 2013; Wang et al. 2020).

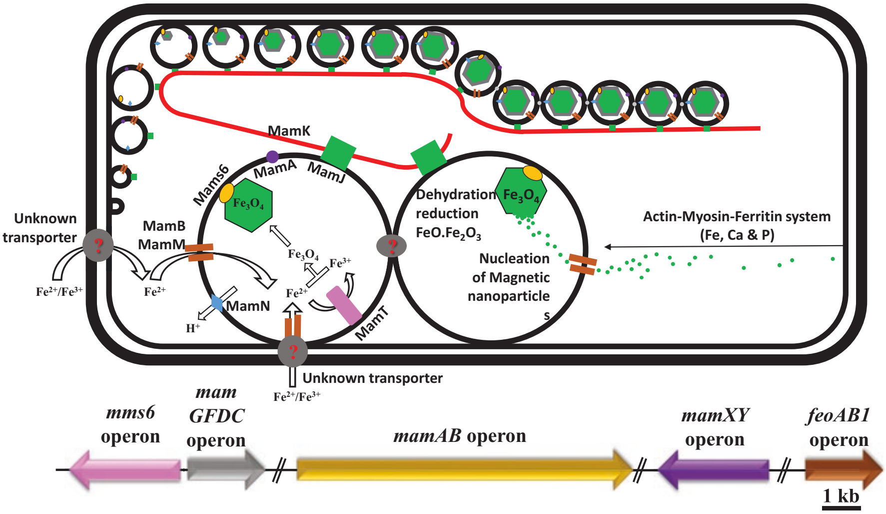

Fig. 4.1 Microbial magnetotactic machinery. Reported in (**a**) eukaryotes and (**b–l**) prokaryotes

Rediscovering the magnetotactic bacteria in nature, Blakemore (1975), studied a group of north-migrating bacteria that exhibited intracellular chains of elongated magnetite (Fe_3O_4) or greigite (Fe_3S_4) crystals termed magnetosomes by the process of biomineralization. The magnetites, thus, formed intracellularly were found to be surrounded by a rudimentary bilayer called magnetosome membrane (MM) in a controlled manner by invagination of the inner cell membrane (Blakemore 1975; Monteil et al. 2020).

The microbial diversity and their magnetotactic assemblies are given in Fig. 4.1. Many eukaryotes have been reported with the machinery while bacterial machinery is seen in (Fig. 4.1b) spirilla, (Fig. 4.1c) vibrio, (Fig. 4.1d) coccoids, and even in (Fig. 4.1e–l) rods (Alphandéry 2020). The arrangement of magnetosomes differs among the rods and vibrio as seen in Fig. 4.1. The magnetotaxis affects the microbial magnetosome arrangements (Fig. 4.1e–g and Fig. 4.1h–l). Thus, the magnetotactic ability can be considered as an ecophysiological trait with potential biotechnological applications (Wang et al. 2020). The bacterial diversity encompasses the different types of proteobacteria as shown in Table 4.1 covering the last 5 year reports of magnetotactic bacteria isolation from different habitats throughout the world.

3 Biomineralization

Processes of biomineralization by which organisms form minerals can be classified into biologically induced (biologically induced mineralization or BIM) and biologically controlled (biologically controlled mineralization or BCM) (Bazylinski et al. 2002).

The extracellular iron sequestration involves the siderophore production and supply of Fe^{3+} and Fe^{2+} and their internalization through the cellular boundary (cell membrane and cell wall (Das et al. 2007)). Here, predominantly Fe^{3+} is reduced to Fe^{2+} before internalization and transported to rudimentary magnetosome in the form of ferric hydroxides (Bazylinski et al. 2002; McCausland and Komeili 2020).

BIM makes the extracellular mineral nucleation due to metabolic activity and its byproducts of organisms. Organisms release extracellular metabolic byproducts reacting with environmental compounds or ions resulting in a mineral deposition. Thus BIM is usually an unintended and uncontrolled result of microbial activities. Hence, this lack of control results in impurity in the lattice, and poor minerals formed here are characterized by broad particle size distribution and improper crystallinity and their morphologies (Monteil et al. 2020). The bacterial surfaces including cell walls, polymeric substances (exopolymeric substance (EPS), slimes, sheaths, and biofilms), and dormant spores having high-surface-to-volume ratio act as important sites for ion adsorption, nucleation of minerals, and growth. The negative charges on bacterial surface and EPS can result in nonspecific electrostatic interactions binding cations leading to local mineral supersaturation and crystal nucleation. The BIM-based processes can be active or passive. Passive mineralization involves nonspecific binding of cations in anionic solutions resulting in

Table 4.1 Major reported Magnetotactic bacterial isolation in the last 5 years

Phylum	Organism	Isolation site	Reference
α-proteobacteria	*Chromatiales*, *Magnetospira* sp., ca. Da. *Magnetomortis & Magnetovibrio blakemorei*	Itaipu lagoon in Rio de Janeiro, Brazil	Araujo et al. (2015)
	Alphaproteobacterium MTB-KTN90	Anzali lagoon, Iran	Tajer-Mohammad-Ghazvini et al. (2016)
	Magnetospirillum caucaseum sp. *Magnetospirillum marisnigri* sp. and *Magnetospirillum moscoviense* sp.	Freshwater sediments from three distinct locations in European Russia	Dziuba et al. (2016)
	Magnetospirillum species; orders of *Magnetococcales* and *Rhodospirillales*	Strogino area, Moskva River	Kozyaeva et al. (2017)
	Magnetospirillum sp. ME-1,	East Lake, Wuhan, China	Du et al. (2017)
	Magnetospirillum species and *Magnetovibrio blakemorei* strain MV-1	Seamount of the Mariana volcanic arc near the challenger deep in the tropical western Pacific Ocean	Liu et al. (2017)
	Magnetococcus marinus MC-1	Marine sediments	Ji et al. (2017)
	Magnetospirillium gryphiswaldense MSR-1	Various aquatic habitats in Uttar Pradesh, India	Singh et al. (2018)
β-Proteobacteria	*Herbaspirillum* sp.	Sediments of the acidic freshwater tropical coastal lagoon of Comprida lagoon south hemisphere	Abreu et al. (2018)
	Herbaspirillum sp. TK-2	Sediment in Wudalianchi volcanic barrier lakes, NE China	Xing et al. (2020)
	Burkholderia caryophylli	Water sample	Khalil and Misra (2017)
	Nitrosomonas sp.	Soil nitrifier	Shweta et al. (2018)

(continued)

Table 4.1 (continued)

Phylum	Organism	Isolation site	Reference
γ-Proteobacteria	*Vibrio*	Brackish lagoon in Brazil	Leão et al. (2016)
	Pseudomonas aeruginosa Kb1	Sewage samples	Kabary et al. (2016)
	Thiomargarita and *Beggiatoa*	Ferruginous oxic–anoxic transition zone of Lake Pavin	Rivas-Lamelo et al. (2017)
	Order *Thiotrichales* in the family *Ectothiorhodospiraceae* strain BW-2	Brackish spring in Death Valley, California	Geurink et al. (2020)
δ-Proteobacteria	*Desulfovibrio magneticus* sp. strain RS-1	Aquatic sediment	Chariaou et al. (2015)
	Candidatus Magnetobacterium of Proteobacteria, Candidatus *Magnetobacterium bavaricum* and Candidatus *Magnetoovum chiemensis* CS-04 of the *Nitrospirae* phylum and Candidatus *Omnitrophus magneticus* SKK-01	Surface sediment from Lake Chiemsee, southern Germany	Kolinko et al. (2016)
	Candidatus *Magnetomorum rongchengroseum*	Sediments of Yuehu Lake, China	Du et al. (2017)
	Desulfamplus magnetovallimortis	Brackish desert spring	Descamps et al. (2017)
ε-Proteobacteria	Magnetotactic bacteria	Sediments of the acidic freshwater tropical coastal lagoon of Comprida lagoon south hemisphere	Abreu et al. (2018)
Algae	*Chlamydomonas reinhardtii*	Lake	Santomauro et al. (2018)
Consortium	*Magnetotactic bacteria*	Lonar lake	Waghmare et al. (2018)

nucleation and growth of mineral crystals (Qin et al. 2020). While active mineralization is due to the metabolite mediated guidance of the surface crystallization of minerals due to the redox transformations of cationic or anionic minerals on bacteria. This is augmented by anaerobic habitats of aquatic substratum where the presence of air is limited for redox conditions and can thus involve sulfur along with iron for magnetosomes (Frankel 2005; Wang et al. 2020).

In BIM, this process is enhanced due to the tighter control of the nucleation and growth stages of minerals by an organism. Thus the mineral nucleation is controlled by organisms by organizing the space availability for mineral deposition. The organic matrix formed increases the compartmentalization and further supersaturation of mineral deposition leading to further growth in crystals in an ordered manner. The complete process and mechanism are not yet fully understood (Bazylinski et al. 2002).

4 Biomagnetism

Magnetism by elements is due to the presence of unpaired electrons exhibited in three broad categories of magnetism (Dia-, Para- and Ferro/Ferri-magnetism). When magnetic moments of all the elements in the metal are oriented to cancel one another nullifying the net magnetic moment is negative or diamagnetism. When the atoms of the molecule show the same magnetic moment where the spin and orbital moments of electrons do not cancel out but produce paramagnetism. In the absence of an applied magnetic field, paramagnetic elements cancel each other and their atomic moments point at random (McCausland and Komeili 2020). In the presence of an applied field, the atomic moments turn toward the direction of the field and in absence of opposing forces, all the atoms and thus the whole specimen would align toward the direction of the magnetic field. Ferro- or ferri-magnetism is seen when the metal specimen retains the magnetism permanently even after the removal of magnetic field application (Cullity and Graham 2009; Wang et al. 2020).

5 Physiology of Magnetosome and Magnetic Nanoparticle Biosynthesis

5.1 *The Magnetic Nanoparticles*

The magnetism of biomineralized magnetite nanocrystals is largely controlled by their domain states—superparamagnetic (SP), single domain (SD), and multidomain (MD) state. Usually the size of SD magnetite crystals of dimensions < 100 nm has maximal magnetization and permanent magnetic dipole moments; SP are smaller magnetite particles ($\leq$ 35 nm) without permanent dipole moments while MD has larger particles ($\geq$ 100 nm) with different magnetic orientation and a lower average magnetization. Thus, in a magnetotactic bacterium, the flagella and magnetosomes are arranged in the bacterial ultrastructure to help it in magnetically oriented taxis (Klumpp and Faivre 2016).

5.2 Magnetosome Biosynthesis

BIM is extremely important for anaerobic environments as they can use these redox metals for electron transport and sequestration. Within the bacterial cell, vesicular deposition of metallic minerals occurs where control capabilities exist for nucleation of metallic minerals of Fe and Mn (Bazylinski and Frankel 2004; Qin et al. 2020).

The magnetosome biosynthesis (Arakaki et al. 2018; Qin et al. 2020) involves,

- *Vesicle formation:* Mms16, MpsA, MamA, MamI, MamL, MamQ, and MamY.
- *Chain formation:* MamJ and MamK.
- *Ion transport:* MagA, MamB, MamH, MamM, and MamZ.
- *Redox control:* AOR, MamE, MamP, MamT, and MamX.
- *Crystal formation:* Mms5, Mms6, Mms7, Mms13, MamF, MamG, MamO, FtsZm, and MmsF.

The magnetosome membrane is formed due to the inner membrane invagination concurring with the onset of mineralization guided by magnetosome-associated protein MamA (Richter et al. 2007; McCausland and Komeili 2020). Among the two major iron transporter genes—*mamM* and *mamB*, the stability of MamB protein depends on the presence of MamM by heterodimer complex formation. The genes namely—*mamC*, *mamD, mamG,* and *mms6* are often seen as coherent clusters in all MTB encoding the magnetic particle membrane specific protein (Mms) (Alphandéry 2020). Here, mamC and *mms6* code for membrane anchor proteins, and it was seen that the mamGFDC cluster directly affects the biomineralization process within the magnetosome. Mms6 was also reported to control the size and shape of the magnetite nanoparticle crystals within the magnetosome. *mamI*, *mamQ,* and *mamL* are the transmembrane segment genes and mamXY gene cluster encoded MamY protein while *mamE*, *mamO*, *mamM,* and *mamN* were transport genes controlling the proteins of magnetosome membrane (Fig. 4.2). The intracellular acidic protein encoded by *mamK* helps to arrange the magnetosomes within the cell in conjunction with the interaction with magnetosome surface protein encoded by *mamJ* gene. The proteins encoded by *mamN* and *mamT* are known for the transport of H^+ ions out of magnetosome and antramagnetosome conversion of Fe^{2+} to Fe^{3+} which further dehydrates to $FeO.Fe_2O_3$ to magnetite crystals (Fe_3O_4) (Yan et al. 2012; Qin et al. 2020; Wang et al. 2020).

5.3 Magnetite Symmetry in Magnetosomes

Devouard et al. (1998) first reported the different combinations of compatible magnetite (described under *Fd3m* space group) microscopic (transmission electron microscopy) symmetry making up the magnetite crystals in magnetosomes. The distortions and elongations of the crystals occur due to the anisotropy in the growth

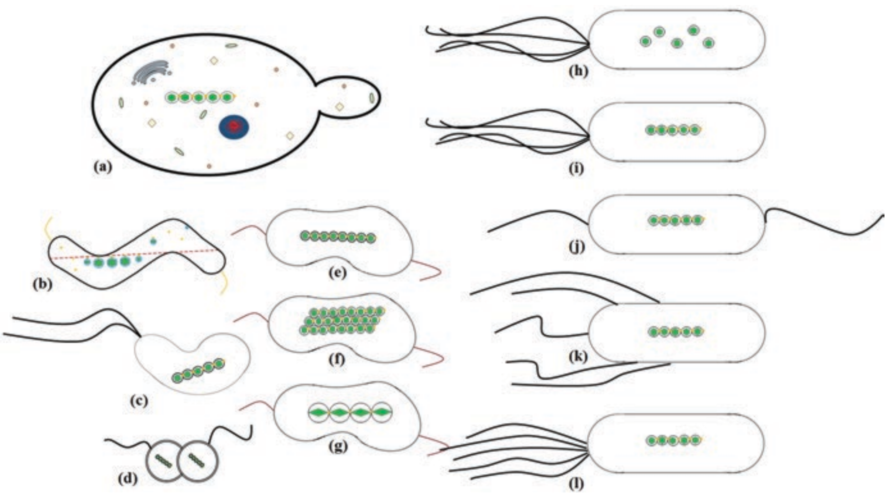

Fig. 4.2 *The biosynthesis of magnetosomes.* The gene cassettes of magnetosome biosynthesis are given at the outset while their protein products and functions are given in the bacterial cell

environment (like the flow of preferential diffusion along certain directions; in magnetosomes flux of ions through the membranes of the vesicle surrounding the crystal) or anisotropy in sites of growth (usually seen due to the presence of screw dislocations) (Alphandéry 2020). Hence the consistent distortions seen in magnetosome symmetry in bacteria are species specific. These crystals of magnetite with elongated habits are usually seen with combinations of—cube, octahedron, and dodecahedron with distortions making up a wide range of shapes (Fig. 4.3) (Devouard et al. 1998; Jacob and Suthindhiran 2016).

The magnetosomes have various advantages over synthetic magnetic nanoparticles (chemically synthesized). The magnetite domain structure among the bacteria ranges between 10 and 120 nm as a single magnetic domain (SD) and shows broad size distribution. While the synthetic magnetic nanoparticles can be synthesized by single or multidomain and super magnetic segments using thermal decomposition, oxidative precipitation, sol-gel method, microemulsion, and solvo-thermal method exhibiting high dispersion and narrow size distribution. Nevertheless, in both the methods, the quantity of dissolved residual oxygen decides the nanoparticle crystal morphologies. This drawback is overcome in biological nanoparticle synthesis by controlled magnetite accumulation in the magnetosomes. Here the compartmentalization of nanoparticle synthesis ensures the controlled mineral growth in optimum metals (Fe), redox conditions, and pH environment. The SD magnetic nanoparticles align parallelly at room temperature and form uniform magnetism, while synthetic magnetic nanoparticles synthesized by chemical precipitation are usually superparamagnetic in nature due to their irregular size and shape (thus holding nonuniform magnetization). Thus, biomagnetism is ferromagnetic and synthetic magnetism

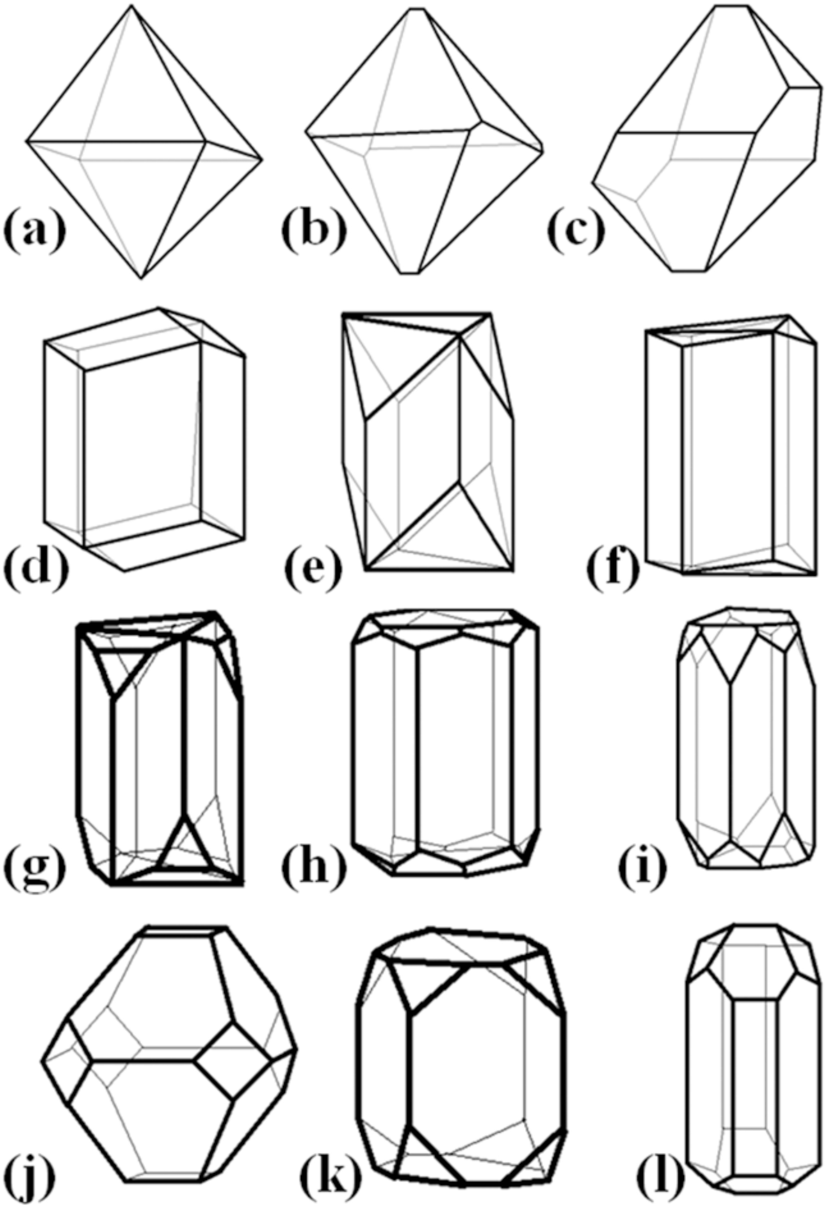

Fig. 4.3 The magnetite crystal symmetries. The *Fd3m* symmetry of magnetite crystal combinations—(**a**) Octahedron, its distorted structure (**b**) and elongated structure (**c**); (**d**) Dodecahedron, its mixtures with octahedron structure as (**e**) distorted and (**f** and **g**) elongated structures; (**h**) mixtures of distorted cube + octahedron + dodecahedron and (**i**) elongated symmetry of **h**. While the magnetite crystal symmetry of cuboctahedron (**j**) and its different elongated structures (**k** and **l**) are also given (Devouard et al. 1998) (produced with permission from Mineralogical Society of America)

is super-paramagnetic without the remnants and coercion (Jacob and Suthindhiran 2016; Alphandéry 2020).

6 Biotechnological Applications Based on MTB and Magnetosomes

The MTB based biogenic magnetite biosynthesis results in characteristics like narrow size distribution, stable and standard shape, high levels of purity and higher crystallinity, good dispersivity, high biocompatibility (nontoxic), better T_2 reducing effect are unique and superior to synthetic nanoparticles. Thus, the MTB application falls into two major categories—as living bacterial cell and as extracted magnetosomes.

6.1 Applications Using Magnetotactic Bacteria

The motile MTB has applications in cell separation, bioremediation, as a specific molecule carrier, and for identifying magnetic domains of hard materials (Fig. 4.4 and Table 4.2).

6.1.1 Bioremediation

MTB belonging to alpha-proteobacteria show diversity in respiratory capacities including and reduction abilities of metals like—Fe(III), Zn, Ni, Cu, and Pb and have been reported for the ability of metal ion mineralization when exposed to metals other than Fe. *Magnetospirillum magneticum* AMB-1 has been reported to be able to uptake and mineralize Tellurium—an alloy component toxic metal and crystallize both magnetite and Te as separate inclusions within the cell (Jacob and Suthindhiran 2016). *Desulfovibrio magneticus* was used to recover Cadmium present in the growth medium and *Magnetospirillum gryphiswaldense* was able to reduce gold nanoparticles on the bacterial cell surface (Araujo et al. 2015).

6.1.2 Cell Separations

Blood cell sorting can be carried out through the separation of monocytes and granulocytes after phagocytosis of MTB—magnetic purification from blood (Araujo et al. 2015; McCausland and Komeili 2020).

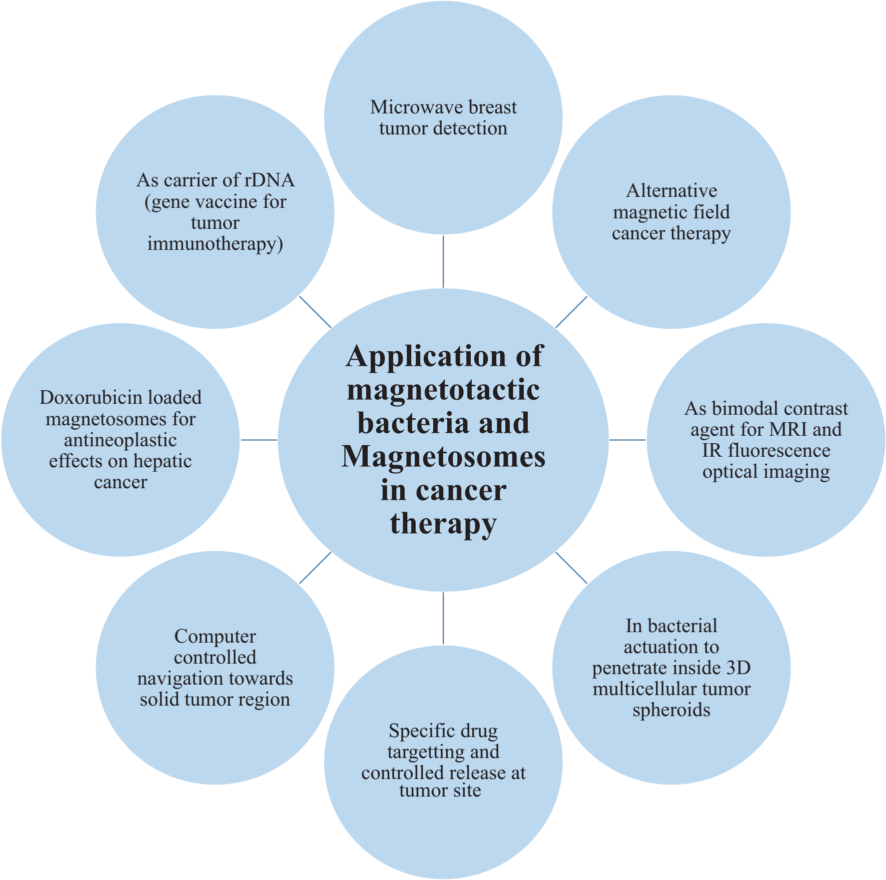

Fig. 4.4 Applications of magnetic nanoparticles

6.2 Applications Using Magnetosomes

6.2.1 Drug Delivery

The core issue in designing and developing a novel drug delivery system involves precise, time-bound, and careful drug delivery at a target site with a sustained release for maximum therapeutic effects (Prasad et al. 2017). Magnetosomes that are used as nanocarriers traversed through the blood–tissue barrier to reach the target cells. To contact cytoplasmic targets, nanocarriers use specific endocytosis and transcytosis transport mechanisms across the cellular barriers. The nanocarriers, due to their narrow size distribution can cross the blood–brain barrier and through the skin epithelial cells, which normally hamper the delivery of drugs at target sites. Nanocarriers show better biodistribution of therapeutic agents and pharmacokinetics because of their high surface to volume ratio and minimizing the toxicity by

Table 4.2 Application of MTB and magnetosomes

No.	MTB and magnetosomes	Application	References
1.	*Magnetospirillum magneticum* AMB-1	Fluorescent nanoprobes	Alphandéry et al. (2017)
2.	*Magnetospirillum gryphiswaldense*	Tumor therapy	Sun et al. (2008)
3.	*M. gryphiswaldense* MSR-1	Isolation and purification of DNA or RNA	Liu et al. (2010)
4.	*Magnetospirillum gryphiswaldense* MSR-1	Cancer diagnosis and targeted therapy in experimental animals.	Dasdag (2014)
5.	*Magnetospirillum magneticum* AMB-1	Recovery and bioaccumulation of selenium granules	Tanaka et al. (2016)
6.	*Alphaproteobacterium* MTB-KTN90	Cobalt separation	Tajer-Mohammad-Ghazvini et al. (2016)
7.	*Desulfovibrio magneticus*	Recovery of cadmium present in the growth medium	Arakaki et al. (2002)
8.	*Magnetospirillum gryphiswaldense*	Reduced gold ions to gold nanoparticles	Cai et al. (2011)
9.	*Magnetospirillum magneticum* AMB-1	To degrade certain pesticides	Ginet et al. (2011)
10.	*Magnetospirillum gryphiswaldense* MSR-1	Carrier of recombinants to produce a genetic vaccine	Tang et al. (2012)
11.	*Magnetospirillum magneticum*	Magnetic resonance imaging (MRI)	Islam et al. (2018)
12.	*Magnetococcus marinus* MC-1	Robotic agents to enhance displacement control and swarm formation for drug delivery platforms	Loghin et al. (2017)
13.	*Magnetospirillum gryphiswaldense*	Gene delivery vehicles	Alsaiari et al. (2016)
14.	*Magnetospirillum gryphiswaldense* MSR-1	Self-assemble into a rotary motor	Vincenti et al. (2019)
15.	*Magnetospirillum caucaseum* SO-1	Freshwater ecosystems near Pavia, Italy	Grouzdev et al. (2017)
16.	*Ovoid magnetotactic* MO-1	Magnetic hyperthermia mediated Staphylococcus aureus killing	Chen et al. (2016)
17.	Microbial consortium	Non-Newtonian nanoliquids thin film	Palwasha et al. (2018)
18.	MTB and/or magnetosomes	Cancer therapy	Mathuriya (2015)
19.	MTB	Separate heavy metals and radionuclides	Bahaj et al. (1998)

(continued)

Table 4.2 (continued)

No.	MTB and magnetosomes	Application	References
20.	MTB	Autonomous bacterial microbots Magnetic logic gates	Jacob and Suthindhiran (2016)
21.	Magnetosome	Immunoassays, cell separation, bioremediation gene therapy	Araujo et al. (2015)
22.	Magnetosome	Detection of a magnetic domain in hard material	Schüler and Frankel (1999)
23.	Magnetosome	Fluorescent biological labels, drug and gene delivery, bio detection of pathogens, detection of proteins, probing of DNA structure, tissue engineering, tumor destruction via heating (hyperthermia), separation and purification of biological molecules and cells, MRI contrast enhancement, Phagokinetic studies	Salata (2004)
24.	Magnetosome	Hyperthermia protocols (treatment of cancer by localized heating), drug carriers, and nuclear magnetic resonance	Pankhurst et al. (2003)
25.	Magnetosomes	Microsatellite polymorphisms, tracking of stem cells and dendritic cells	Vargas et al. (2018)
26.	Magnetosomes	As an antibacterial agent, reaction rate enhancement agent, navigational device	Li et al. (2011)

target site accumulation. As they exhibit the characteristics of enhancing the solubilization of hydrophobic compounds, oligonucleotides, and peptides in them, they are suitable for parenteral administration (Qin et al. 2020).

The biocompatible nanoparticles made up of magnetite (Fe_3O_4) and maghemite (Fe_2O_3) have been researched for cancer therapy (using hyperthermia), gene therapy, sorting of stem cells, and also MRI and DNA analysis. Purified magnetosomes from *Magnetospirillum gryphiswaldense* were found to be nontoxic to mouse fibroblast in vitro even after the treatment of sterilized nanoparticles (Xiang et al. 2007) and bacterial magnetosomes (BMs) particles loaded with doxorubicin (DOX) by covalent attachment (Sun et al. 2008) were evaluated for inhibition of tumor growth with lower cardiac toxicity (Li et al. 2011; Qin et al. 2020).

6.2.2 Hyperthermia

Controlled heating of magnetic nanoparticles for targeted cell necrosis is termed as magnetic hyperthermia. This phenomenon is used in cancer treatment by the administration of nanoparticles (even from bacteria) inside the body at the tumor site that deals with intracellular heat stress by applying an external magnetic field. The temperature ranging from 41 to 46°C or up to 50°C to destroy the tumor cells (Jacob and Suthindhiran 2016). Synthetic nanoparticles that are presently used for hyperthermia heat nonselectively damaging the surrounding healthy tissues as compared to magnetosomes (Alphandéry 2020). The magnetosomes, which are arranged in chains, can be easily internalized by the cells and thus facilitate homogenous distribution inside the tumor cells (Araujo et al. 2015). Due to their symmetry as SD, the magnetosomes have an additional characteristic of possessing uniform magnetic moment at any temperature (Jacob and Suthindhiran 2016; Qin et al. 2020). Thus, having lesser side effects than chemotherapy and radiotherapy; tissue specificity with respect to synthetic nanoparticles enabled to be used as a diagnostic tool for biotechnological applications (Usov and Gubanova 2020).

6.2.3 Magnetic Resonance Imaging (MRI)

It is a diagnostic tool used for noninvasive molecular imaging of cells and cellular activities. The cell tracking method of the MRI method involves the chemical coupling of targeting peptide-like super paramagnetic Fe-oxide nanoparticles, which are usually degraded by normal cellular activities such as mitosis. Magnetosomes can be used as positive and negative contrasting agents for differentiating the healthy and pathological tissues. Also, it has a high detection sensitivity compared to synthetic nanoparticles (Hartung et al. 2007; Jacob and Suthindhiran 2016; Qin et al. 2020).

6.2.4 Antibacterial Agent

At present, antibiotic resistance has become more challenging as the microorganisms can withstand the effects of antibiotics in use, and hence, the use of silver in antimicrobial therapy is increasing (Aziz et al. 2016; Koch et al. 2021). Antimicrobial nanoparticles have been engineered by covering the biomagnetic cores with a layer of a silver ring with a ligand gap (Mahmoudi and Serpooshan 2012). The magnetic nanoparticles exhibit marginal antimicrobial activity that can be enhanced by treating it with herbal leaf extracts (Arokiyaraj et al. 2013).

6.2.5 Biosensor

The development of MTB biosensor can be used to detect micron sized biological entities. *Bacillus subtilis* can synthesize selenium (Se) nanoparticles with size ranging from 50 to 400 nm with characteristics such as good adhesive ability, high surface to volume ratio, and good biocompatibility made an enhancing material for building an HRP (Horseradish peroxidase) biosensor. This biosensor has a good electrocatalytic activity for the reduction of H_2O_2. These selenium (Se) nanoparticles have a wide range of applications in the detection of H_2O_2 in pharmaceuticals, food, clinical, and environmental analyses. Au–Ag alloy nanoparticle biosynthesis by yeast cells can be applied to fabricate a sensitive electrochemical vanillin sensor. This sensor has practical application in a vanillin monitoring system and is used for determining vanillin from vanilla bean and vanilla tea. Similarly, biosensors of gold-based nanoparticles with glucose-oxidase (GOx) enhancing the enzyme activity, and thus, can be used for the determination of glucose content in commercial injections (Li et al. 2011).

6.2.6 Functionalized Magnetosomes

Magnetosomes can be functionalized and be carried out by surface modification of cell membranes by two major methods. The first method involves the modification of dispersed magnetosomes chemically while in the second method, the magnetosome surface/membrane (MM) proteins are modified by genetic manipulations. Using these methods, biomolecules like DNA, proteins, peptides, and hormones can be functionalized along with magnetosome surface for their applications (McCausland and Komeili 2020). The presence of MM, thus, increases the biotechnological application potential of the magnetososmes. Here, the biomolecule based charges on the magnetosome surface helps in further modifications with a potential for possibilities of various cross-linkers. While synthetic nanoparticle synthesis involves the coprecipitation technique, the structural defects persist with the need for their stabilization and glutaraldehyde and PEG coating for any applications to manifest. Various methods are used for chemical modifications of magnetosomes such as immobilization of myosin, biotinylation, and conjugation of amine modified oligonucleotides. Aminosilane compounds are also used for surface modification of the magnetosome membrane for DNA extraction (Ginet et al. 2011; Jacob and Suthindhiran 2016; Xiang et al. 2017).

6.2.7 Nucleotide Polymorphism Detection

One of the major biomedical applications of magnetosomes is single nucleotide polymorphism (SNP) for the detection of hypertension, diabetes, cancer, cell sorting, and DNA extraction (Matsunaga et al. 2007; Jacob and Suthindhiran 2016; McCausland and Komeili 2020).

6.2.8 Immunoassays

Magnetosome membrane surface modifications leading are used for immunoassays. To detect small molecules such as toxic detergent, environmental pollutants and hormones can bind to the surface of the magnetosome membrane using a specific antibody (Li et al. 2010; Jacob and Suthindhiran 2016; Qin et al. 2020).

6.2.9 Geology, Paleontology and Astrobiology

It is known that a major part of sedimentary rock magnetite (Fe_3O_4) is magnetic in nature, and thus, may even contain bacterially synthesized biomagnets due to natural magnetization by earth after magnetotactic bacterial death. Magnetosomes and MTB have been reported to be in use by aquatic and aerial organisms as a navigational device for spatial orientation in freshwater and marine habitats by interaction with the earth's magnetic field (Yan et al. 2012; Jacob and Suthindhiran 2016; Qin et al. 2020).

7 Future Perspectives

The rudimentary membranes of vesicles making up the magnetosomes are under study for possible uses in drug delivery systems. The vesicular systems for compartmentalization of metallic minerals inside bacteria can be used for segmented accumulation of bacterial products in vivo. The biomeneralization ability of bacteria can be used for bioaccumulation or bio-mining of metallic minerals.

8 Conclusion

Magnetotactic bacteria produce biomagnetic nanoparticles having immense industrial applications. The present manuscript also enlists the genetic cassettes involved in the magnetosome production and genetic manipulation for magnetic nanoparticle biosynthesis. Thus, the manuscript also discusses the use of biomagnetism in biotechnological, biomedical industries, and also as therapeutic agent application potential. The magnetosome formation and its lipid membrane could also be used for micelle formation and nano-emulsions that can be used for drug delivery. Thus, the present review can help the future work on biomagnetism based on bacterial magnetosomes.

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Chapter 5
Benefits of Chitosan-Based and Cellulose-Based Nanocomposites in Food Protection and Food Packaging

Josef Jampílek and Katarína Kráľová

Contents

1 Introduction

Potential risks represented by nonbiodegradable plastics are one of the serious problems which must be solved in the near future and therefore nowadays interest is growing to consume food products without chemical additives, which requires design of modern technologies to prevent food contamination and to reduce food-borne illnesses (Khan et al. 2016). Din et al. (2020) presented an overview of

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recently engineered biodegradable plastics utilized for packaging applications, use of which can contribute to reduction/elimination of waste accumulation in water reservoirs and utilizing of noxious chemical reagents and can provide cheap and biodegradable materials of natural origin as an alternative to commonly used plastics. Bio-nanocomposites (NCs) consist of two major components, in which biopolymer (continuous phase) is a matrix and the second component is reinforcement agent (dispersed phase) showing nanoscale dimensions (1–100 nm) (Sharma et al. 2020). Bio-NCs that are usually prepared by solution intercalation or melt intercalation from biodegradable resources (e.g., polysaccharides, lipids, proteins, and biodegradable synthetic polymers reinforced with nanofillers) may be utilized also for fabrication of nanofibers in order to enhance stability and improve bioavailability and controlled release of the active ingredient. Moreover, they are suitable to be used as active packaging enabling prolongation of the shelf life of food (Maftoonazad and Ramaswamy 2018; Jampílek and Kráľová 2018a). Different characteristics of biodegradable polymers used in food packaging applications were overviewed by Wroblewska-Krepsztul et al. (2018). However, biopolymers face some constraints, particularly due to their poor mechanical and barrier properties (Souza et al. 2017). For example, biodegradable packaging films and coatings fabricated from polysaccharides (e.g., such as cellulose, starch, chitosan (CS), alginate, pectin) exhibit fine barrier properties against the transport of O_2 and CO_2, while tensile strength (TS) of these films vary from each other and the values of percentage of elongation are far from reaching the values estimated for synthetic polymers (Cazon et al. 2017).

Agricultural crops, fruits, vegetables, and food products require packaging for protection from physical damage, contamination, deterioration, and to ensure increased shelf life and facilitated transport to consumers (Prasad et al. 2014, 2017a, b). Besides suitable physical and mechanical properties, the packaging must ensure that the packed products will not have any foul odor (Samanta et al. 2016; Jampílek and Kráľová 2018a). In order to suppress food deterioration, access to O_2 of food products may be suppressed via removal of O_2 from the packaging headspace and/or by addition of antioxidants to films and coatings resulting in improved antioxidant properties of food surfaces (Sahraee et al. 2019). Recent progress in the use of different edible coatings for shelf-life prolongation of fresh-cut vegetables and fruits was presented by Yousuf et al. (2018).

Traditional food packaging consists of nondegradable plastics, which is rarely recyclable and produces immense waste adversely impacting the environment. Therefore, recently increased attention is focused on the development of biodegradable bio-based materials able to extended shelf life of food products. However, as mentioned above, such bio-based materials are characterized with insufficient barrier and worse mechanical properties compared to conventional food packaging materials, which could result in a shorter shelf life of food. The physico-mechanical and functional properties of bio-based polymers can be improved and their antimicrobial activity enhanced by incorporation of different nanomaterials and such bio-NCs films can efficiently prevent food from the spoilage (Samanta et al. 2016; Al-Tayyar et al. 2020). Antimicrobial agent(s) incorporated in polymer film in antimicrobial packaging can suppress the growth and activities of targeted harmful microorganisms (Sung et al. 2013; Jampílek and Kráľová 2017). For example, many plant essential oils (EOs) exhibit significant antimicrobial efficacy but due to their low water solubility, bioavailability, volatility, and stability in the food system, their application in food packaging in order to replace chemical preservatives harmful to health requires appropriate encapsulation into nanoscale carriers to form nanoemulsions, microemulsions, or solid lipid nanoparticles (NPs) (Prakash et al. 2018; Jampílek et al. 2019). By the incorporation of EO or their components into edible/biodegradable films reduced doses of active ingredients are necessary to obtain comparable biological effects (Sanchez-Gonzalez et al. 2011; Jampílek and Kráľová 2018a, 2018b). Nanostructured antimicrobials are characterized with higher surface area-to-volume ratio when compared with their bulk counterparts (de Azeredo 2013; Jampílek and Kráľová 2015). The biodegradability and compostability of food nanopacking materials were discussed by Gutierrez (2018).

By addition of NPs with antimicrobial properties, e.g., metal NPs to polymers antimicrobial packaging materials ensuring enhanced quality and safety of food during extended storage of food products could be fabricated (Jampílek and Kráľová 2018a; Dobrucka and Ankiel 2019; Prasad et al. 2017c). The recent findings related to antimicrobial compounds of natural origin incorporated in nanoscale structures exhibiting pronounced antimicrobial activity against pathogenic microorganisms attacking food products were summarized by Lopes and Brandelli (2018). For introduction of antimicrobial compounds into food packaging materials, direct and indirect techniques can be utilized and controlled release of antimicrobial agents from food packaging materials is desirable (Jampílek and Kráľová 2018b). However, such active packaging materials must have required barrier properties, transparency, TS, and other characteristics ensuring the necessary food protection and food safety (Khaneghah et al. 2018). Impact of various additives on functional properties of composites prepared from seaweed-derived polysaccharides (alginate, carrageenan, and agar) showing biocompatibility, availability, gelling capacity, and encapsulation efficiency (EE), which can be used for food and pharmaceutical applications, was analyzed by Khalil et al. (2017).

This chapter comprehensively summarizes the findings related to CS-based and cellulose-based NCs suitable for food protection and food packaging. Beneficial impact of nanofillers including cellulose nanofibers and nanocrystals as well as cellulose and CS nanowhiskers in NC biopolymer films on the improvement of mechanical properties and thermal stability and essential oils or metal NPs, which could pronouncedly contribute to enhanced antimicrobial activity of NC films, are highlighted. CS- and cellulose-based NC films suitable for edible coatings and extension of shelf life of food products are discussed as well.

2 Chitosan

Chitosan (CS) is deacetylated derivative of chitin, a high-molecular-weight linear polycationic heteropolysaccharide consisting of β-(1→4)-linked 2-amino-2-deoxy-D-glucopyranose (β-D-glucosamine) and *N*-acetyl-β-D-glucosamine copolymers (Fig. 5.1). It can be prepared by partial alkaline *N*-deacetylation of chitin that is

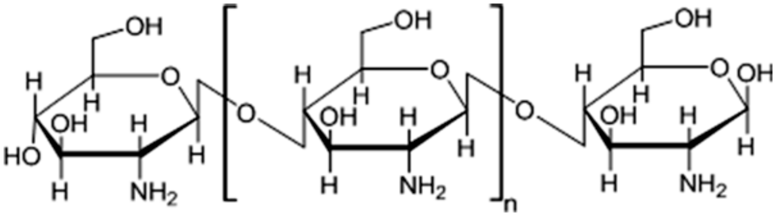

Fig. 5.1 Structure of chitosan

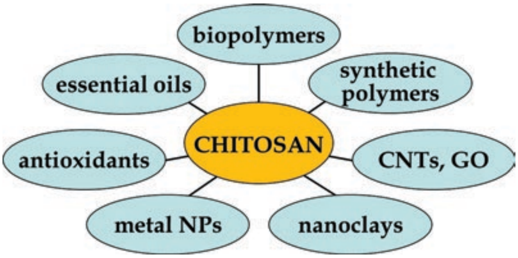

Fig. 5.2 Most frequent constituents on chitosan-based nanocomposites

usually extracted from shrimp and crab shells (Kumar et al. 2020). CS is biocompatibile, biodegradabile, and hydrophilic, can be easily modified and form films, gels, NPs, microparticles (MPs), and beads, whereby it is nontoxic, shows high bioavailability, and chemical resistance. Moreover, it has affinity to metals or proteins and shows excellent antimicrobial activity and therefore it is frequently used in pharmaceutical/medicinal applications as well as in food industry (Shariatinia 2019; Tyliszczak et al. 2019).

CS-based films with multiple functionalities could be fabricated by different methods, including direct casting, dipping, coating, extrusion, and layer-by-layer assembly and in food packaging applications, they are frequently utilized as antibacterial, barrier, and sensing films (Wang et al. 2018a).

To the factors affecting the antimicrobial activity of CS belong the environmental conditions such as pH, neighboring components, physical form, and the structural properties of the cell wall of the target microorganisms as well as its molecular weight, degree of deacetylation and degree of substitution of CS, its concentration, and original source. The antimicrobial potential of CS can be improved by incorporating in nanoscale systems with further biologically active compounds of natural origin, metals, or drugs (Hosseinnejad and Jafari 2016; Perinelli et al. 2018). Most frequent constituents on CS-based NCs are shown in Fig. 5.2.

2.1 Chitosan-Based Nanocomposites for Food Protection

CS was reported to cause simultaneous permeabilization of the cell membrane to small cellular components associated with a considerable membrane depolarization of bacteria resulting in pronounced antibacterial properties (Raafat et al. 2008). As mentioned above, the biodegradability, significant antimicrobial effectiveness, and film-forming properties of CS biopolymer predestine its use in food packaging and food preservation to ameliorate food quality and safety and prolong the shelf-life of fresh meat, dairy products (e.g., cheese), and bread in the form of CS-based films or coatings (Kumar et al. 2020). An overview devoted to CS-based edible films and coatings was presented by Elsabee and Abdou (2013). Basavegowda et al. (2020) in a review paper focused on the mode of action, toxicity, and food shelf life-enhancing effects of bimetallic and trimetallic NPs exhibiting strong antimicrobial and antioxidant properties applied in food packaging.

Thin layer formed on food surface, which can be eaten as an integral part of the food product, is known as edible packaging. Edible coating formed directly on the food surface as thin layer can improve shelf life of vegetables and fruits. On the other hand, the edible films could be formed also as thin layers separately and wrapped on food surface later. However, because the properties of such films (e.g., the mechanical properties, water vapor permeability (WVP), film color) do not achieve those of conventional packaging materials, it is desirable to improve them by incorporation of nanomaterials–nanofillers (e.g., nanostarch, nanocellulose, CS NPs/chitin NPs, nanoproteins, and nanolipids) (Jeevahan and Chandrasekaran 2019a). The quality of edible coatings and films is affected mainly with temperature, environmental humidity, interactions of polymer chains, and the hydrophilicity/lipophilicity of packaging materials (Sahraee et al. 2019). Xing et al. (2019) presented a comprehensive review related to fabrication, antimicrobial properties, and respective mechanisms of action, surface, and physical qualities of edible coatings and films with incorporated NPs showing antimicrobial activity and their application to vegetables and fruits as well. The antimicrobial activity of edible coatings and films could be connected primarily with (i) the electrostatic interaction between the cationic polymer or free metal ions and the negatively charged cell membrane, (ii) the photocatalytic reaction of NPs, (iii) the detachment of free metal ions, and (iv) partially also with the antimicrobial effectiveness of edible materials. Due to the interaction between biopolymers (e.g., CS, starch) and nanofillers (clay, inorganic, organic, or carbon nanostructures) the functionality of NC materials can be improved resulting, for example, in better barrier properties, improved mechanical strength, antioxidant and antimicrobial effectiveness or thermal stability, which can be utilized in the food industry and for food packaging (Jamroz et al. 2019). Active food packaging systems able to release antimicrobial agents into food can improve food quality and/or stability. Controlled release of antimicrobials from the packaging material and need of smaller amount of active ingredient for the same effect as well as low costs are considered as benefits and could be intensified by application of nanostructured antimicrobials. However, before practical application of such packaging materials migration of nanostructures onto food and their possible toxicity could be estimated (Azeredo et al. 2019).

The CS and nanoclay NC, which exhibited fine antibacterial activity when introduced into a film at 3 and 1%, respectively, was able to prevent Gouda cheese against microbial contamination caused by *Escherichia coli*, coagulase-positive *Staphylococcus*, *Salmonella* spp., or mold and yeast (Mohammadzadeh-Vazifeh et al. 2020). Bio-NCs based on CS-reinforced montmorillonites (MMTs) (Cloisite® Na^+ or Cloisite® Ca^{2+}) incorporated with *Rosmarinus officinalis* EO or *Zingiber officinale* EO, which were tested as active packaging to fresh poultry meat stored 15 days at 5 ± 2 °C effectively prolonged the shelf life of tested fresh meat and it was observed that compared to neat CS film the nanoclays incorporated in biocomposite suppressed lipid oxidation by 50% and microbiological contamination by 6–16% and the EOs improved the barrier to oxidation (Pires et al. 2018). NC CS films prepared by addition of a hybrid fabricated by adsorption of thyme EO into sodium–MMT or organomodified MMT exhibited excellent antioxidant effectiveness and significant antimicrobial activity against *E. coli* and in tests performed with chicken breast fillets packaged under vacuum low lipid oxidation values were observed suggesting that such films could be used for active packaging of food products (Giannakas et al. 2019).

Polyethylene terephthalate punnets containing thyme oil and sealed with CS/boehmite NC lidding films pronouncedly decreased the incidence and severity of brown rot caused by *Monilinia laxa* in artificially inoculated peach fruits (cv. Kakawa) held at 25 °C for 5 days as well as decreased incidence of brown rot to 10% when naturally infected fruits were stored for 7 days at 0.5 °C and 90% relative humidity (RH) or for 3 days at the simulated market shelf conditions (15 °C, 75% RH) (Cindi et al. 2015).

Coating green tomatoes with a nanoscale SiO_x/CS complex film delayed weight loss and softness as well as loss of the titratable acids and total soluble solids in green tomatoes resulting in significantly extended shelf life of fruits and prevented them from oxidation stress. Favorable impact of this film on postharvest quality of tomatoes was probably caused by the lower rate of O_2/CO_2 transmission coefficient, suppressed growth of foodborne pathogenic bacteria, higher activities of antioxidants, and scavenging of reactive oxygen species (ROS) as well as anti-browning activities of related enzymes (Zhu et al. 2019).

Alginate (ALG) and ALG/CS composite films (fabricated using component ratio of ALG/CS of 65:35 and 82.5:17.5, respectively) containing natamycin inhibited the growth of *Debaromyces hansenii*, *Penicillium commune,* and *Penicillium roqueforti* already at concentration 0.01 g natamycin per gram of biopolymer, while those with fourfold greater concentration of natamycin exhibited beside very good antimicrobial also suitable functional attributes (da Silva et al. 2013). Gelatin/CS nanofibers prepared using a ratio 1:6 containing 40% of encapsulated Shirazi thyme with diameters 97–343 nm showed bactericidal effect against *Clostridium perfringens* and did not exhibit marked negative impact on color and sensory properties of sausages compared to sample containing 120 ppm nitrite suggesting that such nanoformulation would be suitable as nitrite substitute for meat products (Vafania et al.

2019). Layer-by-layer edible coating on strawberries (*Fragaria* × *ananassa* Duch.) using CS and carboxymethyl cellulose (CMC) or coating with 1% CS pronouncedly suppressed the loss of fruit firmness and aromatic volatile compounds of fruits, showing only minor impact on the total soluble solids and total acidity contents, considerably decreased the levels of primary metabolites involved in carbohydrate, fatty acids and amino acids metabolism, and the contents of secondary metabolites involved in terpenoid, carotenoid, phenylpropanoid, and flavonoid metabolism after 8 days of storage (Yan et al. 2019). Polylactic acid (PLA)/CS composite films fabricated by embedding nanosized CS (0.5%, 1%, and 2%) in a PLA matrix using polyethylene glycol (PEG) as cross-linking agent and polyvinyl alcohol (PVA) as plasticizer showing antimicrobial activity against aerobic microorganisms used for packing of prawn meat, were able to suppress the microbial growth and retain the biochemical quality of tested meat samples (Fathima et al. 2018).

A combination of nisin/gallic acid/CS coating with packaging ensuring atmosphere with high O_2 content (80% O_2 + 20% CO_2) was recommended by Cao et al. (2019) to preserve fresh pork, while the shelf life of minced beef meat was found to be prolonged by 2 weeks using CS film incorporating ethanolic extract of propolis (1 and 2%) separately and in combination with cellulose NPs (1 and 2%) (Shahbazi and Shavisi 2018). Genipin cross-linked antimicrobial CS-cellulose NC films with immobilized nisin and ethylenediaminetetraacetic acid (EDTA) on the surface and irradiated by low-dose γ-irradiation of 1.5 kGy inhibited the growth of *Lactobacillus* spp. as well as psychrotrophs and mesophiles in fresh pork loin meats and enhanced the microbiological shelf life of meat sample (>5 weeks) and after 35 days of storage reduced the count of *E. coli* and *Listeria monocytogenes* in tested meat by 4.4 and 5.7 log CFU/g, respectively (Khan et al. 2016). The ε-polylysine/CS nanofibers effectively suppressed *Salmonella typhimurium* and *Salmonella enteritidis* on chicken, maintaining the color and flavor of the meat indicating that could be used as powerful antibacterial material in food packaging and preservation systems enabling the shelf life prolongation (Lin et al. 2018).

CS-hydroxypropyl methylcellulose (HPMC) films doped with TiO_2 and neem powder, which were investigated for preservation of grape and plums, maintained unchanged polyphenol oxidase and peroxidase activity for 10 days and 3 weeks, respectively, whereby good sensory and textural qualities and extended shelf life of the grape up to 10 days were observed (Priya et al. 2014). The bio-NC materials fabricated using CS/PVA mixture with loaded TiO_2 NPs (0.5–2%) used in the coating of Ras cheese were able to reduce the weight and moisture losses, while did not exhibit impact on the normal ripening changes in the microbiological, chemical, and textural properties of the cheese and mold growth on the cheese surface was found to be completely eliminated using coating film with 2% TiO_2 NPs (Youssef et al. 2019a).

The wrapping with ZnO NPs-entrapped gelatin bio-NC film with CS nanofiber pronouncedly suppressed the growth of inoculation bacteria in cheese and chicken fillet samples, and after 12 days of storage the organoleptic characteristics of food samples were not significantly impaired and the weight loss achieved 18.91 ± 1.96 and 36.11 ± 3.74%, for chicken fillet and cheese, respectively (Amjadi et al. 2019b).

Films of bio-NCs consisting of CS, guar gum, and ZnO NPs green synthesized using *Roselle calyx* extract showed ameliorated mechanical, permeability, antimicrobial, and antioxidant properties compared to those without ZnO NPs and coating of the bio-NC film containing 3% ZnO NPs on Ras cheese protected its surface for ca. 3 months from microbial growth (El-Sayed et al. 2020). CS-cellulose acetate phthalate films incorporating 5% (w/w) ZnO NPs fabricated by solvent casting method showed the most optimal TS and stiffness, low surface wettability, and high contact angle value up to 90°, better thermal stability and barrier properties and prolonged the shelf life of black grapefruits up to 9 days. The biodegradability of the NC films containing 2–7.5% (w/w) ZnO NPs ranged from 30 to 50% in 4 weeks (Indumathi et al. 2019). ZnO NPs-CS NC coatings on polyethylene (PE) films used for packaging of okra samples stored at 25 °C were found to reduce the total bacterial concentrations by 63% as compared to uncoated control, caused two times reduction in total fungal concentrations compared to this of CS-treated samples, did not affect pH, total soluble solids, moisture content, and weight of the packed okra and thus, maintained its quality (Al-Naamani et al. 2018).

NC film consisting of carboxymethyl chitosan (CMCS) and MgO NPs exhibited better thermal stability, UV shielding performance, and water-insolubility compared to pure CMCS film suggesting its suitability to be used as food packaging, especially in the case of food containing high amounts of water. Moreover, MgO NPs contributed to increased elasticity and ductility of the film already at low (1.0%) filler content and the NC showed great antimicrobial activity against *L. monocytogenes* and *Shewanella baltica* (Wang et al. 2020a).

ZnO-Ag NC green synthesized using *Thymus vulgaris* leaf extract entrapped into poly(3-hydroxybutyrate-co-3-hydroxyvalerate)–CS biopolymer improved the mechanical properties and antimicrobial activity of the biopolymer. The results of sensory evaluation of chicken breast refrigerated over a period of 15 days using the above-mentioned biopolymer with encapsulated ZnO–Ag NC confirmed that it has potential to replace the traditional synthetic polymers used for food packaging of poultry products (Zare et al. 2019). Degradable film consisting of CS–rice starch NC with incorporated AgNPs and ZnO NPs reduced the overall microbial contamination on the surface and prolonged the shelf life of packed peach fruits compared to unpackaged fruits as well as fruits packaged with control film (films with incorporated AgNPs being most effective in the prevention of fruit weight loss), ensured lowest microbial counts on the surface of the fruit and lowest percent (9.6%) increase in total soluble solids (Kaur et al. 2017).

Red claw crayfish-extracted CS and its NCs with AgNPs applied as coatings on fresh-cut melon reduced its respiration rate, retained a steady-state atmosphere (12.6–16.2 kPa of CO_2/2.3–3.7 kPa of O_2) within packages after 9–10 days, prevented the softening under storage, ensured better sensory properties compared to the uncoated samples, showed lower translucency and also microbicidal reduction (Ortiz-Duarte et al. 2019). Hybrid NC film consisting of CS, gelatin, PEG, and AgNPs showed improved mechanical properties and reduced light transmittance in visible light region and when used for the packaging of red grapes, their shelf life was extended for additional 14 days (Kumar et al. 2018).

CS/AuNPs NCs suitable as indicators of thermal history or frozen indicators for perishable and temperature-sensitive food products providing sharp color change by pink to dark gray upon freezing for one day, which could be potentially integrated with existing packaging sensors, for example in packaging of seafood and meats, were developed by Wang et al. (2018b).

Rosemary extract–CS NC coated on the fillets of *Huso huso*, which were inoculated with *L. monocytogenes*, delayed lipid oxidation by reducing peroxide value and thiobarbituric acid production in the samples compared to the control during 16 days of storage at 4 °C (Jafari, et al. 2017). Vanillin NPs deposited on the surface of CS films using a high-intensity ultrasonic method had no influence on the bulk properties of the CS films but increased the antimicrobial activity compared to neat CS film and pronouncedly increased antibiofilm activity, particularly against the biofilm formation of *E. coli* bacteria. Moreover, vanillin NP-coated CS films were able to completely inhibit microbial growth and markedly inhibited mold and yeast growth on fresh-cut watermelon, melon, and strawberry suggesting that such NC could be applied as biodegradable active packaging materials (Buslovich et al. 2018).

CS films incorporated with apricot kernel EO-containing oleic acid as the major fatty acid and high amount of *N*-methyl-2-pyrrolidone showing powerful antioxidant and antimicrobial activity at a ratio 1:1 enhanced water resistance as well as water vapor barrier property by 41% and TS value by 94%, while the elongation percentage value increased pronouncedly only for the film with oil:CS ratio of 0.125 and at higher ratio sharp decrease was observed. Compared to neat CS films this NC film exhibited significant antimicrobial and antioxidant properties and effectively suppressed the fungal growth on packaged bread slices (Priyadarshi et al. 2018).

2.2 Chitosan-Based Nanocomposite for Food Packaging

CS is a biocompatible, nontoxic, and biodegradable polymer. CS-based nanomaterials are characterized with notable physicochemical properties such as high surface area, porosity, TS, conductivity, photoluminescence, and better mechanical properties compared to pure CS (Shukla et al. 2013). It was reported that TS values of CS-based films are similar to those estimated in high-density PE films (Cazon et al. 2017). Flexible biodegradable food packaging as well as edible food coatings fabricated using CS can be used as an alternative for packaging materials prepared from nonbiodegradable plastics (Priyadarshi et al. 2019).

Researchers have also focused on strategies to improve the properties of CS through crosslinking agents, plasticizers, fillers (e.g., NP, whisker, or fibers) incorporated into CS or by adding natural extracts or oils blended with other polymers. Mujtaba et al. (2019) summarized the findings related to progress in the fabrication of CS-based films for food technology. The presence of –NH_2 and –OH groups on CS enables facile crosslinking with numerous nanomaterials, which can be utilized in CS NC-based biosensors for bio-detection applications due to their high sensitivity, selectivity, and stability enabling detection of many targets (Jiang and Wu 2019). Advances and industry challenges related to the application of metal and nonmetal-engineered NPs in food contact materials providing active and intelligent properties when used in packaging were analyzed by Hannon et al. (2015).

Plasticized hemicelluloses/CS-based edible films, which were reinforced by 5% cellulose nanofiber (CNF), showed 2.3-fold higher TS, and the films containing 20–30% glycerol as plasticizer showed TS ranging from 31.02 to 38.56 MPa and tensile strain at break (TB) in the range of 10.07–15.98%, respectively, suggesting that these films can be used for food-packaging applications (Xu et al. 2019a). Addition of CS NPs to HPMC and papaya puree films improved mechanical, thermal, as well as water vapor barrier properties of the films suggesting that their use as packaging material can prolong the shelf life of food (Lorevice et al. 2014). Cellulose/CS films with incorporated pH-responsive indicator carrot anthocyanins were designed by Tirtashi (2019) for intelligent food packaging. For the monitoring of spoilage in pasteurized milk, the color change at varying pH values (pH 2–11) was used, whereby the color of the indicator was stable during one-month storage at 20 °C. By deposition of CS/tannic acid bilayers on CNF mats with fiber diameters of 300–400 nm using layer-by-layer technology, antibacterial mats with improved hydrophilicity and mechanical properties showing >86% antibacterial activity against *E. coli* (>86%) and *S. aureus* (99%) were fabricated, which could be used for food packaging or wound dressing (Huang et al. 2019).

A ternary blend edible film fabricated using CS, gelatin, and cinnamon EO characterized with low transparency at 600 nm exhibited fine UV protection and showed higher thermal stability, contact angle, and elongation at break, but lower TS, crystallinity, and wettability than neat CS films. The powerful antimicrobial activity of this ternary blend edible film against *S. aureus* and *E. coli* was reflected in minimum inhibitory concentration (MIC) values of 52.06 μg/mL for both bacteria and minimum bactericidal concentration (MBC) values of 52.06 and 104.12 μg/mL for *S. aureus* and *E. coli*, respectively (Guo et al. 2019). Bio-NC films fabricated by incorporating CS/gallic acid (GA) NPs into a konjac glucomannan (KGM) film, in which CSGA NPs interacted with KGM through H bonds in a bio-NC matrix, showed pronouncedly ameliorated not only mechanical and barrier properties but also antimicrobial activity against *E. coli* and *S. aureus* at applied concentrations 5–10% CSGA NPs (Wu et al. 2019b). CS-KGM-cassava starch–AgNPs composite films showing resistance against moisture and antimicrobial effectiveness for food-packaging applications were designed by Nair et al. (2017).

CS nanofillers incorporated into sago starch (SS) formulations showed beneficial impact of the TS (88 MPa vs. 46 MPa for the SS film) and lower weight loss at heating than SS film (60% loss up to 390 °C vs. 67% at 375 °C) (Fauzi et al. 2019). Nanocrystalline cellulose (NCC) in transparent and biodegradable CS/guar gum (GG)/NCC film contributed to improved TS and reduced air permeability in comparison to pure CS/GG films and CS/GG composite films reinforced with NCC could be successfully used for food packaging applications (Tang et al. 2018).

CS/ε-polylysine bio-NC films fabricated using sodium tripolyphosphate (TPP) as cross-linking agent showed significant antimicrobial effectiveness against

S. aureus and *E. coli* with the increasing ratio of ε-polylysine, whereby sustained release of ε-polylysine closely related to TPP concentration was observed (Wu et al. 2019a).

Lignin NPs (1 or 3 wt%) as constituents of binary and ternary polymeric films based on PVA and CS contributed to improved TS and Young's modulus of PVA and produced a toughness effect in CS matrix as well; also pronouncedly ameliorated the thermal stability of such NCs was observed and the films were able to inhibit the bacterial growth of *Erwinia carotovora* subsp. *carotovora* and *Xanthomonas arboricola* pv. *pruni* indicating that prepared films could be applied in food packaging applications (Yang et al. 2016). New biocomposite films based on CS/PVA and MMT functionalized with thiabendazolium exhibited improved mechanical properties with Young's modulus ranging from 66.98 to 143.43 MPa and TS of 24.95–34.65 MPa, respectively and showed higher antimicrobial activities against *E. coli*, *S. aureus,* and *Pseudomonas aeruginosa* compared to the pure film (El Bourakadi et al. 2019). Koosha and Hamedi (2019) designed intelligent CS/PVA NC films containing anthocyanins from black carrot and bentonite nanoclay showing good thermal stability. While addition of bentonite reduced the TS and WVP of CS/PVA films, addition of anthocyanins had positive effect on both characteristics of CS/PVA films. Addition of anthocyanins and 5% bentonite caused 44.38%, 69.95%, and 75.20% growth inhibition of *S. aureus, P. aeruginosa,* and *E. coli*. Moreover, the added amounts of bentonite and anthocyanins affected the color of the NC films. Addition of sonochemically synthesized lignin NPs of 10–50 nm to PVA/CS NC hydrogel caused considerable increase in its thermal stability (Ingtipi and Moholkar 2019). Composite films from cellulose (3–5%), CS (0–1%), and PVA (0–4%) showed ameliorated mechanical properties, very good properties against UV radiations, and appropriate transparency value and were characterized with water-absorbing capacity. It was found that CS and PVA improved the mechanical properties of cellulose-based films, cellulose, and CS ameliorated the UV light-protecting effect of the films and PVA ameliorated the film transparency (Cazon et al. 2018). Eco-friendly bio-NC films based on PVA/CS reinforced with cellulose nanocrystals (CNCs; ca. 15 nm in diameter) isolated from rice straw showed comparable transparency level to that of neat PVA/CS film, but increased the TS and thermal stability compared to the PVA/CS films and exhibited good antifungal and antibacterial activity (Perumal et al. 2018).

A flexible, transparent, thermally stable bio-NC of CS/polyvinyl pyrrolidone (PVP) film reinforced with CNFs (9–11 nm and 100–200 nm) showing improved thermal stability and mechanical and barrier properties suitable for food packaging applications was designed by Kumar et al. (2019). Biopolymer NC films fabricated by casting film-forming emulsions containing CS/Tween 80/rosehip seed oil with dispersed MMT nanoclay were found to be flexible, with better mechanical, gas, and water vapor barrier properties. Moreover, they exhibited antioxidant activity and effective antibacterial activity against *Bacillus cereus*, *E. coli*, and *S. typhymurium* (Butnaru et al. 2019).

By addition of *N*-(2-hydroxyl)-propyl-3-trimethylammonium chitosan chloride to sodium CMC-based films, new composite materials with enhanced physicochemical properties suitable for food and drug packaging were fabricated by Wang et al. (2018c). Chicken breast fillets packaged with CS- and polycaprolactone-based bilayer films incorporated with grape seed extract (15% w/w) and nanocellulose (2% w/w), which were maintained 15 days under refrigerated conditions, showed lower levels of thiobarbituric acid reactive substances and considerable reduction in the counts of mesophilic aerobic bacteria and coliform bacteria compared with controls suggesting that such bilayer materials represent an active packaging material for food products delaying the microbial growth and oxidation and extending the shelf life during refrigerated storage (Sogut and Seydim 2019). Bao et al. (2018) designed CS-xylan/cellulose nanowhiskers (CNW) NC films, in which reinforcement effects of CNW nanofillers were reflected in improved TS and elongation at break of the NC films; good antibacterial activity was mediated by CS, and antioxidant activity was connected with the presence of xylan.

NC film consisting of CS and spherical polyaniline NPs (45–100 nm) showing mechanical, electrical, and antimicrobial properties suitable to be used in intelligent food packaging was fabricated by Mohammadi et al. (2019a). With increasing polyaniline concentration in the film increased antifungal activity against *Aspergillus niger* and antibacterial activity against *E. coli*, enhanced TS and elastic modulus, while decreased electrical resistance of the film was observed. Oliveira et al. (2019) designed electrical conducting blends prepared from CS and a conductive polymer polyaniline (PANI) utilizing benefits of a rapid electrical response of PANI and the high magnitude of the electrical response of CS, which are suitable as smart packaging for food. In contact with food, these blends exhibiting electrical conductivity can monitor changes in its physicochemical properties.

CS-based composite consisting of CS, bentonite (BT), and poplar hot water extract (10 wt%) showed UV light transmittance at 280 nm by 99.36%, i.e. higher than the film containing only CS and BT, and also its oxidation resistance was 9.65-fold of this estimated with CS-BT film. Moreover, the composite film had a denser structure and improved mechanical and water vapor barriers properties (Sun et al. 2019a). CS/clay/glycerol NC films showed improved thermal stability due to the presence of clay and glycerol and clay component pronouncedly ameliorated also the TS and tensile modulus of CS films, whereby the best strength and stiffness as well as water resistance showed CS films containing 5 wt% of clay and 20 wt% of glycerol. The presence of both clay and glycerol strongly reduced the ductility of CS (Kusmono and Abdurrahim 2019). Habel et al. (2018) designed a high-barrier, biodegradable food packaging consisting of a PLA foil (25 μm) furnished with a glycol CS–clay NC coating (1.4 μm), in which the barrier side of the foil inhibited bacterial colonization, while the uncoated PLA side ensured biodegradability. Unmodified MMT or activated food-grade MMT/CS biocomposites containing high amounts of MMT and low amounts of CS (70:30, 75:25, 80:20, % w/w) were reported to be appropriate carriers, which can covalently immobilize the protease reaching immobilization yield of 18% and 14–17%, respectively (Cacciotti et al. 2019). NCs of CS with octadecylamine MMT supplemented by *Nigella arvensis* seed (black cumin) extract at doses 1–5% exhibited stronger antibacterial activity against *E. coli* and *Salmonella enterica* serotype *Typhimurium* SL 1344 compared to *S. aureus* and *Streptococcus mutans* ATCC 25175 showing potential to prevent the antimicrobial formation when used as packing materials (Ilk et al. 2018).

Composite films consisting of CS and graphene oxide (GO) characterized with denser structure showed improved mechanical strength and lower UV light transmission and considerably higher WVP, compared to pure CS film and their complete degradation in soil compost was observed within 20 days. Increasing GO oxidation degree ameliorated mechanical strength and light barrier properties of composite films suitable for food packaging (Lyn et al. 2019). The antibacterial activity of CS–Ag NC against *S. aureus* and *E. coli* was reported to increase with increasing concentration of AgNPs in the NC up to 0.03 M and then remained constant (Fahimi and Ghorbani 2019). Khawaja et al. (2018) tested antibacterial activity of GO and NCs consisting of GO and AgNPs, GO, and CS as well as GO–CS–AgNPs against *S. aureus*, *S. mutans*, *E. coli*, *Klebsiella pneumoniae*, *P. aeruginosa,* and *S. typhi* and found that the activity decreased as follows: GO–CS–AgNPs > GO–Ag > GO–CS > GO, GO–CS–AgNPs NC being particularly effective showing potential to be applied as biomaterial or in food industry. Soft and tough CS-iron oxide-coated GO NC hydrogel films showing suitable thermal and mechanical properties and considerable antimicrobial activities against methicillin-resistant *S. aureus* and *E. coli*, as well as against the opportunistic dermatophyte *Candida albicans* were reported as suitable materials to be used not only in biomedical applications but also in the food industry (Konwar et al. 2016). Advantages and health risks of the use of carbon nanotubes (CNTs) composite materials in food packaging were discussed by Xu (2018).

CS-based NC films, in which AgNPs green synthesized using *Nigella sativa* extract with average particle size of 8 nm were unevenly distributed over the CS matrix, showed improved TS and elongation and lower WVP compared to CS films. Moreover, these NC films showed a sustained pH-dependent release of AgNPs and Ag^+ ions and notable antibacterial and antioxidant activity showing promising potential to be used for food packaging (Kadam et al. 2019). The incorporation of anthocyanin-rich purple corn extract (PCE) and AgNPs into CS film pronouncedly improved the mechanical strength, water vapor and light barrier ability, antioxidant effectiveness, and antimicrobial properties of CS film, which was connected with the synergistic effect between PCE and AgNPs. Moreover, due to abundant anthocyanins in PCE, the films responded to different pH buffers with color change suggesting that they were recommended as an excellent active and intelligent food packaging material (Qin et al. 2019). CS-based active NC films with bacterial CNCs and AgNPs showing mean particle sizes of 20–30 and 35–50 nm, respectively, which were homogenously dispersed in CS matrix showed pronouncedly improved sensibility to water, WVP, and mechanical properties compared to neat CS film as well as powerful antibacterial activity against foodborne pathogens indicating their suitability as packaging material for increasing shelf life of packaged foods (Salari et al. 2018).

By incorporation of MMT–CuO-90 NC (fabricated by heating at 550 °C for 90 min) into the CS films at concentration 3% w/w an increase of TS, and elongation at break by more than 50% and reduction of the WVP by ca. 55% and 32%, respectively, was observed, whereby these films were found to be more effective against *B. cereus* and *S. aureus* than against *P. aeruginosa* and *E. coli*. Moreover, the presence of MMT–CuO-90 NC in the CS film could improve its mechanical properties and reduce both UV transition and water solubility showing minor impact on the transparency of the film (Nouri et al. 2018).

The gelatin-based NC containing CS nanofibers and ZnO NPs showed fine mechanical and water barrier properties due to its high dense and less permeable structure and due to the synergistic effect between CS nanofibers and ZnO NPs increased antibacterial activity of NC was observed (Amjadi et al. 2019a). Novel biodegradable composite films for food packaging based on CS biopolymer with incorporated ZnO NPs (40–80 nm; 1 and 3% (w/v)) and *Melissa officinalis* EO (0.25 and 0.5% (w/v)) showing antimicrobial activity were prepared. With the increasing concentrations of ZnO NPs and EO water solubility and WVP of films showed a decrease, while their TS and antibacterial properties increased. However, while with increasing ZnO NPs the film opacity increased, increasing amounts of EO exhibited opposite effect reflected in increased transparency (Sani et al. 2019). Biodegradable films prepared from Mahua oil-based polyurethane and CS with entrapped ZnO NPs containing 5% ZnO NPs in the composite showed improved TS and stiffness, enhanced hydrophobicity, barrier properties, and antibacterial properties of the biodegradable film, which lost 86% of weight after one month in the soil. On the other hand, the shelf life of carrot pieces wrapped with the NC film was prolonged up to 9 days and the film with ZnO NPs was able to reduce the bacterial contamination much more than the PE film (Sarojini et al. 2019). CS-ZnO NC coatings on PE films were able to completely inactivate and prevent the growth of food pathogens, while films coated with CS reduced the viable cell counts of *S. aureus*, *E. coli*, and *S. enterica* after 24-h incubation only tenfold compared to the control suggesting that PE films coated with CS-ZnO NC represent an active packaging material which can prolong the shelf life of food (Al-Naamani et al. 2016).

CS antimicrobial film containing 1% TiO_2 NPs evenly distributed in CS film matrix was characterized with improved TS, water barrier, and ethylene photocatalytic degradation properties, and showed antimicrobial activity against bacteria (*E. coli*, *S. aureus*, *P. aeruginosa*, and *S. typhimurium*) and fungi (*Penicillium* and *Aspergillus*) (Siripatrawan and Kaewklin 2018). Effective inactivation of *S. aureus* by CS-TiO_2 NC film designed for packaging, in which TiO_2 NPs (Degusa 25) were dispersed in CS matrix, was reported by Kustiningsih et al. (2019). Potential of antimicrobial CS-TiO_2 composite film damaging membranes with subsequent leakage of cellular substances for food packaging applications was highlighted also by Zhang et al. (2017). Food packaging films based on CS, TiO_2 NPs, and black plum peel extract was characterized with better mechanical strength and barrier properties against UV–vis light and water vapor, stronger free radical as well as ethylene scavenging activities and antimicrobial activity than CS film. The abundant anthocyanins were responsible for the sensitivity of the film color to pH (Zhang et al. 2019). Ethylene photodegradation activity at exposure to UV light showed also active packaging made from CS containing TiO_2 NPs, which also retarded the ripening process and quality changes of the packaged tomatoes (Kaewklin et al. 2018).

Starch–CS films with incorporated TiO_2 NPs functionalized with the alkoxysilane exhibited improved TS by 33% and the insertion of Ag nanodots also ameliorated antimicrobial effectiveness of the starch–CS films (Vallejo-Montesinos et al. 2020). TiO_2 NPs added to zein/CS composite films pronouncedly ameliorated the thermal stability and mechanical properties of films and using 0.15 wt% TiO_2 NPs resulted in the TS of the zein/CS/TiO_2 films of 28.33 ± 1.53 MPa. The composite films showed higher antibacterial effect *S. aureus* compared to *E. coli* and *S. enteritidis*, whereby the antibacterial effect at exposure to UV light was better than that observed at dark conditions (Qu et al. 2019).

As biodegradable active packaging materials with good antibacterial and antioxidant activities, water vapor and oxygen barrier properties and thickness the NC based on CS and CMC and containing *Ziziphora clinopodioides* EO (1 and 2%) and methanolic *Ficus carica* extract (1%) were recommended by Shahbazi (2018).

By incorporation of 0.5% *Codium tomentosum* seaweed extract into CS-based edible films, the film solubility and elasticity increased by 50 and 18%, respectively, while the puncture strength and energy at break decreased by 27% and 39%. On the other hand, addition of this extract in the ALG films pronouncedly reduced film solubility (6%), WVP (46%), and elasticity (24%) without an impact on thermal properties (Augusto et al. 2018).

Synthetic melanin-like NPs (MNPs) reinforced CS NC films showed enhanced ultraviolet blocking and mechanical properties and high antioxidant activity. In addition, the presence of MNPs also increased the hydrophobicity and swelling ratio of the NC films, whereby the water vapor barrier property and thermal stability of the films were not impaired (Roy et al. 2020). Similarly, functional CS-based films with incorporated curcumin (1 wt%) showed improved swelling ratio, UV-blocking, water vapor barrier property, and surface hydrophobicity compared to the neat film and exhibited high antioxidant activity, whereby slower release of encapsulated curcumin was observed compared to films prepared using carrageenan or agar (Roy and Rhim 2020). Biodegradable food packaging hybrid film consisting of PVA, CS, xylan, and hydroxyapatite with incorporated curcumin was evaluated as suitable intelligent packaging enabling real-time fish freshness assessment based on the visible and sharp color changes (Vadivel et al. 2019).

Functional composite films of CS with sulfur nanoparticles (SNP), in which SNPs were dispersed evenly in the CS matrix, showed enhanced mechanical strength, water vapor barrier property, hydrophobicity, and antimicrobial activity compared to neat CS film, whereby the highest antimicrobial activity against foodborne pathogenic bacteria *L. monocytogenes* and *E. coli* resulting in complete sterilization within 12 and 6 h, respectively, was observed with SNPs capped with CS composite film (Shankar and Rhim 2018).

3 Nanocellulose and Bacterial Cellulose

In vascular plants, cellulose consists of β-(1→4)-linked D-glucopyranose chains laterally bound by H-bonds forming microfibrils with a nanosized diameter, which are further organized in microfibril bundles (Fig. 5.3) (Klemm et al. 1998).

Using mechanical disintegration of cellulose fibers showing a width ca. 20–50 nm and length of several micrometers, which contain both crystalline and amorphous regions, cellulose nanofibers (CNFs; known also as nanofibrillated cellulose) with high length-to-diameter aspect ratios can be fabricated. On the other hand, nanocrystaline cellulose (NCC), cellulose nanocrystals (CNCs), and cellulose nanowhiskers (CNWs) are cylindrical rods of crystalline cellulose showing 5–10 nm and length: 20–1000 nm (Hutten 2016). The use CNFs, CNCs, and CNWs as reinforcement fillers in composites can considerably ameliorate their mechanical properties (Perumal et al. 2018; Ukkund et al. 2019; Jampílek and Kráľová 2020). Cellulose nanomaterials as nanoreinforcements for polymer NCs were discussed by Dufresne (2018). Electron microscope images of CNFs extracted from trees are shown in Fig. 5.4. For fabrication of CNFs, CNCs, and CNWs, various cellulose source materials, including agricultural waste can be used (Sangeetha et al. 2017; Jampílek and Kráľová 2020). CNFs were isolated for example from banana peels (Tibolla et al. 2019), wheat straw fibers (Fan et al., 2018), rice straw pulp (Hassan et al. 2018), pineapple leaf (Balakrishnan et al. 2017), sugarcane bagasse (Patil et al. 2018), or coconut palm petiole residues (Xu et al. 2015), while CNCs were fabricated from rice straw (Perumal et al., 2018), rice husks (Kargarzadeh et al. 2017), mango seed shells (Silva et al. 2019), or sugarcane bagasse (Kassab et al. 2019). It could be mentioned that the use of agricultural waste for preparation of CNFs and CNCs is favorable not only due to low costs, but using this approach woody species playing a substantial role in moderating the climate could be preserved that is particularly desirable under changing climatic conditions (Jampílek and Kráľová 2020).

Bacterial cellulose (BC) is an extracellular polymer produced by many microorganisms (the best producer, the *Komagataeibacter* genus, uses semisynthetic media and agricultural wastes). BC is characterized by the nanoporous structure and it contains high water content and numerous free –OH groups (Cacicedo et al. 2016). It could be underlined that BC is produced as naturally nanostructured membranes, capable to grow in a medium containing

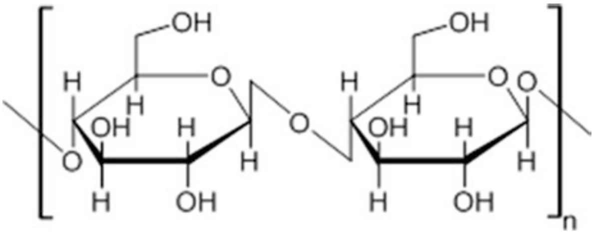

Fig. 5.3 Structure of cellulose

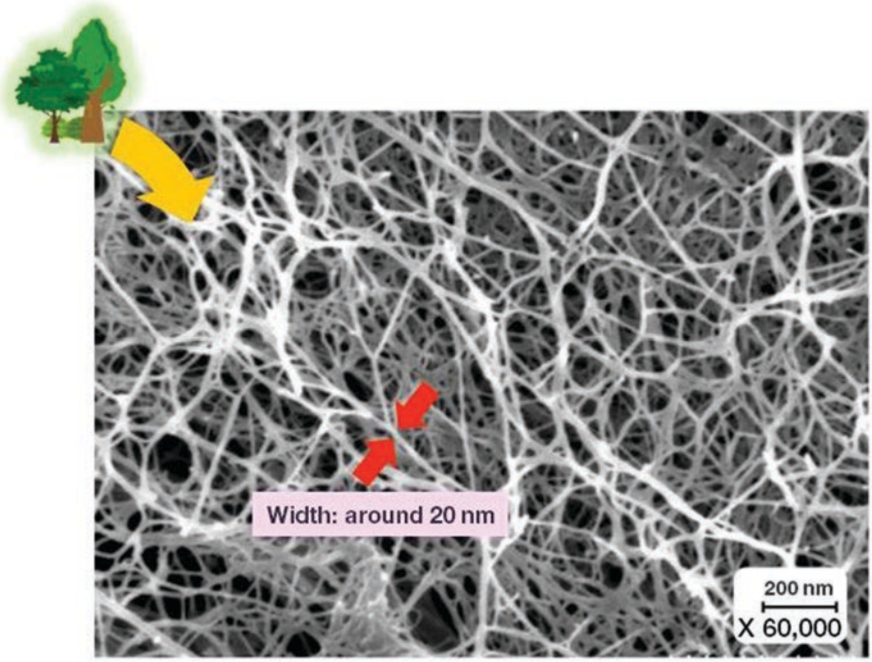

Fig. 5.4 Electron microscope image of nanofiber cellulose extracted from trees (Nippon, 2019)

other biopolymers, resulting in formation of bio-NCs. Moreover, it can be impregnated with other components or disintegrated into nanofibrils or nanocrystals and therefore the use of BC nanostructures for food packaging application is favorable (Azeredo et al. 2017).

3.1 Nanocellulose-Based Nanocomposites Used for Food Protection

New sustainable eco-friendly antimicrobial and antioxidant active ingredients could be introduced in food packaging to achieve improved safety and quality of food products and reduce adverse impact on the environment. Introduction of such active compounds in edible packaging could lower and/or limit the environmental impact, whereby edible and eco-friendly food packaging can also reduce the waste (Fortunati, et al. 2019). Dhar et al. (2019) in a review paper evaluated the properties of nanocellulose and its strategic modifications to design active food packages enabling real-time monitoring of food quality, while Hemavathi and Siddaramaiah (2019) highlighted the crucial role of polymers in food supply chain as a packaging material able to store, protect, and preserve food from spoiling and damage.

Nsor-Atindana et al. (2017) analyzed the functionality and nutritional aspects of microcrystalline cellulose (MCC) providing beneficial impact on gastrointestinal physiology, and hypolipidemic effects and affecting the expression of several enzymes involved in lipid metabolism; MCC was investigated as a functional ingredient in various food products as discussed as well.

Incorporation of MMT and ε-poly-(L-lysine) (PL) into CMC matrix resulted in improved UV and water vapor barrier properties, TS and hydrophobicity of CMC film, and effective antimicrobial activities against bacteria (*S. aureus* and *E. coli*) as well as phytopathogenic fungi (*Botrytis cinerea* and *Rhizopus oligosporus*) reflected in >90% inhibition rate of microbial growth at 7.5 wt% of PL. When strawberries were coated with a film-forming solution of the composite CMC/MMT/PL with 7.5 wt% PL, their shelf life was prolonged for 2 days (He et al. 2019).

CMC film coated with ZnO NPs, which was used as the packaging material for pork meat for 2 weeks of cold storage at 4 °C, was able pronouncedly suppress the rising in total volatile basic nitrogen and pH levels, limited decline of lightness and redness, and maintained the water-holding capacity compared to the control meat samples and under cold conditions caused increased occurrence of cell membrane rupture in *S. aureus* (Suo et al. 2017). Chicken breast meat packed with NC films based on CMC, okra mucilage (OM), and ZnO NPs and stored at 4 °C pronouncedly suppressed the growth of *S. aureus* counts and lactic acid bacteria and considerably suppressed lipid oxidation and total volatile nitrogen due to the presence of okra mucilage and ZnO NPs resulting in extended shelf life of meat products. The best antimicrobial effect and suppression of undesirable changes in the meat samples and higher sensorial score under chilling storage was observed with the film consisting of CMC/OM50%/ZnO NPs (Mohammadi et al. 2019b).

NC prepared via Schiff base reaction by anchoring nisin to the cellulose beads mixed with γ-Fe_2O_3 NPs exhibited susceptible magnetic response and good thermal stability and showed long-term antimicrobial effectiveness against *Alicyclobacillus acidoterrestris* DSM 3922 suggesting its suitability to be used in food industry (Wu et al. 2019c).

Active packaging based on cellulose–CS–Ag/TiO_2 NC tested for storage of clarified butter showed peroxide value of 2.72 mEq O_2/kg and lower counts of molds and yeasts (5.8 CFU/g) and *E. coli* (6.12 CFU/g) after 6 months of storage (Apjok et al. 2019).

3.2 Nanocellulose-Based Nanocomposites Used for Food Packaging

Nanocellulose (NCel) materials are derived from cellulose, the most abundant biopolymer on our planet. NC hydrogels based on NCel or reinforced with NCel are characterized with superior mechanical properties, biocompatibility, and biodegradability and can provide a slow and controlled release profile of incorporated active ingredients (Nascimento et al. 2018). Polymers obtained from celluloses, CS, and other native or modified carbohydrate polymers (e.g., starches, glucans, pectins, and gums), could be used for fabrication of self-assembled polymer composite materials, including films, hydrogels, micelles, and particles and can be used as encapsulating agents of food additives, food coatings, or as edible films. Considering their mechanical properties and sensitivity to temperature, pH, individual ions, ionic strength, and enzymes, they can provide a base for the design and fabrication of advanced materials for food industry (Valencia et al. 2019). Recent finding related to hydrogels and aerogels incorporating NCel, including physical and chemical cross-linking strategies, postmodifications, or gel structure control were discussed by De France et al. (2017).

A review paper of Khalil et al. (2019) discussed matrix filler combinations suitable for fabrication of neutral or negatively charged polysaccharides-based composite films with improved mechanical and barrier properties suitable not only for food packaging but applicable also in agriculture, biomedicine as well as constructions sector. Fabrication of eco-friendly biopolymer composites used for green packaging, novel processing techniques used to produce high-performance lignocellulosic reinforced materials with better properties, green modification of organoclay by antibacterial natural compounds, and the use of green-modified organoclays as compatibilizing and reinforcing material for different incompatible biopolymers (e.g., CS, CMC, and PLA) was discussed by Moustafa et al. (2019). Idumah et al. (2019) summarized recent findings related to actual trends in the fabrication and characterization of polymer NCs as biodegradable and environment-friendly packaging materials. A review paper summarizing recent findings related to the progress in the design of new nanomaterials for food packaging and discussing the possible mechanisms of antibacterial activity of certain biologically active nanomaterials and their impact on health was presented by Huang et al. (2018). Polymeric NCs and nanoscale coatings suitable for food packaging were overviewed also by Vasile (2018). Youssef and El-Sayed (2018) in a review paper focused on the degradable packaging materials showing notable performance, excellent mechanical properties, thermal stability, and antibacterial activity as well as on the use of bio-NCs in various packaging applications. Golmohammadi et al. (2017) discussed the feasibility of NC applications in (bio)sensing technology in order to obtain analytical information in various fields (e.g., in medical diagnostics, monitoring of the environment, for ensuring high level of food safety, physical/mechanical sensing and labeling, or in bioimaging applications). The researchers emphasized that in the near future the NC (bio)sensing platforms could replace currently used (bio)sensors based on plastic, glass, or conventional paper platforms. A critical review focused on the biological impact of NCel was presented by Endes et al. (2016), drawing the attention to certain forms of NCel, which due to their specific physical characteristics could represent some hazard to living organisms. Gomez et al. (2016) in their review paper analyzed applications of NC as a stabilizing agent, functional food ingredient, and in food packaging suggesting potential use of NCel as a stabilizing agent in food emulsions, as dietary fibers, and as materials able to reduce the caloric value of food.

Biomedical, food, and nutraceutical applications of NCs containing green cellulose nanomaterials fabricated from renewable sources and characterized with excellent mechanical strength and biocompatibility were overviewed by Amalraj et al. (2018). The recent progress in the utilization of cellulose-based nanomaterials in food and nutraceutical applications was overviewed by Khan et al. (2018). The use of NCel in green food packaging with emphasis on the several types of biopolymers with NCel fillers forming bio-NCs was analyzed by Vilarinho et al. (2018).

A composite cassava starch films fabricated with stearic acid-modified MCC or NCC as strength agent using the casting method showed reduced thermal stability but enhanced mechanical and hydrophobic properties compared to neat starch films. Use of 0.5% MCC and 1.5% NCC resulted in the TS increase of cassava starch film by 484.5 and 327.7%, respectively, while addition of 2% MCC and 0.5% NCC increased film hydrophobicity by 65.0 and 30.3%, respectively, suggesting more favorable enhancement effect of MCC (Chen et al. 2020). CMC nanocrystals showing diameters of 30–50 nm incorporated in cassava starch film resulted in improved mechanical and water barrier properties and better water solubility compared to incorporation of CNCs suggesting that hydrophilic modification of CNCs used for reinforcement of films resulted in improved physicochemical properties of these composite films (Ma et al. 2017). CNF–bengkoang starch bio-NC film prepared with ultrasonication containing 2 wt% of CNF showed TS of 9.8 ± 0.8 MPa, which was by 160% higher than that of neat starch film and exhibited also lowest moisture absorption and WVP, highest thermal resistance, and high transparency compared to the bio-NC films containing lower CNF amounts (0.1–1.5%) (Mahardika et al. 2019). Corn nanostarch-based NC film loaded with 8.0 wt% CNCs modified by crosslinking with citric acid, and subsequently amidated with CS exhibited a 230.0% increase in TS compared to pure corn nanostarch film and showed a decrease of the moisture absorption ability and WVP by 25.6 and 87.4%, respectively, with simultaneous increase of the water contact angle value by 18.1% as well as higher antimicrobial activities against *S. aureus* and *E. coli* (Chen et al. 2019). Corn distarch phosphate/NCC films with incorporated nisin and ε-polylysine showed synergistic antimicrobial activity against *E. coli* and *S. aureus*, ameliorated mechanical and barrier properties, higher thermal stability and thus, they could be recommended as active food packaging material (Sun et al. 2019b). Rice starch-based edible films, which were fabricated via solution casting with addition of NCel extracted from banana pseudostems (2–10%), were characterized with improved mechanical and barrier properties suggesting their suitability to be applied for food packaging (Jeevahan and Chandrasekaran 2019b).

PLA/starch NC films reinforced with CNFs isolated from MCC exhibited improved TS, Young's modulus, and reduced air permeability compared to neat PLA/starch films (Mao et al. 2019).

In starch/CNWs composite films fabricated by casting of the mixtures of starch/CNWs homogenous aqueous suspensions and subsequent drying, the layers of CNWs were located within starch matrices in a parallel direction to NC film surfaces, whereby increasing amount of CNWs resulted in increased layer thickness. In such self-assembled multilayer structures, both the interaction and evaporation rate of the solvent affect the NPs dispersion and they can serve as an appropriate material for food packaging ensuring favorable mechanical and gas barrier properties (Liu et al. 2017).

A multilayer structure, in which layers of cellulosic nanomaterials providing O_2 resistance are coated with other layers of polymers that provide moisture resistance and tightness, may be an alternative to packaging materials dominated by synthetic plastics (Wang et al. 2018d). By incorporation of cellulose microfibres into cellulose agar bio-NC films the TS increased from 38.8 ± 3.2 to 49.4 ± 4.3, the elongation at brake showed ca. 6% increase and films showed reduced swelling; increased degradation rate in soil suggested their suitability for food packaging applications (Raj et al. 2019). Biodegradable biocomposites consisting of high-pressure microfluidized cellulose fibers and carrot minimal processing waste (33 wt%) showed TS of ca. 30 MPa, ca. 3% elongation at break, and Young's modulus of ca. 2 GPa indicating its suitability to be applied for food packaging (Otoni et al. 2018).

CNFs composite films containing lignin particles of colloidal dimensions (CLPs) designed by Farooq et al. (2019) were found to be strong, ductile, and waterproof and provided antioxidant activity and UV-shielding with improved visible light transmittance; approx. double toughness of films was achieved at application of an optimal CLPs content (10 wt%) when compared to a neat CNF film without added lignin particles.

Soy protein-based films incorporating CNCs and pine needle extract exhibited improved mechanical property, antioxidant ability, and water vapor barrier capacity suggesting their suitability to be used as an active food packaging material (Yu et al. 2018). Investigation of the impact of CNFs on morphological, mechanical, optical, and barrier properties of biopolymers isolated from whey protein showed that in the films containing up to 4% CNFs these were well dispersed in the whey protein matrix and acted as reinforcing agent making the bio-NC films more resistant and less flexible (Carvalho et al. 2018).

Biodegradable bio-NCs based on plasticized sugar palm starch and 1.0 wt% nanofibrillated celluloses obtained from sugar palm fibers exhibited improved mechanical and thermal stability and water barrier of the starch polymer and this bio-NC material prepared from natural sources could be applied for plastic packaging and food containers (Ilyas et al. 2020). Study of the impact of polyol-based plasticizers on physicochemical properties of CNCs-filled ALG bio-NC films showed that although the presence of plasticizers markedly impaired the TS and the elastic modulus of the neat ALG films and pronouncedly increased the elongation at break, these characteristics were improved by incorporation of CNCs into the films. Moreover, the presence of both CNC and plasticizers in ALG bio-NC films decreased WVP and moisture uptake of these films and the films exhibited good optical transparency suggesting their potential to be used for packaging applications (El Miri et al. 2018). Bio-NC film consisting of cellulose NPs prepared from the nonedible part of jackfruit (*Artocarpus heterophyllus*), PVA, and fennel seed EO exhibited sevenfold increase in TS and sixfold increase in elongation at break compared to neat PVA film due to incorporation of cellulose NPs and can represent an convenient alternative for traditional food packaging materials (Jancy et al. 2020).

Addition of 10% nanoscale BC to the agar-based edible films considerably reduced moisture content, water solubility, and WVP and increased the TS of films to 44.51 MPa, while the elongation at break increased with increasing BC concentrations only in the range 0–5%, and then decreased in the presence of 8–10% BC (Wang et al. 2018e).

Bio-NCs consisting of ionically cross-linked CS and CMC serving as matrix for CNC nanoreinforcement agent achieved TS of 60.6 MPa, Young's modulus of 4.7 GPa, and water vapor transportation rate of 7982 g μm/m^2 per day when the applied CNC concentration was 10 wt%. On the other hand, composites with <5 wt% CNC were found to be a significant barrier coating against penetration of liquids (water, oil) on the paperboard substrate (Chi and Catchmark 2018).

Due to blending of ALG with needle-shaped CNWs (length: 200–400 nm, diameter: 15–30 nm), which were isolated from the mulberry pulp, the elastic modulus and TS of the composite ALG-based film increased by 35 and 25%, respectively, compared to pure ALG film, while no change in WVP was observed when for the blending 4 wt% CNW was applied (Wang et al. 2017).

Antimicrobial composite films fabricated from xylan and hydroxyethylcellulose using citric acid and PEG-400 as crosslinker and plasticizer with incorporated β-cyclodextrin/sodium benzoate and cured for 40 min achieved TS up to 62.3 MPa and very low oxygen permeability calculated through the oxygen gas transmission rate multiplied by the average film thickness (1.0 cm^3 μm m^{-2} d^{-1} kPa^{-1}) and showed high antimicrobial activity against *S. aureus* indicating its great potential in the field of sustainable food packing materials (Yang et al. 2019).

A mixture of the κ-carrageenan, CNC, and glycerol was used to prepare bio-NC films by solution casting, which showed improved mechanical and barrier (water and UV) properties and thermal stability compared to pure κ-carrageenan films, particularly when 7–9% CNC was used (Yadav and Chiu 2019). Ameliorated mechanical properties of κ-carrageenan-based NC films reinforced with CNCs were also reported by Kassab et al. (2019).

Strong antibacterial properties against both *E. coli* and *S. aureus* exceeding 99% showed also PVA films containing BC and ε-polylysine exhibiting strong antibacterial activity also after reusing twice, whereby the biocomposite films had improved thermal stability and mechanical properties compared to pure PVA films (Wahid et al. 2019). By oxidation of CNFs and CNCs using periodate oxidation the introduced dialdehyde groups can act as a crosslinking agent. Introduction of these fillers containing dialdehyde groups (DCNF and DCNC, respectively) in PVA films enhanced their water resistance. However, while DCNC exhibited only chemical network reinforcement effect, DCNF induced physicochemical networking effect to PVA (Lee et al. 2020). Biodegradable conductive NC fiber membrane fabricated by in situ polymerization of indole in the presence of electrospun BC nanofibers activated in acidic medium showed good antibacterial activity against *S. aureus* and *E. coli* and could be used in food packaging as well as in biomedical preparations, electronic devices, and biosensors (Cai et al. 2018). Addition of nanofillers, NCC, and chitin whiskers (CHW) to biodegradable poly(butylene succinate) (PBS) restricted the mobility of polymer chains, while nucleation and recrystallization of polymer were stimulated resulting in the increased crystallinity degree from 65.9 to 75.6%. An increase of TS of the neat PBS-based films (23.2 MPa) was observed following CHW and NCC addition to 43.6 and 32.9 MPa, respectively. Using a compatibilizer, methylene diphenyl diisocyanate, at a dose of 4% in PBS films containing 3% NCC a decrease in O_2 transmission rate from 737.7 to 23.8 cc/m^2/day was observed, while water vapor transmission rate declined from 83.8 to 30.8 g/m^2/day (Xu et al. 2019b). Poly(propylene carbonate)/poly(3-hydroxybutyrate)-based bio-NCs reinforced with CNCs showed improved oxygen barrier properties, which at application of 1 wt% CNCs increased ca. 18-fold, suggesting the promising potential of such bio-NCs to be used as degradable material for food packaging (Jiang et al. 2020). PVP-CMC hydrogel films with incorporated BC and guar gum (GG) showed improved elastic and load-bearing capacity as well as barrier and hydrophobic properties and were found to be 80% biodegradable in 28 days in vermicompost (Bandyopadhyay et al. 2019). In the NCs of poly(butylene adipate-co-terephthalate) reinforced with CNCs fabricated by solution casting method and then covered with Ag thin film by magnetron sputtering, the surface modification caused higher degree of crystallinity of CNCs and decreased their length and diameter. CNCs addition enhanced the storage modulus of the polymer by >200%, contributed to better thermal and mechanical properties and the NC inhibited *E. coli* biofilm formation (Ferreira et al. 2019). By incorporation of polydopamine-functionalized MCC into a konjac glucomannan films were prepared showing improved mechanical properties, pronouncedly reduced WVP, and high thermal stability, which could be recommended as prospective food packaging material (Wang et al. 2019).

A composite of the CMC-based film with functionalized halloysite nanotubes fabricated via adsorbing metal ions on uniformly charged acid-treated halloysite nanotubes showed a considerably improved mechanical and water vapor barrier properties and thermal stability as well as significant antimicrobial activity against both *E. coli* and *L. monocytogenes* (Wang and Rhim 2017). Bio-NC films prepared by incorporation of two types of bentonite with the platelet aspect ratios 300–500 (PGN) and 150–200 (PGV), respectively, into CNF matrix showed lower CNF degradation temperature and strength compared to neat CNF films. The PGN-containing samples were more hydrophilic and at 15% PGN the water vapor transmission rate decreased from 425 to 375 g/m^2 per day, while higher PGN amounts exhibited adverse impact; PGN also intensively suppressed the O_2 passage in dry state and to a lower extent at increased RH (Zheng et al. 2019). Cellulose NC foams containing low amounts of surface-modified MMT exhibited pronouncedly better thermal, mechanical, and barrier properties than the pure cellulose foam and could represent a good alternative to expanded polystyrene foam trays for dry food packaging (Ahmadzadeh et al. 2015). Corn starch/MMT/CNF composite films prepared using one-dimensional (1D) CNFs and two-dimensional MMT plates showed increased TS and Young's modulus and transparency, while reduced moisture susceptibility compared to neat starch film suggesting that using binary fillers with different geometric shapes and aspect ratio biodegradable starch-based NCs suitable for food packing and preservation can be designed (Li et al. 2019a). NC with PEG and

Na-MMT nanofillers strongly improved the tensile mechanical properties of CMC film resulting in up to 260% increase of modulus, up to 250% increase in the strength and up to 300% increase in elongation and a ca. fivefold decrease in WVP compared to neat CMC film suggesting its applicability in edible food packaging (Fiori et al. 2019).

In cellulose-based composite foams prepared using nanoclay the presence of nanoscale clay in the cellulose matrix contributed to better uniformity of foam structure as well as to higher density, compressive strength, and Young's modulus suggesting that such composite foams could replace the commercial synthetic foams applied for packing of food products (Ahmadzadeh et al. 2016).

By integrating hydroxyapatite (HAp) NPs into a CNF matrix using the one-directional freeze-drying technique NC films were prepared, which can function as ammonia sensors and could be used as indicators for freshness in smart and biodegradable food packaging materials. The gas-sensing performance was affected mainly by the amount and morphology of HAp, its distribution within the microporous CNF matrix, and doping on its surface; at application 5 wt% of HAp the detection limit of NH_3 was 5 ppm, the sensitivity reached up to 575%, and response/recovery was achieved in 210/30s (Narwade et al. 2019).

Idumah et al. (2020) in a review paper devoted attention to surface treatment approaches of some nanomaterials (e.g., cellulose, nanoclay, halloysite nanotubes, graphene, and CNTs) and their impact on properties of composite films applied for packaging, highlighting the innovations in polymeric NC packaging materials and electrical sensors for food and agriculture. In ternary NC of poly(3-hydroxybutyrate-co-3-hydroxyvalerate) (PHBV)/CNC/GO fabricated via a simple solution casting method containing 1 wt% covalently bound CNC–GO NCs prepared by chemical grafting, the TS and elongation to break increased by 170.2 and 52.1%, respectively, and maximum degradation temperature (T_{max}) increment showed an increase by 26.3 °C compared to neat PHBV; the ternary NC also showed very good barrier and antibacterial activity as well as lower migration level for food stimulants than the neat PHBV or binary noncovalent NCs of CNC and GO (1:0.5 wt%) (Li et al. 2019b).

Addition of thyme EO (20–40% w/w) to the bio-NCs of whey protein isolate (WPI) and CNF resulted in reduced WVP, increased crystallinity index, and glass transition temperature. The formed films were less rigid and elastic and showed a decrease in TS, elongation at break, puncture strength and deformation, and elastic modulus. The color of bio-NC films containing EO was less yellow, showing a tendency to green, less saturated, and less transparent than the WPI–CNF films (Carvalho et al. 2020). Methylcellulose (MC)/CNC-based NC films containing encapsulated nanoemulsion of oregano and thyme EOs with the size 100 nm and showing a slow release (35%) of volatile components over 3 months of storage, improved TS and decreased water barrier properties, were able to reduce the fungal growth in infected *Oryza sativa* plants during 2 months of storage at 28 °C, whereby these favorable properties could be enhanced by irradiation of bioactive films at 750 Gy (Hossain et al. 2019). Active NC films based on soy protein isolates, clove EO, and microfibrillated cellulose (MFC) with diameters of 50–60 nm, a length of 485 ± 2 μm, a high aspect ratio of 8800, and 35.5% of crystallinity, in which MFC reinforced the protein matrix, showed increased mechanical strength and Young's modulus of the films, enhanced barrier properties to O_2 and water vapor; increased antioxidant properties and antimicrobial activity against bacteria with increasing MFC content were observed. On the other hand, clove EO increased the O_2 permeability and decreased WVP (Ortiz et al. 2018).

Soy protein-based packaging materials with the incorporated CNFs, pine needle extract (PNE), and lactic acid showed enhanced TS due to the presence of CNFs and significantly improved light barrier property mediated by CNF and PNE. Films containing PNE also showed pronounced antioxidant activity and antimicrobial effectiveness against foodborne pathogens (*S. aureus*, *E. coli*, *L. monocytogenes*, and *S. typhimurium*), although CNFs mitigated the release of both active compounds from the film matrix (Yu et al. 2019a).

Yang et al. (2020) designed multi-nanofibers composite film based on hybridization of bacterial CNF/CS, in which curcumin (Cur) MPs/NPs were dispersed. This composite film exhibited better mechanical strength and barrier property due to the presence of bacterial CNF as well as notable antioxidant capacity and antibacterial effectiveness and was able to detect pH change and trace amount of H_3BO_3 suggesting its suitability as a smart and active food packaging material.

Multifunctional NC/metal or metal oxide (e.g., AgNP, ZnO NP, CuO NP, and Fe_3O_4 NP) hybrid nanoscale materials characterized with high antibacterial efficiency, ultraviolet barrier, and mechanical properties could be recommended not only for food packaging, but also for biopharmaceutical, biomedical, and cosmetics formulations (Oun et al. 2020). Antibacterial CMC-based nanobiocomposite films containing three types of metallic NPs (AgNPs, CuO NPs, and ZnO NPs) at concentrations 2 wt% showed improved mechanical properties and lower WVP values than the pure CMC film and films containing individual NPs in the same concentration. Moreover, the CMC films with incorporated metallic NPs exhibited antibacterial properties against *S. aureus* and *E. coli* (Ebrahimi et al. 2019).

In CNF/AgNPs NCs fabricated using UV irradiation the AgNPs with mean size ca. 28 nm coated on CNFs interfered with the formation of intra-chain and interchain H-bonds of cellulose and the NC showed significant antimicrobial activities against *S. aureus* and *E. coli* (Yu et al. 2019b). As a suitable material for food packaging applications, cellulose NC films with in situ generated AgNPs using tamarind nut powder as a reducing agent showing good antibacterial activity and improved mechanical properties were recommended by Mamatha et al. (2019). NC films fabricated from a mixture of cellulose acetate and nearly spherical AgNPs with sizes 5–18 nm, green synthesized using different polyphenolics, showed significant antibacterial activity against *E. coli*, *S. aureus*, *S. typhi*, *B. cereus,* and *K. pneumoniae* but low activity against *Pseudomonas* spp. and released less AgNPs than the allowed limit indicating that they could be applied as a food packaging system (Marrez et al. 2019). Composites of CNC–AgNPs with sizes up to 30 nm prepared using dialdehyde cellulose nanocrystal as both reducing and stabilizing agent showed notable antibacterial activities against *S. aureus* and *E. coli* and their addition into the pulp resulted in handsheets exhibiting pronounced antibacterial activities, higher mechanical properties, and a reduced air permeability; such composites could be applied in food packaging materials (Xu et al. 2019c). BC–AgNPs composites containing <2% (w/w) AgNPs showed better antimicrobial activity than colloid Ag with the same concentration and were found to protect foodstuff from microbial spoilage for 30 days, while in foodstuff stored in regular polythene bag spoilage was detected within 15 days. Consequently, the BC–AgNPs composites with Ag concentration <2% are suitable as a lining of regular food packaging material in order to prolong shelf life till one month (Adepu and Khandelwal 2018). TS of CNC/Ag/ALG bio-NC films designed by Yadav et al. (2019) increased up to 57%, while WVP decreased up to 36% compared with neat ALG films and the bio-NC films also showed improved UV and water barrier properties than the pure ALG films. PVA added to the antimicrobial films fabricated by incorporating AgNPs into NC at concentration 3 wt% contributed to 20-fold rise in the elongation at break of the films compared to pure NC film, improved oxygen barrier capacity, and a moderate improvement of WVP was observed as well. Moreover, such NC films exhibited significant antimicrobial activities against *E. coli*, showing growth inhibition of naturally present bacteria for at least 10 days at 4 °C (Wang et al. 2020b). A biodegradable packaging film based on CMC/PVA-zeolite doped with Au^{3+} possessed TS up to 8.69 kgf/mm^2 compared to 2.05 kgf/mm^2 of the neat CMC/PVA film; NC fim showed enhanced water vapor transmission and gas transmission rate due to the presence of zeolite doped with Ag^+ or Au^{3+} and exhibited improved antimicrobial properties (Youssef et al. 2019b).

Cellulose-based papers modified with Ag-TiO_2 NCs tested as packaging were found to be most effective in the preservation of bread nutritional compounds, while those modified with Ag–TiO_2–zeolite NC were able to prolong the bread microbiological safety for 10 days at 20 °C and for 12 days at 4 °C, i.e. 2 days longer than the cellulose-based papers modified with Ag-TiO_2 NC (Mihaly-Cozmuta et al. 2017). A blend suspension of wheat gluten containing 7.5% CNCs and 0.6% TiO_2 NPs applied to coat commercial packaging unbleached kraft paper with three coating layers resulted in an increase in breaking length and burst by 56 and 53%, respectively and papers coated with suspension containing TiO_2 NPs showed >98.5% decrease in number of viable bacteria compared to TiO_2 NPs-free coated paper (El-Wakil et al. 2015).

The NC of agar and CMC with MMT modified by Ag showed strong antibacterial activity against *E. coli* and *Bacillus subtilis* indicating its suitability to preserve food by controlling foodborne pathogens and spoilage bacteria when used as packaging material (Makwana et al. 2020). Cellulose acetate-based nanobiocomposite films containing green-synthesized AgNPs/gelatin-modified MMT nanofiller and thymol showing not only improved TS and oxygen barrier, antioxidant properties and antimicrobial activities against bacteria and fungi suitable for active food packaging use were designed by Dairi et al. (2019).

Addition of increasing concentrations of CuO NPs (1, 1.5, and 2%) to bio-NCs based on the biodegradable branched polysaccharide kefiran and CMC increased contact angle and ultimate TS and decreased WVP and elongation at break; improved color parameters and percentage of light transmission with increasing CuO NPs concentration and inhibitory effects against *E. coli* and *S. aureus* were estimated as well indicating that such NCs can be utilized in food packaging (Hasheminya et al. 2018). In bio-NCs films based on kefiran-CMC carbohydrates with incorporated CuO NPs and *Satureja khuzestanica* EO the simultaneous application of CuO NPs and EO pronouncedly enhanced the physical and mechanical properties of the films, caused synergistic effect on antimicrobial properties against *E. coli* and *S. aureus* and considerably changed the color parameters and percentage of UV and visible light transmission (Hasheminya et al. 2019).

Films based on BC modified by polypyrrole-ZnO NPs NC, which can be applied in antioxidative food active packaging and smart packaging, were designed by Pirsa et al. (2018). Zhao et al. (2017) developed hierarchically structured cellulose@ZnO NCs based on the formation of hierarchical three-level structures induced by self-assembly, namely cellulose/ZnO nanofibers, layers, and microfibers, and in the final step, ZnO MPs were deposited onto the surface of cellulose/ZnO microfibers. As the crucial driving force for the formation of cellulose/ZnO nanofibers, the electrostatic attraction between cellulose and ZnO was estimated. Such cellulose@ZnO NC showed increased antibacterial activities against *E. coli* and *S. aureus* and could be applied in food packaging materials. Poly(3-hydroxybutyrate) (PHB) modified by BC nanofibers using plasma treatment showed an increase of stiffness and strength as well as improved antibacterial activity reflected in growth inhibition of *E. coli* (by 63%) and *S. aureus* (44%), respectively. Application of the ZnO plasma coating manifested as continuous layer of self-aggregated ZnO NPs on PHB surface strongly affected the mechanical and thermal properties of PHB-BC NC and completely inhibited *S. aureus* growth (Panaitescu et al. 2018).

4 Conclusion

The population of our planet is growing rapidly, so it is necessary to ensure the production of the necessary amount of healthy crops, but also to focus on reducing food waste by extending the shelf life of food. Therefore, the use of suitable packaging that has suitable mechanical properties, thermal stability, gas barrier properties, and electrical conductivity and exhibits notable antimicrobial activity able to reduce spoilage as well as eliminate negative effects on human health is necessary. Currently, mass-used plastic packaging is not biodegradable and causes enormous environmental pollution. Moreover, various toxic agents are released during its combustion. For example, during the combustion of polyethylene, polypropylene, and polystyrene, toxic monomers of these plastics are formed, which have a negative effect on the nervous system and blood circulation. Although some plastic packagings can be recycled, a significant part accumulates in landfills, but also reache the seas and oceans, where they endanger marine animals in the ingestion of plastic waste. The solution is an effective transition to the use of biodegradable biopolymers—materials from natural renewable sources (very often residues from other products, i.e. reuse of existing waste), which include cellulose and chitosan. The rapid development of nanotechnologies has enabled the production of efficient nanocomposites, based on the incorporation of so-called "nanofillers" (e.g., essential oils, metal NPs, cellulose nanofibers, cellulose whiskers, etc.) into a matrix of biopolymers, thereby improving the mechanical, barrier, and antimicrobial properties of nanocomposite films that can be used as biodegradable packaging or edible coatings. Instead application of synthetic preservatives, prolonging the shelf life of foods can be achieved by incorporating compounds with antimicrobial activity in their bulk, but mainly in nanosized form into biodegradable films from natural sources used as packaging. By appropriate selection of the nanocomposite components, the prepared film can act as an active/intelligent coating that is able to monitor changes in temperature, pH, various decomposition products, or the presence of bacteria in a real time. Let us therefore believe that these more environmentally friendly and at the same time more food- and consumer-protective packaging will, after thorough toxicological and environmental tests, become a common packaging in which food and other products intended for consumption will be packed.

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Chapter 6
Nanotechnology for Biofuels: Progress and Pitfalls

Avinash P. Ingle, Indarchand Gupta, and Mahendra Rai

Contents

1 Introduction

The extensive use of fossil fuels and continuous depletion in their reserves has posed various severe challenges like environmental pollution, emission of greenhouse gases, problems in fulfillment of future energy demands, etc. (Srivastava

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2019). In this sense, biofuel production has become much more important due to its other advantages, including its low carbon footprint (Ramos et al. 2016). It is believed that biofuels have the potential to replace the need of fossil fuels. Biofuels are renewable energy sources usually produced from biomass and different biological sources, such as fuelwood, charcoal, livestock manure, microbial biomass, agricultural waste and its byproducts, energy crops, etc. (Perea-Moreno et al. 2019). These fuels can be found in solid, liquid, and gaseous forms. Among these, solid biofuels usually contain fuelwood, charcoal, and wood pellets; liquid biofuels comprised of bioethanol, biodiesel, etc.; however, gaseous biofuels include biogas (Maishanu et al. 2019).

The biofuels have got considerable attention from the scientific community and hence, to date intensive research has been carried out in the area of biofuels to move toward sustainable and renewable energy systems (Perea-Moreno et al. 2019). It is true that biorefining (biofuel) industries are rapidly growing and are believed to have a significant role in managing various environmental concerns including pollution and climate change, in addition to the production of renewable energy (Rai and Da Silva 2017). Nonetheless, for many years, biofuels or bioenergies' projected contributions to the global energy supply have remained relatively constant, accounting for about 10–11% of the overall global supply of primary energy (Maishanu et al. 2019).

Currently, biofuels produced from nonfood feedstocks offer a promising alternative due to their universal availability, noncompetitive nature toward food crops, and low cost. Nevertheless, the production of biofuels from such feedstock has some disadvantages such as energy-intensive processes, tedious downstream processing, higher production cost, etc. (Balan 2014; Sikarwar et al. 2017). The development of state-of-the-art biorefining technologies by improving the different components of the biofuel industry must therefore be completed soon. These include the biomass and feedstock treatment process, the design of reactors, the quality of output, process optimization, production costs, and the availability of different biofuels on the market (Hussein 2015).

In this context, nanotechnology that is considered as the most rapidly emerging science has the potential to build robust nanotechnology-based systems with long-term stability and low input cost. The reports available proved that nanotechnological solutions can be effectively used in the enhanced, sustainable, and economically viable production of biofuels (Rai et al. 2016). Currently, various nanomaterials have been fabricated and used directly or indirectly for biofuel and energy-related applications (Trindade 2011). The exceptional properties of nanomaterials such as their high surface area, high degree of crystallinity, catalytic activity, stability, adsorption capacity, etc. make them potential candidates for biofuel production. Nowadays, nanomaterials such as magnetic nanoparticles attracting considerable focus because these can be recover and reused for multiple reactions due to their magnetic nature (Ingle et al. 2018, 2020a, b; Abd-Elsalam et al. 2019). The investigations done so far suggested that nanomaterials can be successfully used in various technologies and applied in biofuel production such as pretreatment of feedstocks (Ingle et al. 2018); enzymatic hydrolysis of pretreated biomass (Rai et al. 2019), transesterification, anaerobic digestion, pyrolysis, gasification, hydrogenation, etc.

(Nizami and Rehan 2018). Moreover, it was reported that these technologies singly or in combination found to be efficient, economical, and environment friendly. Nevertheless, most of these developments are still used at a laboratory and pilot scale and would be a promising way forward when implemented on a commercial scale to replace traditional systems. The purpose of this chapter is to discuss the current and significant applications of different nanomaterials in biofuel production. The development of groundbreaking nanotechnology in biofuels production and various related challenges are also addressed.

2 Different Generations of Biofuels

Depending on the utilization of different feedstocks, biofuels can be divided into three major generations (Fig. 6.1) as discussed below.

2.1 *First-Generation Biofuels*

The production of first-generation biofuels usually involved the use of food-based feedstocks such as vegetable oils, animal fat, sugar, starch, etc. (Cherubini 2010). They are commonly used for the production of biodiesel, bioethanol, biomethanol, biogas, and biobutanol (Dahiya et al. 2018). Among these, sugarcane, sugar beet, and starch found in corn/wheat crops were commonly used for the production of bioethanol. Whereas, biodiesel is mostly produced from oil-based crops like rapeseed, soybeans, rapeseed, and palm oil (Guan et al. 2007; Banković-Ilić et al. 2012). Corn or maize (*Zea mays*) is one of the highly cultivated grains across the globe (FAO 2020). The enzymatic hydrolysis of corn converts the glucans from corn to

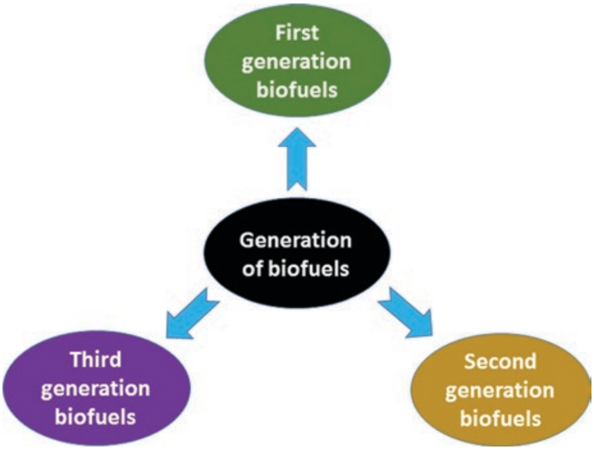

Fig. 6.1 Schematic representation of different generations of biofuels

glucose, which after fermentation yields bioethanol with the use of yeasts (Schwietzke et al. 2009). Corn can also be used to produce biodiesel. The corn oil can be obtained from whole ground kernels, germ, and whole stillage by mechanical, chemical, enzymatic methods. The food crops like sugarcane and sugar beet contain high content of sucrose and hence they are used for the production of sugar (Lajolo et al. 2020). Approximately, 12–20% of sugar is present in beet and hence, it is an important feedstock for the biofuel (bioethanol) production (Marzo et al. 2019). All of these methods have their own advantages and drawbacks.

Soybean (*Glycine max*) is another important first-generation feedstock traditionally used for the production of biodiesel. During this process, the soybean oil is extracted from grains, refined, abd subjected to transesterification process, thus, producing biodiesel and glycerin (Barreiros et al. 2020). Commonly, homogenous and heterogeneous transesterification catalysis approaches are used for the production of biodiesel from soybean oil. Homogeneous catalysis is a simple, rapid, and high-yielding process, whereas, heterogeneous catalysis process is an eco-friendly alternative (Farobie and Matsumura 2017; Fonseca et al. 2019). Moreover, it is important to note that the biofuel production from different feedstocks varies, depending upon country, climate, availability of technological expertise, etc. (Alexiades et al. 2018). The major issue with the use of first-generation biofuels is these feedstocks are food-based and generally used for consumption by large population. Therefore, utilization of such feedstocks for biofuel production may compete for food which may lead to rise in food prices.

2.2 Second-Generation Biofuels

The second generation of biofuels has gained considerable attention in the world, as food and food products do not compete with the feedstocks used for the production of such biofuels. It mainly involves the use of lignocellulosic biomass and other nonedible crops such as husks, bagasse, shells, cobs, leaves straw, stalks, energy crops, etc. (Gírio et al. 2010). Among these, lignocellulosic biomasses are mostly preferred for biofuel production under this category. Lignocellulosic biomasses are rich in carbohydrate polymers such as cellulose and hemicellulose which contains high amount of fermentable sugar which can be easily used for the production of biofuels like bioethanol (Philippini et al. 2017). Lignocellulosic materials can be obtained from sugarcane, switchgrass (*Panicum virgatum*), *Miscanthus*, *Arundo* donax, and bamboo etc. (Ballesteros and Manzanares 2019). Besides, starchy biomass is another feedstock used for the production of second-generation biofuels. It is mainly obtained by processing of corn, rice, wheat, and soybean. Oily and protein fraction obtained from seeds can be used for biodiesel production (Verma and Kumar 2020).

2.3 Third-Generation Biofuels

Third-generation biofuels mainly include biodiesel and bioethanol, which are produced from algae (Bhatia et al. 2020). Algae is considered as important feedstock because it can be grown abundantly in laboratory and hence, higher productivity of biofuels can be achieved as compared to plants such as corn and switchgrass (Chung et al. 2011). Depending upon the species, algae consist of varying amount of carbohydrates, proteins, and lipids. The carbohydrate-rich algae are preferred for the production of bioethanol, whereas microalgae having high concentration of lipids can be used for the biodiesel production (Ramachandra and Hebbale 2020; Aziz et al. 2017).

3 Nanotechnology for Biofuels

It is a well-known fact that in recent past utilization of nanotechnology in general and nanomaterials in particular for biofuels production have been tremendously increased due to their several outstanding benefits over conventional methods. It was reported that nanotechnology can play a crucial role in the modification of different conventional technologies routinely used biofuel production. Recent progress of nanotechnology in the production of different biofuels has been briefly discussed below.

3.1 Nanotechnology in Bioethanol Production

Bioethanol is one of the most important biofuels among the liquid fuels. The production of bioethanol from nonfood feedstocks such as a variety of biomasses, waste from various industries, etc. has gained considerable interest in the past few decades (Bušić et al. 2018). To date, many conventional technologies have been developed and used in the production of bioethanol from above-mentioned feedstocks. Usually, the production of bioethanol is performed through three different steps (Ingle et al. 2018). First step is the pretreatment of feedstock, in this step, the feedstock used is subjected to hydrolysis using physical, chemical, and biological methods to break the complex structure of biomass (Kumar and Sharma 2017). The second step is enzymatic hydrolysis, in this step cellulosic pulp obtained after pretreatment of biomass is hydrolyzed using cellulase enzyme to obtain fermentable sugar, i.e., glucose. The final step is fermentation, in which glucose obtained after enzymatic hydrolysis is fermented into ethanol using suitable microorganism (Ingle et al. 2018; Rai et al. 2019). Above-mentioned conventional approaches for bioethanol production are common in practice all over the world, but these techniques have certain limitations such as requirement of specialized equipments (reactors), less efficient, energy-intensive, non-environmental friendly, high input cost, etc.

(Perea-Moreno et al. 2019). Considering the recent progress in the field of nanoscience particularly in biofuel production, it is believed that nanotechnology can play a pivotal role in bioethanol production.

Nanomaterials are reported to have potential applications in both the initial steps of bioethanol production, i.e., pretreatment and enzymatic hydrolysis of feedstock. As far as pretreatment of biomass is concerned, some of the recent studies proved that different nanomaterials (nanocatalysts) can be used as promising alternative to conventional catalysts commonly used for pretreatment of feedstocks (Ingle et al. 2018; Arora et al. 2020). Usually, the interaction of nanomaterials used in the pretreatment improves the chemistry of the biomass at a molecular level (Schell et al. 2003). Currently, functionalized nanomaterials instead of normal nanomaterials are most commonly used as solid acid catalysts which mainly involved acid-functionalized magnetic nanoparticles, carbon-based nanoparticles, mesoporous silica nanoparticles, etc. Qi et al. (2018) developed a novel nanocatalyst using hydrothermal carbonization approach using microcrystalline cellulose and sulfuric acid. Further, its efficacy in pretreatment of corncob was evaluated; the results obtained showed a promising activity, which was confirmed from the generation of high amount of xylose (78.1%), the liberation of high amount of xylose indicated the removal of hemicellulosic fraction from biomass. Most recently, Ingle et al. (2020a, b) demonstrated catalytic efficiencies of two different acid-functionalized magnetic nanocatalysts, i.e., alkylsulfonic acid-functionalized magnetic nanoparticles and butylcarboxylic acid-functionalized magnetic nanoparticles for the pretreatment of sugarcane bagasse and sugarcane straw. The findings obtained demonstrated the positive catalytic efficacy of the magnetic nanocatalyst compared with the usual acid catalyst. In addition, these magnetic nanocatalysts were also found to be recoverable and reusable for the next two cycles of pretreatment and to remain active with little decrease in catalytic efficiency. Apart from these, there are a few reports which suggested the application of nanomaterials in biomass pretreatment, e.g., sulfonated magnetic carbonaceous acid nanoparticles in the hydrolysis of various lignocellulosic biomasses such as jatropha, bagasse, and Plukenetia hulls (Su et al. 2015), sulfonic acid functionalized silica-coated crystalline Fe/Fe_3O_4 core/shell magnetic nanoparticles in the hydrolysis of lignocellulosic biomass (Wang et al. 2015).

Similarly, nanotechnology in general and nanomaterials in particular reported to play important role in enzymatic hydrolysis of biomass. Generally, cellulase enzyme in free form is used for the enzymatic hydrolysis, which cannot be recovered and reused at the end of reaction and hence, initial input cost of conventional enzymatic hydrolysis is high. This problem can be easily overcome with the help of nanotechnology, i.e., through the application of nanomaterials as a solid support for the immobilization of cellulase enzyme. Such immobilization would help to design an efficient and economically viable nanobiocatalysts for the enzymatic hydrolysis of biomasses with facility of easy recovery and reuse for multiple reactions (Rai et al. 2019).

To date, different kinds of nanomaterials such as metal oxide nanoparticles, magnetic nanomaterials, etc. have been used for the immobilization of cellulase recovered from different sources. Cherian et al. (2015) successfully immobilized cellulase obtained from *Aspergillus fumigatus* JCF on manganese oxide nanoparticles (MnO_2NPs) and further used for enzymatic hydrolysis. It was reported that MnO_2NPs can act as a superior support for the cellulase immobilization and also enhanced the catalytic activity of enzyme. Similarly, in another study, cellulase immobilized on cobalt oxide nanoparticles (Co_3O_4NPs) also reported to play effective role in hydrolysis of pretreated miscanthus leaves. Moreover, immobilized cellulase can be reused for multiple cycles of hydrolysis and it was found that it can retain 75% of the activity even after fourth cycle (Cherian et al. 2017). Like, metal oxide nanomaterials, different magnetic nanostructures are gaining huge interest as a potential support for immobilization of a variety of cellulase because these nanobiocatalysts have added advantages of efficient recovery and reuse due to their strong magnetic nature.

3.2 Nanotechnology in Biodiesel Production

Biodiesel is a renewable fuel which is commonly produced from vegetable oils, microbial oils, animal fats, and waste oils through transesterification reactions using different homogeneous and heterogeneous catalysts such as enzyme catalysts, base catalysts, acid catalysts (Ingle et al. 2020c). Like bioethanol, nanotechnology reported to have enormous applications in biodiesel production. In this context, different nanomaterials have been used as effective catalysts in transesterification reactions which are the basic reactions used for biodiesel production. Nanocatalysts have several advantages over other conventional catalysts used in biodiesel production which mainly include good selectivity, high reactivity, high yield, reduction of the reaction time, and recovery and reuse of catalysts after the esterification process (Ingle et al. 2020c).

Different kinds of nanomaterials have been successfully exploited as nanocatalysts in the transesterification of various feedstocks which mainly include metal-oxide-based nanocatalysts, magnetic nanocatalysts, nanohydrotalcites, nanozeolites, etc. Among these, the metal-oxide-based nanocatalysts are considered the most promising as far as biodiesel conversion is concerned. Banković-Ilić et al. (2017) demonstrated the effective use of different forms of calcium oxide (CaO) nanocatalysts, e.g., neat, doped, loaded, etc. or waste for transesterification of different feedstocks. It was observed that among tested nanocatalysts, neat CaO nanocatalysts showed low ability to form biodiesel which was overcome by using doped and loaded CaO-based nanocatalysts. Similarly, Bharti et al. (2019) evaluated the catalytic efficacy of CaO nanocatalysts in the production of biodiesel from soybean oil. After optimization of various reaction parameters, maximum conversion of biodiesel (97.61%) was reported at catalyst amount of 3.675 wt%, alcohol to oil molar ratio of 11:1, and reaction temperature of 60 °C for 2 h. In another study, Degfe et al. (2019) demonstrated the production of biodiesel from waste cooking oil using CaO nanocatalysts. The highest conversion of waste cooking oil to biodiesel, i.e., 96% was recorded at 50 °C, 1:8 waste cooking oil to methanol ratio, 1 wt% catalyst load for 90 min reaction time.

Similar to CaO nanocatalysts, magnesium oxide (MgO) nanocatalyst synthesized through solgel method was found to be effective in the production of biodiesel from waste cooking oil. The maximum yield of 80% at 2% w/w MgO nanocatalyst, methanol to oil molar ratio of 10:1 (v/v), at 60 °C for 2 h, stirring rate of 250 rpm, and calcination temperature of 600 °C was recorded (Amirthavalli and Warrier 2019). Moreover, Esmaeili et al. (2019) reported the application of MgO nanocatalyst in the conversion of *Moringa oleifera* seeds oil in biodiesel through transesterification reaction. A comparatively higher biodiesel yield (93.69%) with the optimum reaction conditions like methanol-to-oil molar ratio of 12:1, and 1 wt% catalyst loading, at 45 °C for 4 h of reaction time was recorded.

Besides, various other metal-oxide heterogeneous nanocatalysts such as sulfated zirconium oxide (ZrO_2) and ZrO_2-based bifunctional heterogeneous nanocatalysts have been used for the production of biodiesel from *Jatropha curcas* L. oil (Raia et al. 2016) and microalgae (*Nannochloropsis* sp.) (Abd Rahman et al. 2019), respectively. In another study, Baskar and Soumiya (2016) suggested the use of ferromagnetic (Iron (II) doped) zinc oxide (ZnO) nanocatalysts for the production of biodiesel which were synthesized using coprecipitation method. Further, the authors examined the catalytic efficacy of these nanocatalysts in esterification of castor oil in multiple cycles after recovery of this magnetic nanocatalyst. The maximum yield of 91% was recorded up to fourth cycle of reaction, however, after that it was found to be reduced to 87%. This study proposed the recovery and reuse of same ZnO based nanocatalyst for multiple cycles of esterification.

Apart from metal oxide nanocatalysts, nanohydrotalcites are another kind of materials which are quite prevalent in nature and these are gaining growing interest day by day in the production of biodiesel (Ingle et al. 2020c). Nanohydrotalcites are the anionic clays or aluminum–magnesium-layered double hydroxides. Deng et al. (2011) synthesized hydrotalcite-derived nanoparticles with Mg/Al oxides by a coprecipitation method using urea as precipitating agent and further evaluated their catalytic efficacy for transesterification of Jatropha oil. The promising catalytic activity with 95.2% yield of biodiesel was reported. Moreover, Dias et al. (2012) demonstrated application of cerium modified Mg–Al hydrotalcites in the methanolysis of soybean oil for the production of biodiesel, the results obtained showed up to 90% conversion of biodiesel using this catalyst. These reports confirmed that nanohydrotalcites can be effectively used as potential catalysts for the ecofriendly production of biodiesel.

Zeolites are another kind of catalysts which reported to have promising applications in industrial production of biodiesel due to the presence of strong acid sites, high surface area, shape selectivity, and unique molecular sieving properties (Al-Ani et al. 2018). Therefore, considering the effective catalytic applications of zeolites, currently scientists have designed and fabricated nanozeolites for enhanced production of biodiesel. de Vasconcellos et al. (2018) evaluated the efficacy of nanozeolites with various crystallographic structures functionalized with (3-aminopropyl) trimethoxysilane (APTMS) and cross-linked with glutaraldehyde as solid supports for immobilization of lipase obtained from *Thermomyces lanuginosus* (i.e., enzyme–nanozeolite complexes) for biodiesel production from microalgae oil. The results obtained revealed that thus synthesized enzyme–nanozeolite complex is highly effective in conversion of microalgae oil to biodiesel, more than 93% of biodiesel yield can be obtained using these lipase-nanozeolite complex. All the above-discussed studies proved that nanotechnological solutions can be used for enhanced, efficient, economically viable, and sustainable production of biodiesel from a variety of feedstocks.

3.3 Nanotechnology in Biogas Production

The production of biogas from wastes via anaerobic digestion (AD) is the most common approach at the same time it is very challenging. Actually, slow rate of biodegradation and the presence of impurities in biogas propose the whole process for several risks (Pieta et al. 2018). However, recent research studies in the field of nanotechnology indicated that application of nanoparticles in the AD process can influence the performance and stability of the process (Abdelwahab et al. 2020). Among various nanomaterials, metal oxide nanoparticles due to their unique physical and chemical properties like small size, high surface to volume ratio, better surface structure, strong catalytic action, and solubility reported to have promising application in enhanced biogas production (Yang et al. 2012; Gottschalk et al. 2013).

Considering these facts, Abdelsalam et al. (2016) studied the potential of iron oxide (Fe_3O_4) nanoparticles (20 mg/L) on biogas and methane (CH_4) production from cattle dung slurry. The findings recorded showed that the addition of Fe_3O_4 nanoparticles at above-mentioned concentration increased the biogas and CH_4 production by 1.7 and 2.0 times, respectively. In another study, Wang et al. (2016) demonstrated that the addition of 100 mg/g of total suspended solid (TSS). Fe_2O_3 nanoparticles also increase CH_4 production by 117%. Similarly, recently, Hassanein et al. (2019) studied the efficacy of iron oxide (Fe_3O_4) nanoparticles on biogas production from poultry litter at three different concentrations, i.e., 15, 50, and 100 mg/L. It was reported that the application of 100 mg/L of Fe_3O_4 nanoparticles enhanced the production of biogas (CH_4) by 25.6% as compared to the control.

On the contrary, there are few studies which reported negative effect of nanoparticles on production of biogas. Mu et al. (2011) evaluated the effect of titanium dioxide (TiO_2), silicon dioxide (SiO_2), Aluminium oxide (Al_2O_3), and zinc oxide (ZnO) nanoparticles on the AD of waste-activated sludge at various concentrations (i.e., 6, 30, and 150 mg/g TSS). The results obtained showed that CH_4 production was not affected by the addition of TiO_2, SiO_2, and Al_2O_3 nanoparticles at all the above-mentioned concentrations, as well as by the addition of 6 mg/g TSS ZnO nanoparticles. However, it significantly decreases to 77.2% and 18.9% upon the addition of 30 and 150 mg/g TSS of ZnO nanoparticles, respectively. These findings revealed that the solubilization process was not affected by addition of any kind of nanomaterials but hydrolysis, acidogenesis, and methanogenesis can be affected by high dose of ZnO nanoparticles. Similar results were recorded by Alvarez and Cervantes (2012) when they studied the effect of γ-Al_2O_3 nanoparticles on the AD process of granular sludge. The above-discussed studies suggested that application of nanomaterials in biogas production can affect the process positively or negatively. Therefore, selection of nanomaterials and optimization of their concentration is very important to achieve the high yield of biogas.

4 Challenges in the Application of Nanomaterials for Biofuel Production

As discussed in earlier section, nanoparticles offer significant contribution to the production of biofuels. In general, the production and applications of nanomaterials in various products may lead to their presence in the environment. They may be released into the air, soil, and water bodies. Hence, the concerns regarding their human and environment health effects need to be considered (Gupta et al. 2012). Many studies have reported that nanoparticles can be released into the environment. Nanoparticles released into the water bodies can interact with aquatic flora and fauna. In aquatic medium, they readily release ions, causing toxic effects. For instance, it has been reported that the stable colloidal suspension of nanoparticles interacts with the microalgae (Sadiq et al. 2011). It is followed by the uptake of nanoparticles by microalgae cells, resulting into the toxic effects on them. Aluminium oxide nanoparticles have been shown to inhibit the growth of the microalgae. It shows the shading effect of nanoparticles on microalgae cell surface thereby inhibiting the photosynthesis activity. Chen et al. (2014) reviewed the toxicity of nanomaterials on biomass and concluded that cerium dioxide nanoparticles show higher toxicity to both thermophilic and mesophilic microorganisms as compared to the silver nanoparticles, TiO_2 nanoparticles, aluminium oxide nanoparticles, and SiO_2 nanoparticles. Likewise, there has been focus on the toxic effects of nanoparticles on aquatic plants, in terms of seed germination and root growth. At cellular level, nanoparticles interact with the cell membrane and disturb its integrity. After reaching inside the cell, they induce accumulation of reactive oxygen species. Catalytically active nanoparticles produce reactive oxygen species. The reactive oxygen species induce the oxidative stress and thereby affecting the normal functioning of cells and organs of aquatic organisms. Nanoparticles have also been shown to cause DNA damage. All of these events lead the nanoparticle exposed cells to apoptosis (Gupta et al. 2012; Aziz et al. 2014, 2015, 2016, 2019). These studies suggested that nanomaterials used in biofuel industries can cause toxicity to environment and living forms present in it if released into the environment. Considering the adverse effect of nanomaterials, it is a challenging task to perform their safe applications. Therefore, there is a need to study the toxic effects of nanomaterials and to issue the regulatory guidelines. Such measures can help to use nanomaterials for production of biofuels without risk.

5 Conclusions

Nanotechnology is a leading technology for scientific advancement and provides valuable opportunities for the enhancement of established biofuel technology. The widespread application of nanotechnology in biofuel production is receiving more attention due to several advantages over conventional methods. Nanotechnological approaches are found to be efficient, sustainable, and economically viable. Although nanotechnology has promising applications in biofuel industries, the toxicological studies performed on nanomaterials so far indicated that, nanomaterials used in different processes of biofuel production can be toxic to the living forms in the environment including human beings. Therefore, further extensive studies are necessary to study all the toxicological aspects of nanomaterials. Moreover, additional efforts are required to develop even more efficient nanotechnological processes, so that such technologies can be used as promising alternatives and completely replace the existing conventional methods of biofuel production.

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Chapter 7
Biosynthesis of Nanoparticles from Bacteria and Thallophytes: Recent Advances

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Contents

1 Introduction

Nanotechnology is introduced particularly as an exciting and developing technology at the size of 10^{-9} m, clearing the obstacles among biology, chemistry, and physics. In particular, it is described as the design, description, production, and utilization of

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The original version of this chapter was revised. The name of the author "Hossein Motamed" has been removed. The correction to this chapter is available at https://doi.org/10.1007/978-3-030-61985-5_23

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structures, devices, and systems with controlling the dimension at the range of nanometer (Stylios et al. 2005, Shanti et al. 2011, Rana et al. 2020). At the nanoscale, there are two crucial methods: "Top-down," the manufacturing of nanostructured matters via taking bulk matter and turning it into the favorite shape containing integrated circuit development, and the "Bottom-up" technique, constructing up nanostructures molecule-by-molecule or atom-by-atom viz., nanotubes, and quantum dots (Majumder et al. 2007). Nanotechnology phrase is traced back to the Greek word, meaning "dwarf," while in scientific and technological domains, the prefix "nano" is 10^{-9}, viz. 0.000000001 (Shanti et al. 2011). Richard Feynman, an outstanding physicist, proposed the nanotechnology platform upon his lecture titled as "there is plenty of room at the bottom" at California Institute of Technology. He offered a scientific vision on miniaturizing the materials through manipulation and control of their size at nanoscale, well known as "Nanotechnology" (Sahoo et al. 2007). He proposed the technology to construct nano-object, atom-by-atom, and molecule-by-molecule utilizing the toolbox (Ochekpe et al. 2009). Feynman lecture gave birth to some new definitions such as nanotechnology, nanoscale, nano-object, and nano-engineering, instead of phrases like small size, small things, and miniaturization (Feynman 1960). Notwithstanding the popularity of nanotechnology in contemporary years, it cannot be considered as a novel science, given some historical instances such as Lycurgus glass cup in British Museum, seemed to be jade green in natural light and red color when exposing to the bright light, due to the utilization of NPs of silver and gold (Smith 2006b), and carbon in manufacturing the vehicle tires, while the red and yellow colors are seen at sunsets considering the existence of NPs in the atmosphere (Smith 2006a). Some other ancient examples ascribed to nanotechnology can be mentioned: the weapons fabricated by Indian craftsmen and artisans utilizing nanotechnology, the cave paintings attributed to 2000 years ago, famous sword of Tipu Sultan with carbon NPs, and Ajanta paintings. In 1902, Richard Zsigmondy conducted the first seeing and scale measurements of NPs utilizing an ultramicroscope. Norio Taniguchi, the University of Tokyo, was the first to utilize the term "nanotechnology" to explain the capability of engineering materials at the nanoscale (Miyazaki and Islam 2007). In the 1980s, the possibility of imaging the individual atoms or molecules in addition to their manipulation, prompted considerable development in nanotechnology (Cortie 2004). Indeed, the present popularity of nanotechnology owes to the speeches and books of Eric Drexler in 1986 titled as "Engines of creation: the coming era of nanotechnology." In addition, carbon nanotubes were discovered by Saumio lijima in 1991. Flowingly, the national nanotechnology initiative was introduced by the United States in 2000, all opening the window for the advancement in nanotechnology (Verma et al. 2011a). There is an increasing need to grow clean, nontoxic, and eco-friendly techniques (green chemistry) for the synthesis of NPs. The use of biological organisms in this field is quickly attracting a lot of attention, thanks to its increasing success and simplicity of NPs formation.

Nanotechnology is broadly expected to provide economically favorable products and technically efficient solutions in different fields of use (Verma et al. 2011a). Now, although nanotechnological products are accessible in markets, it is yet a very serious field of fundamental study. In different words, nanotechnology implies a growing influence on life science (Matija 2004). It is ascribed to a group of technologies utilized to various existing industries, generally in three overlapping areas including nanomaterials, nanobiotechnology, and nanoelectronics. Therefore, it is used in a variety of areas such as electronics, environment, metrology, materials, robotics, transport, healthcare, pharmaceutics, information technology, agriculture, etc. (Dibirdik et al. 2010; Mehrotra et al. 2010; Lukianova-Hleb et al. 2011, Usman et al. 2020, Shafiq et al. 2020). Nanotechnology is frequently considered as a rather young field, considerably improving ways of life. In life science, its applications contain medical devices, pharmaceuticals, gene therapy, biotechnology, diagnostics, tissue engineering, and drug delivery (Nakamura et al. 2011; Nanjwade et al. 2011; Pandurangappa and Lakshminarasappa 2011; Elgindy et al. 2011; Patil et al. 2011). Because of the wide variety of applications of nanotechnology, it possesses various advantages in different countries, such as cheaper and clean energy; improved transport systems; cleaner drinking water, due to nanofilters capable of entrapping toxins and organisms; improved healthcare system owing to the introduction of nanotechnology-aided systems for diagnosis, monitoring, and treatment of terrible diseases; cleaner environment via removing the pollutants through remediation; construction of novel products while modification of present products at the nanoscale, leading to an industrial revolution that may change human life drastically (Macoubrie 2004). Despite the potential uses of nanotechnology, it has some hazards; for example, NPs like cobalt, copper, and so on present inflammatory and toxic impacts on human cells (Roco 2003), the fatality of the chemical weapons made-up from NPs are more than the current ones, carbon nanotubes—cytotoxic causes granulomas in laboratory animals lungs (Oberdörster et al. 2005). Because of the vast uses and benefits of nanotechnology in different fields, social, ethical, and safety researches ought to show how to maximize the advantages and decrease the hazards (Shanti et al. 2011). New synthesis techniques have been a remarkable field in nanoscience and technology for NPs (e.g., quantum dots, metal NPs, carbon nanotubes, graphene, and their compounds) over the last decade (Hoffmann et al. 1995; Huang et al. 2006; Kim et al. 2007; Laurent et al. 2008; Livage et al. 1988; O'Neal et al. 2004; Oskam 2006; Sastry et al. 2003; Su et al. 2014, Ghahari et al. 2018). Two separate basic techniques of synthesis (namely, top-down and bottom-up techniques) were studied in the current literature to achieve NPs of the desired shapes, sizes, and functionalities (Fig. 7.1). In the past, NPs were prepared via several methods of synthesis such as sputtering, ball milling, lithographic techniques, and etching (Guozhong 2004). In addition, the use of a bottom-up method (wherein NPs are developed from simpler molecules) includes numerous approaches such as solgel processes, chemical vapor deposition, spray pyrolysis, atomic or molecular condensation, and laser pyrolysis (Singh et al. 2018). Remarkably, NPs morphological parameters (e.g., shape and size) can be controlled via changing the reactions' conditions (e.g., pH and temperature) and chemicals' concentrations. In any case, if these synthesized NPs are subjected to the particular uses, they may encounter the following challenges or limitations: (i) absence of comprehension in key mechanism and modeling factors, (ii) stability in hostile surroundings, (iii) need for skilled operators, (iv) expansive analysis requirements, (v) bioaccumulation/toxicity characteristics, (vi) problem in structures and assembling of devices, and (vii) recycling/reusing/regenerating. Besides, in the real world, it is favorable that the properties, behavior, and types of NPs ought to be promoted to reach the above-mentioned topics.

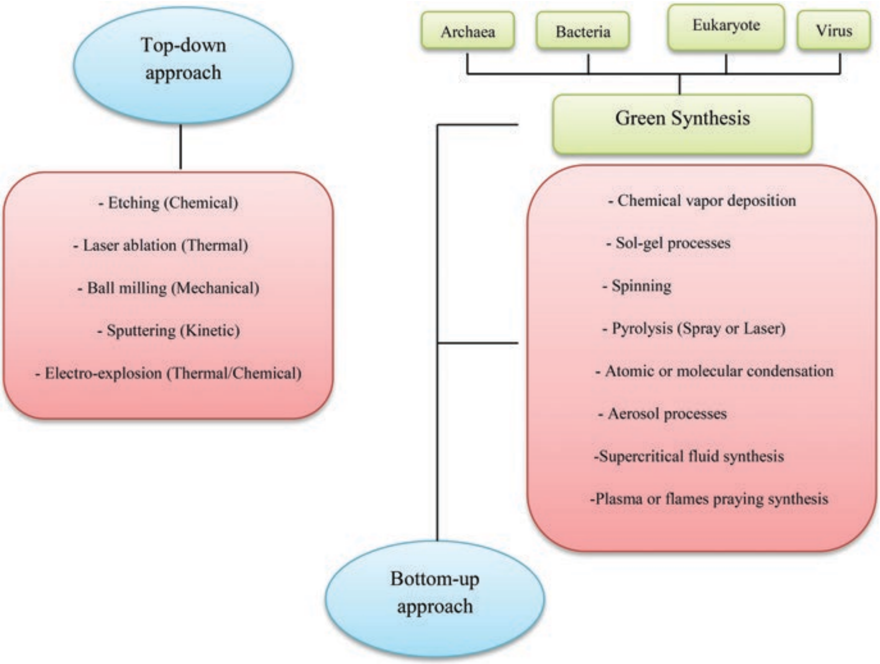

Fig. 7.1 Various synthesis methods accessible for the preparation of metal NPs

However, these limitations create novel and extraordinary opportunities in this recently emerged research field (Singh et al. 2018).

Fundamentally, the green production of NPs, synthesized via regulation, control, clean up, and remediation procedures will straightly modify their eco-friendly aspect. Therefore, a number of fundamentals of green synthesis can be demonstrated with some maneuvers, such as inhibition/minimization of waste, a decrease of derivatives/contaminations, as well as the use of safer (or nontoxic) solvent/auxiliaries and a renewable feedstock (Singh et al. 2018). Through the application of the green synthesis methods, the unwanted or harmful by-products are not produced. To achieve this aim, the use of natural resources (such as organic systems) and ideal solvent systems is vital. Metallic NPs were synthesized using green synthesis technique, leading to the accommodation of different biological materials such as fungi, bacteria, plant extracts, and algae, identified together as biogenic NPs (Fig. 7.2) (Singh et al. 2018, 2020, Grasso et al. 2020; Srivastava et al. 2021). Green synthesis approaches associated with biological precursors are dependent on different reaction factors like pressure, temperature, solvent, and pH (basic, acidic, or neutral). A vast array of studies have been carried out on the main features of such NPs, aiming at using them in antimicrobials, optical imaging, molecular sensing, catalysis, biomedical diagnostics as well as labeling of biological systems (Singh et al. 2018; Srivastava et al. 2021; Maddela et al. 2021).

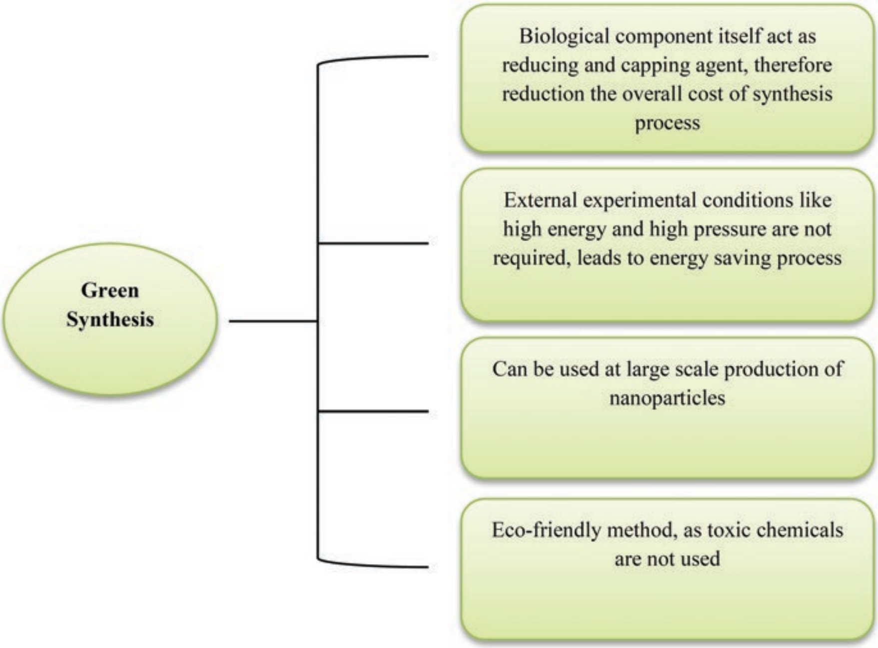

Fig. 7.2 Main advantages of green synthesis approaches

2 Biological Components for Green Synthesis

Numerous physical and chemical synthesis methods need highly toxic reductants, high radiation, and stabilizing agents, potentially causing fatal impacts on the life of both marine and humans. Conversely, the green production of metallic NPs is a single-step (one-pot) environmentally consistent bio-reduction technique needing rather low energy to initiate the reaction. Besides, the stated technique is economical (Dahoumane et al. 2016; El-Rafie et al. 2013, Husen and Siddiqi 2014, Patel et al. 2015, Siddiqi and Husen 2016, Wadhwani et al. 2016).

3 Synthesis of NPs by Bacteria

In the field of NPs biosynthesis, bacteria have attracted noticeable attention among the microorganisms (Table 7.1). *Bacillus subtilis* 168 is capable of reducing Au^{3+} ions, resulting in the production of nano-scaled octahedral gold particles (5–25 nm) inside bacterial cells through incubation of the cells with gold chloride under ambient temperature and pressure conditions (Southam and Beveridge 1994; Beveridge and Murray 1980; Fortin and Beveridge 2000). *Shewanella* algae, a Fe (III)-reducing bacterium, can reduce Au (III) ions in anaerobic environments (Konishi et al. 2004).

Table 7.1 Biosynthesis of different NPs from bacteria and reaction conditions

Microorganism	Nano	Substrate	Shape	Reaction condition Temp (°C)	pH	Time (h)	Size (nm)	Mode of biosynthesis	Reference
Acinetobacter sp.	Fe_3O_4	$K_3Fe(CN)_6 + K_4Fe(CN)_6$	Quasi-spherical	RT	6.4–6.6	24	10–40	Extracellular	Bharde et al. (2005)
	γ-Fe_2O_3+ Fe_3O_4		RT			48	50–150		
	Si/SiO_2	K_2SiF_6	27	27	ND	48	10	Extracellular	Singh et al. (2008)
Aeromonas sp.	Ag	$[Ag(NH_3)_2]^+$	FCC	60	ND	48	6.4	Extracellular	Mouxing et al. (2006)
Arthrobacter globiformis	Au	$HAuCl_4$	Spherical	RT	ND	36–48	8–40	Extracellular	Kalabegishvili et al. (2012)
Azoarcus sp.	Se	Na_2SeO_3	Spherical	30	6.5	168	Anaerobic 90	Intracellular	Fernández-Llamosas et al. (2016)
							Aerobic 174		
Bacillus amyloliquefaciens	Ag	$AgNO_3$	Spherical	33	ND	48	<140	Extracellular	Ghiuţă et al. (2018)
	CdS	$Cd(NO_3)_2 + Na_2S$ + surfactin	Cubic/ Hexagonal/ Spherical	RT	7.2	1	3–4	Extracellular	Singh et al. (2011)
Bacillus brevis	Ag	$AgNO_3$	Spherical	RT	ND	Overnight	41–68	Extracellular	Saravanan et al. (2018)
Bacillus cereus	Ag	$AgNO_3$	Spherical	RT	Neutral	72	11–16	Extracellular	Sunkar and Nachiyar (2012)
	Ag	$AgNO_3$	Spherical	37.5	ND	24	10–30	Extracellular	Prakash et al. (2011)

Microorganism	Nano	Substrate	Shape	Reaction condition			Size (nm)	Mode of biosynthesis	Reference
				Temp (°C)	pH	Time (h)			
Bacillus endophyticus	Ag	$AgNO_3$	Spherical	28	ND	72	5.1	Extracellular	Gan et al. (2018)
Bacillus funiculus	Ag	$AgNO_3$	Spherical	40	ND	1	10–20	Extracellular	Gurunathan et al. (2013)
Bacillus licheniformis	Ag	$AgNO_3$	Hexagonal/ Spherical/ Triangular	25	7.5	72	77–92	Extracellular	Elbeshehy et al. (2015)
	Au	$HAuCl_4$	Nanocubes	RT	ND	48	10–100	Extracellular	Kalishwaralal et al. (2009)
Bacillus megaterium	Ag	$AgNO_3$	Spherical/ Irregular	RT	ND	48	80–98.56	Extracellular	Saravanan et al. (2011)
	Au	$HAuCl_4$	Spherical	26	3.2	4.5	1.9	Extracellular	Wen et al. (2009)
Bacillus methylotrophicus	Ag	$AgNO_3$	Spherical	28	ND	48	10–30	Extracellular	Wang et al. (2016)
Bacillus persicus	Ag	$AgNO_3$	Hexagonal/ Spherical/ Triangular	25	7.5	72	92	Extracellular	Elbeshehy et al. (2015)
Bacillus pumilus	Ag	$AgNO_3$	Hexagonal/ Spherical/ Triangular	25	7.5	72	80	Extracellular	Elbeshehy et al. (2015)
Bacillus safensis	Ag	$AgNO_3$	Spherical	RT	ND	0.13	5–95	Extracellular	Lateef et al. (2016)
Bacillus selenitireducens	Te	Te(IV)	Nanorods	RT	ND	78	~10	Extracellular	Baesman et al. (2007)

(continued)

Table 7.1 (continued)

Microorganism	Nano	Substrate	Shape	Reaction condition Temp (°C)	pH	Time (h)	Size (nm)	Mode of biosynthesis	Reference
Bacillus sp.	Ag	$AgNO_3$	Lattice fringes	RT	ND	168	5–15	Intracellular	Pugazhenthiran et al. (2009)
	Ag	$AgNO_3$	Spherical	RT	ND	24	42–94	Extracellular	Das et al. (2014)
Bacillus subtilis	Ag	$AgNO_3$	FCC	30	4.3	168	6.1	Extracellular	Reddy et al. (2010)
	Ag	$AgNO_3$	Spherical	RT	ND	0.083	5–25	Extracellular	El-Shanshoury et al. (2011)
	Co_3O_4	$CoCl_2$	Rod-shaped	RT	ND	30	~2 to 5	Extracellular	Shim et al. (2011)
	Se	Na_2SeO_3	Spherical	35	ND	48	50–400	Extracellular	Wang et al. (2010)
	TiO_2	$TiO(OH)_2$	Spherical/Oval	60	ND	0.16–0.33	66–77	Extracellular	Kirthi et al. (2011)
				RT		48	20	Extracellular	Gurunathan et al. (2015)
Bacillus tequilensis	Ag	$AgNO_3$	Spherical	60	ND	1			
Bhargavaea indica	Ag	$AgNO_3$	Nanobar/Pentagon/Spherical/Icosahedron/Hexagonal/Truncated Triangle/Triangular	25	ND	48	30–100	Extracellular	Singh et al. (2015)

Microorganism	Nano	Substrate	Shape	Reaction condition			Size (nm)	Mode of biosynthesis	Reference
				Temp (°C)	pH	Time (h)			
Brevibacillus borstelensis	Ag	$AgNO_3$	Cubical	37.5	ND	72	5–15	Extracellular	Kumar and Ghosh (2016)
Brevibacillus formosus	Au	$HAuCl_4$	Spherical	heated in a microwave oven	ND	ND	5–12	Extracellular	Srinath et al. (2017)
Brevibacterium casei	Ag	$AgNO_3$	Spherical	37	ND	24	10–50	Intracellular	Kalishwaralal et al. (2010)
	Au	$HAuCl_4$	Quasi-spherical (structured colony)	RT	ND	72	5–7	Extracellular	Kumar et al. (2008b)
	Co_3O_4	$Co(CH_3CO_2)_2$	Nonspherical/ Spherical	35	ND	48	4–10	Extracellular	Ahmad et al. (2013)
Cupriavidus metallidurans	Au	$HAuCl_4$	Decahedral/ Triangular	30	7	96	20–60	Extracellular	Montero-Silva (2018)
Cupriavidus necator	Pd (0)	Na_2PdCl_4	Rod-shaped	30	7	14	3–30	Intracellular	Bunge et al. (2010)
Deinococcus radiodurans	Ag	$AgNO_3$	Spherical	32	6.8	24	4–50	Extracellular	Kulkarni et al. (2015)
	Au	$HAuCl_4$	Spherical/ Triangular/ Irregular	32	7	8	43.75	Extracellular	Li et al. (2016)
Desulfovibrio desulfuricans	Pd	Na_2PdCl_4 or $Pd(NH_3)_4Cl_2$	Spherical	30	7	0.083	~50	Intracellular	Yong et al. (2002)
Enterobacter aerogenes	Ag	$AgNO_3$	Spherical	80	7	12	25–35	Extracellular	Karthik and Radha (2012)

(continued)

Table 7.1 (continued)

Microorganism	Nano	Substrate	Shape	Reaction condition			Size (nm)	Mode of biosynthesis	Reference
				Temp (°C)	pH	Time (h)			
Escherichia coli	Ag	$AgNO_3$	ND	RT	ND	0.083	28.2–122	Extracellular	Shahverdi et al. (2007)
	CdS	$CdCl_2 + Na_2S$	Polycrystalline wurtzite	25/RT	7.2	4	2–5	Intracellular	Sweeney et al. (2004)
	CdTe	$Na_2TeO_3 + CdCl_2$	Spherical	37	ND	168	2–3.2	Extracellular	Bao et al. (2010)
	Pt	Na_2PtCl_4	Spherical	30	2.3	0.5	2.3 (1%) and 4.5 (20%)	Cell surface	Attard et al. (2012)
				20		0.16			
Exiguobacterium sp.	Ag	$AgNO_3$	Spherical	30	ND	12	5–50	Extracellular	Tamboli and Lee (2013)
Geobacillus sp.	Au	$HAuCl_4$	Quasi-hexagonal	65	7	16	5–50	Intracellular	Correa-Llantén et al. (2013)
Gluconacetobacter xylinus	CdS	$Cd(NO_3)_2 + Na_2S$	Spherical	ND	ND	72	30	Extracellular	Li et al. (2009)
Haemophilus influenza	Ag	$AgNO_3$	Spherical	RT	ND	24	80–101	Extracellular	Ajah et al. (2018)
Klebsiella aerogenes	CdS	$Cd(NO_3)_3$	Spherical	37	ND	ND	20–200	Extracellular	Holmes et al. (1995)
Klebsiella pneumonia	Au	$HAuCl_4$	Spherical	37	ND	24	10–15	Intracellular	Prema et al. (2016)
	Se	$SeCl_4$	Spherical	37	7.2	24	100–550	Intracellular	Fesharaki et al. (2010)
Lactobacillus acidophilus	Se	Na_2SeO_3	Spherical	37	ND	48	15–50	Extracellular	Visha et al. (2015)
Lactobacillus sp.	Ag	$AgNO_3$	Spherical	37	4.4	24	2–20	Extracellular	Ranganath et al. (2012)

Microorganism	Nano	Substrate	Shape	Reaction condition			Size (nm)	Mode of biosynthesis	Reference
				Temp (°C)	pH	Time (h)			
	Ag	$AgNO_3$	Several morphologies	RT	4.4	180	15 and ~ 500	Intracellular	Nair and Pradeep (2002)
Lactobacillus sp.	Au	$HAuCl_4$	Various crystal morphologies	RT	4.4	180	20–50 and >100	Intracellular	Nair and Pradeep (2002)
	$BaTiO_3$	$BaCO_3 + TiO_2$	Spherical	1250	3	5	20–80	Extracellular	Jha and Prasad (2010)
	CdS	$CdCl_2 + H_2S$	Spherical	RT/60/RT	a mildly acidic pH	overnight	2.5–5.5	Intracellular	Prasad and Jha (2010)
	TiO_2	TiO_2	Spherical	RT	ND	96	40–60	Extracellular	Prasad et al. (2007)
	TiO_2	$TiO(OH)_2$	Spherical	60	ND	0.16–0.33	8–35	Extracellular	Jha et al. (2009a)
				RT		12–48			
Lactobacillus sporogenes	ZnO	$ZnCl_2$	Hexagonal	RT	6.0–7.5	9	5–15	Intracellular	Prasad and Jha (2009)
Listeria monocytogenes	Ag	$AgNO_3$	Rod	ND	ND	24	62.07	Extracellular	Soni and Prakash (2015)
			Spherical				29.64		
Lysinibacillus sphaericus	Ag	$AgNO_3$	Spherical	70	12	1.25	5–20	Extracellular	Gou et al. (2015)
Magnetospirillum gryphiswaldense	Au	$HAuCl_4$	Spherical	RT (25)	2.5	1	10–40	Cell surface	Cai et al. (2011)

(continued)

Table 7.1 (continued)

Microorganism	Nano	Substrate	Shape	Reaction condition			Size (nm)	Mode of biosynthesis	Reference
				Temp (°C)	pH	Time (h)			
Marinobacter Pelagius	Au	$HAuCl_4$	Spherical/ Triangular	RT	5–6	24	<10 nm (~ 2–6)	ND	Sharma et al. (2012)
Micrococcus yunnanensis	Au	$HAuCl_4$	Spherical	30	7.8	60	53.8	Extracellular	Jafari et al. (2018)
Morganella sp.	Ag	$AgNO_3$	Spherical	37	ND	20	20	Extracellular	Parikh et al. (2008)
	Cu/CuO	$CuSO_4$	Polydispersed/ vary			49	10–30	Extracellular	Saif Hasan et al. (2008)
Mycobacterium sp.	Au	$HAuCl_4$	Spherical	35	ND	24	5–55	Extracellular	Camas et al. (2018)
Myxococcus virescens	Ag	$AgNO_3$	Spherical	ND	ND	48	7–50	Extracellular	Wrótniak-Drzewiecka et al. (2014)
Nocardia farcinica	Au	$HAuCl_4$	Spherical	100	4	<5–10 s	15–20	Extracellular	Oza et al. (2012)
Nocardiopsis sp.	Ag	$AgNO_3$	Spherical	30	7	96	30–90	Extracellular	Manivasagan et al. (2013)
Nocardiopsis valliformis	Ag	$AgNO_3$	Spherical	RT	7	48–72	5–50	Extracellular	Rathod et al. (2016)
Nostoc linckia	Ag	$AgNO_3$	Spherical	RT	ND	8	5–60	Extracellular	Vanlalveni et al. (2018)
Nostoc sp.	Ag	$AgNO_3$	Agglomerated	RT	7	124	51–100	Extracellular	Sonker et al. (2017)
Ochrobactrum anthropi	Ag	$AgNO_3$	Spherical	RT	ND	28	38–85	Intracellular	Thomas et al. (2014)
Ochrobactrum sp.	Ag	$AgNO_3$	Spherical	RT	ND	28	38–85	Intracellular	Thomas et al. (2014)

Microorganism	Nano	Substrate	Shape	Reaction condition			Size (nm)	Mode of biosynthesis	Reference
				Temp (°C)	pH	Time (h)			
Pantoea agglomerans	Se	Na_2SeO_3	Spherical	25	ND	24	<100	Intracellular	Torres et al. (2012)
Paracoccus denitrificans	Pd (0)	Na_2PdCl_4	ND	30	7	14	3–30	Intracellular	Bunge et al. (2010)
Planomicrobium sp.	TiO_2	TiO_2	Spherical	50	ND	0.16–0.33	8.89	Extracellular	Malarkodi et al. (2013)
				RT		12–48			
Plectonema boryanum	Ag	$AgNO_3$	Spherical	25	5	672	1–15	Intracellular/ Extracellular	Lengke et al. (2007)
			Spherical	60	4.7		1–40		
			Octahedral	100	3.3–4.7		5–200		
Proteus mirabilis	Ag	$AgNO_3$	Spherical	37	ND	24	10–20	Intracellular/ Extracellular	Samadi et al. (2009)
Pseudomonas aeruginosa	Au	$HAuCl_4$	ND	37	ND	24	15–30	Extracellular	Husseiny et al. (2007)
Pseudomonas alcaliphila	Se	Na_2SeO_3	Spherical	28	ND	48	50–500	Intracellular/ Extracellular	Zhang et al. (2011)
Pseudomonas deceptionensis	Ag	$AgNO_3$	Spherical	25	ND	48	10–30	Extracellular	Singh et al. (2016)
Pseudomonas fluorescens	Au	$HAuCl_4$	Spherical	37	5–6.50	24–48	50–70	Extracellular	Rajasree and Suman (2012)
	CuO	$CuSO_4$	Spherical/ Hexagonal	30	Neutral	1.5	49	Extracellular	Shantkriti and Rani (2014)
Pseudomonas putida	Ag	$AgNO_3$	Spherical	RT	ND	0.33	6–10	Extracellular	Gopinath et al. (2017)

(continued)

Table 7.1 (continued)

Microorganism	Nano	Substrate	Shape	Reaction condition Temp (°C)	pH	Time (h)	Size (nm)	Mode of biosynthesis	Reference
	Pd (0)	Na_2PdCl_4	Rod-shaped	30	7	14	3–30	Intracellular	Bunge et al. (2010)
Pseudomonas stutzeri	Ag	$AgNO_3$	Hexagonal/ spherical/ Triangular	30	ND	48	~200	Intracellular	Klaus et al. (1999)
Rhodococcus sp.	Ag	$AgNO_3$	Spherical	RT	ND	18	10	Extracellular	Otari et al. (2012)
	Ag	$AgNO_3$	Spherical	ND	7	72	5–50	Intracellular	Otari et al. (2015)
Rhodopseudomonas capsulata	Au	$HAuCl_4$	Spherical	30	6	48	10–20	Extracellular	He et al. (2008)
Rhodopseudomonas palustris	CdS	$CdSO_4$	Spherical	30	7.2	72	8.01	Intracellular	Bai et al. (2009)
Salmonella typhimurium	Cu	$Cu(NO_3)_2$	Spherical	RT	ND	0.67	49	Extracellular	Ghorbani et al. (2015)
Serratia sp.	Ag	$AgNO_3$	Spherical	ND	ND	ND	~10–20	Extracellular	Mishra et al. (2014)
Shewanella algae	Au	$HAuCl_4$	Shaped rod	25	7	0.5	10–20	Intracellular	Konishi et al. (2006)
	Pt	H_2PtCl_6	ND	25	7	1	5	Intracellular	Konishi et al. (2007)
Shewanella loihica	Pd	$PdCl_2$	ND	30	7	48	2–6	Extracellular	Ahmed et al. (2018)
					9		2–12		
Shewanella oneidensis	Ag	$AgNO_3$	Spherical	30	ND	48	~2–11	Extracellular	Suresh et al. (2010)

Microorganism	Nano	Substrate	Shape	Reaction condition			Size (nm)	Mode of biosynthesis	Reference
				Temp (°C)	pH	Time (h)			
	Au	$HAuCl_4$	Spherical	30	ND	48	~2–50	Extracellular	Suresh et al. (2011)
	Fe_3O_4	$Fe(ClO_4)_2$, $FeCl_3$, $FeCl_2$	Rectangular/ Rhombic/ Hexagonal/ Spherical	25	6.97	720	40–50	Extracellular	Perez-Gonzalez et al. (2010)
	UO_2 (IV)	U(VI)	Intricate	30	7	24	1–5	Extracellular	Marshall et al. (2006)
Shewanella sp.	Se	Na_2SeO_3	Spherical	30	ND	168	181	Extracellular	Lee et al. (2007)
				4			68		
				15			50		
Staphylococcus aureus	Ag	$AgNO_3$	Irregular	ND	ND	0.08	160–180	Extracellular	Nanda and Saravanan (2009)
Streptomyces anulatus	Ag	$AgNO_3$	Hexagonal	ND	ND	24	37.96	Extracellular	Soni and Prakash (2015)
			Rod			42.44			
			Spherical			11.53			
			Triangular			28.99			
Streptomyces albidoflavus	Ag	$AgNO_3$	Spherical	RT	ND	72	10–40	Intracellular/ Extracellular	Kumar Buddana (2012)
Streptomyces bikiniensis	Se	SeO_2	Spherical	30	7	6	50–100	Extracellular	Ahmad et al. (2015)
			Spherical			12			
			Rod-like			48			

(continued)

Table 7.1 (continued)

Microorganism	Nano	Substrate	Shape	Reaction condition			Size (nm)	Mode of biosynthesis	Reference
				Temp (°C)	pH	Time (h)			
Streptomyces fulvissimus	Au	$HAuCl_4$	Spherical	30	ND	48	20–50	Extracellular	Soltani et al. (2015)
Streptomyces glaucus	Ag	$AgNO_3$	Spherical	ND	ND	168	4–25	Extracellular	Tsibakhashvili et al. (2011)
Streptomyces griseoplanus	Ag	$AgNO_3$	Spherical	28	ND	96	19.5–20.9	Extracellular	Vijayabharathi et al. (2018)
Streptomyces hygroscopicus	Ag	$AgNO_3$	Spherical	30	6.5	96	20–30	Extracellular	Sadhasivam et al. (2010)
	Au	$HAuCl_4$	Spherical	35	7	96	10–20	Intracellular	Waghmare et al. (2014)
Streptomyces minutiscleroticus	Se	Na_2SeO_3	Spherical	ND	ND	72	10–250	Extracellular	Ramya et al. (2015)
Streptomyces sp.	Ag	$AgNO_3$	Spherical	RT	ND	96	5	Extracellular	Karthik et al. (2014)
	Ag	$AgNO_3$	Spherical	28	ND	48	10–100	Extracellular	Zonooz and Salouti (2011)
Streptomyces sp.	Cu	$CuSO_4$	Colony	28	ND	48	100–150	Extracellular	Usha et al. (2010)
	Zn	$ZnNO_3$	Hexagonal/ Spherical	28	7.2	24/48/72	20–50	Extracellular	Balraj et al. (2017)
Streptomyces viridogens	Au	$HAuCl_4$	Spherical/Rod	30	9	72	18–20	Intracellular	Balagurunathan et al. (2011)
Sulfurospirillum barnesii	Te	Te(VI) or Te(IV)	Irregular Nanospheres	28	ND	24	<50	Extracellular	Baesman et al. (2007)
Thermoanaerobacter ethanolicus	Fe_3O_4	amorphous Fe(III) oxyhydroxide	Needle-like	RT	ND	80	45	Extracellular	Yeary et al. (2005)

Microorganism	Nano	Substrate	Shape	Reaction condition			Size (nm)	Mode of biosynthesis	Reference
				Temp (°C)	pH	Time (h)			
Thermoanaerobacter sp.	Cu	$CuCl_2$	Spherical	65	7.2–7.8	336	70–150 and 5–10	Extracellular	Jang et al. (2015)
Ureibacillus thermosphaericus	Ag	$AgNO_3$	Spherical	65	ND	72	10–100	Extracellular	Juibari et al. (2011)
Vibrio alginolyticus	Ag	$AgNO_3$	Spherical	60–80	ND	24	50–100	Intracellular	Rajeshkumar et al. (2013b)
				RT	ND	4		Extracellular	
Weissella oryzae	Ag	$AgNO_3$	Spherical	RT	ND	12	10–30	ND	Singh et al. (2016)
				25	4–10	48			

ND not determined, *FCC* face centered cubic

In the presence of hydrogen gas and *S. algae*, the reduction of Au ions results in the formation of 10–20 nm gold NPs. *Pseudomonas stutzeri* AG259, the silver-resistant bacterial strain, accumulates silver NPs, together with some silver sulfide, in the cell in which particle size is between 35 and 46 nm (Slawson et al. 1992). The formation of greater particles occurs, when *P. stutzeri* AG259, extracted from silver mine, is located in a concentrated aqueous solution of silver nitrate (50 mM; Klaus et al. 1999). NPs of distinct sizes, both little or greater (over 200 nm) and different morphology are deposited inside the periplasmic space of the bacteria. The various particle sizes are formed probably due to the growth of cells and conditions for the incubation of metal. Besides, the precise mechanisms of reaction, resulting in the formation of silver NPs via this species of silver-resistant bacteria, are up till now to be clarified. Microorganisms' capability to grow in the presence of high metal concentrations may be owing to the particular resistance mechanisms including efflux systems, extracellular complexation or precipitation of metals, alteration of solubility and toxicity by changes in the redox state of the metal ions, and the lack of specific metal transport systems (Mandal et al. 2006). Besides, bacteria without exposure to large concentrations of metal ions can also be utilized to grow NPs. When *Lactobacillus* strains, existent in buttermilk, are exposed to silver and gold ions, the metal NPs are produced in large scale inside the bacterial cells (Nair and Pradeep 2002). Furthermore, the result of exposing lactic acid bacteria, existing in the whey of buttermilk, to the mixtures of silver and gold ions is the production of alloy NPs of silver and gold (Mandal et al. 2006).

In addition to silver and gold NPs, a lot of efforts have been made to develop protocols for the production of semiconductors (the so-called quantum dots) such as ZnS, PbS, and CdS, as a novel class of substances for cell imaging and biological detection, thanks to the conjugation of bio-recognition molecules and semiconducting quantum dots (Chan et al. 2002). When cysteine hydrochloride is present in the growth medium, CdS is participated by *Clostridium thermoaceticum* at the cell surface in addition to in the medium from $CdCl_2$ (Mandal et al. 2006). Cysteine most likely serves as the sulfide source. Upon the exposure of *Klebsiella aerogenes* to Cd^{2+} ions in the growth medium, 20–200 nm CdS are produced on the cell surface. Furthermore, intracellular nanocrystals of CdS, composed of a wurtzite crystal phase, are made as a result of *E. coli* incubation with sodium sulfide and cadmium chloride (Sweeney et al. 2004). Dependent on the growth phase of the cells, the formation of nanocrystal is significantly different, rising around 20-fold in *E. coli* grown in the stationary phase, in contrast to that grown in the late logarithmic phase. As reported by Labrenz et al. (2000), the spherical aggregates of sphalerite (ZnS) particles (with 2–5 nm diameters) are formed inside natural biofilms dominated by sulfate-reducing bacteria of the *Desulfobacteriaceae* family. Besides, in a complex natural system, a combination of microbial and geochemical processes leads to ZnS biomineralization. It is worth mentioning that through the application of this technique, the Zn concentration can considerably decrease under the levels acceptable for drinking water (Mandal et al. 2006).

The synthesis of magnetic Fe sulfide NPs can occur via hiring sulfate-reducing bacteria, following the formation of few nanometer-sized particles on the surface and the separation of magnetic mineral from the solution using a high-gradient magnetic field of 1 T (Watson et al. 1999). Bacterially formed iron sulfide is an adsorbent for an extensive variety of heavy metals and some anions. Because of the high surface area (400–500 m^2/g), high adsorption of radioactive ions occurs, providing an appropriate matrix for the long-term safe storage of some ions, essential for the nuclear industry, especially the pertechnetate ion (TcO^{4-}; Watson et al. 2001).

Small octahedral-shaped magnetic particles (<12 nm) are exclusively produced outside the bacterial cells by a thermophilic fermentative bacterial strain TOR-39 (Mandal et al. 2006). The magnetic crystals biosynthesized in the thermophilic iron-reducing bacteria *Thermoanaerobacter ethanolicus* (TOR-39), through the electrochemical procedure, can be substituted by transition metals like Cr, Ni, and Co (Roh et al. 2001). The magnetotactic bacteria can be used to effectively control the mineralization methods, as a result of which uniform, species-specific magnetic NPs are formed. The magnetotactic bacteria *Magnetospirillium magnetotacticum* produces single-domain magnetic crystals (Fe_3O_4) assembled into the folded chain and flux-closure ring morphologies (Philipse and Maas 2002). Noticeably, as intracellular structures comprising magnetic iron mineral crystals enveloped by a membrane vesicle, magnetosomes exist in all magnetotactic bacteria (Mandal et al. 2006).

According to a haphazard observation, the exposure of alkalothermophilic (extremophilic) actinomycete, *Thermomonospora* sp. to gold ions reduces the metal ions extracellularly, resulting in gold NPs with much polydispersity (Ahmad et al. 2003c). A whole reduction of the 10^{-3} M aqueous $HAuCl_4$ solution at pH = 9.0 and 50 °C caused the formation of spherical and reasonably monodisperse NPs (8 nm). When gold NPs are generated intracellularly in alkalotolerant actinomycete *Rhodococcus* sp., the higher concentration of particles on the cytoplasmic membrane can be observed, compared to that on the cell wall (Ahmad et al. 2003b).

4 Synthesis of NPs by Thallophytes

4.1 Synthesis of NPs by Fungi

To the best of our knowledge, among the eukaryotes, yeasts are hired mostly in the biosynthesis of the semiconductor NPs (Table 7.2). CdS quantum dots are generated intracellularly as a result of *Candida glabrata* exposure to Cd^{2+} ions (Mandal et al. 2006). *Torulopsis* sp., is able to intracellular synthesis of PbS nanocrystals (Kowshik et al. 2002c, b). According to Kowshik et al. (2002c, b), in *Schizo-saccharomyces pombe* yeast cells, the intracellularly synthesized CdS quantum dots show ideal diode characteristics. Biogenic CdS NPs (with the diameters of 1–1.5 nm) have been utilized in the construction of a heterojunction using poly (p-phenylenevinylene). While such a diode shows a current of about 75-mA/cm^2 in the forward bias mode at 10 V, the breakdown happens at ~15 V in the opposite direction. Yeast has been utilized for several years to synthesize intracellular NPs; however, very recently, the

Table 7.2 Biosynthesis of different NPs from fungi and reaction conditions

Microorganism	Nano	Substrate	Shape	Reaction condition Temp (°C)	pH	Time (h)	Size (nm)	Mode of biosynthesis	Reference
Aspergillus aculeatus	Ni/NiO	$NiCl_2$	Spherical	20–60	2–6	5	5.89	Extracellular	Salvadori et al. (2014c)
Alternaria alternata	Au	$HAuCl_4$	Hexagonal/ Spherical/ triangular	RT (37)	ND	24	2–30	Extracellular	Sarkar et al. (2012)
Aspergillus clavatus	Au	$HAuCl_4$	Hexagonal/ Spherical/ Triangular	RT	ND	48–72	20–35	Intracellular	Verma et al. (2011b)
Aspergillus flavus	Ag	$AgNO_3$	FCC	37	ND	72	8.92	Intracellular	Vigneshwaran et al. (2007)
	Mg	MgO	ND	28	ND	48	64 ± 0.8–98 ± 0.3	Extracellular	Raliya et al. (2013)
	ZnS-Gd	Gd $(NO_3)_3 + ZnSO_4$	Polycrystalline	RT	ND	0.17	10–18	Extracellular	Uddandarao et al. (2019)
	PbS	$Pb(CH_3COO)_2 + Na_2S$	Cubic	30	ND	72	35–100	Extracellular	Priyanka et al. (2017)
	Zn	ZnO	ND	28	ND	48	77–>100	Extracellular	Raliya et al. (2013)
Aspergillus oryzae	Au	$HAuCl_4$	Triangular/ Spherical/ Pentagonal/ Hexagonal	25	7	72–120	10–60	Intracellular/ Extracellular	Binupriya et al. (2010)
Aspergillus oryzae	Mg	MgO	ND	28	ND	48	73 ± 0.6	Extracellular	Raliya et al. (2013)
	Zn	ZnO	ND	28	ND	48	94 ± 05	Extracellular	Raliya et al. (2013)

Microorganism	Nano	Substrate	Shape	Reaction condition			Size (nm)	Mode of biosynthesis	Reference
				Temp (°C)	pH	Time (h)			
Aspergillus sp.	Au	$HAuCl_4$	Spherical	30	ND	216	4 – 29	Extracellular	Shen et al. (2017)
Aspergillus sydowii	Au	$AuCl_3$	Spherical	27	ND	72	8.7–15.6	Intracellular/ Extracellular	Vala (2015)
Aspergillus terreus	Ag	$AgNO_3$	Round/Rod/ Uneven	RT	ND	24	16–57	Extracellular	Singh and Vidyasagar (2018)
	Au	$HAuCl_4$	Spherical/rod	RT	10	within few seconds	10–19	Extracellular	Priyadarshini et al. (2014)
	Mg	MgO	ND	28	ND	48	49 ± 0.8	Extracellular	Raliya et al. (2013)
	Zn	ZnO	ND	28	ND	48	84 ± 03, 51 ± 05	Extracellular	Raliya et al. (2013)
Aspergillus tubingensis	P (Phosphorous)	$Ca_3P_2O_8$	Spherical	28	ND	72	28.2	Extracellular	Tarafdar et al. (2012)
	Mg	MgO	ND	28	ND	48	48 ± 0.5–52 ± 0.5	Extracellular	Raliya et al. (2013)
	Zn	ZnO	ND	28	ND	48	>100	Extracellular	Raliya et al. (2013)
Aspergillus versicolor	Ag	$AgNO_3$	Spherical	35	ND	120	5–30	Extracellular	Elgorban et al. (2016)
Aspergillus welwitschiae	Te	K_2TeO_3	Oval/Spherical	30	ND	48	60.8	Extracellular	Elsoud et al. (2018)

(continued)

Table 7.2 (continued)

Microorganism	Nano	Substrate	Shape	Reaction condition			Size (nm)	Mode of biosynthesis	Reference
				Temp (°C)	pH	Time (h)			
Bipolaris nodulosa	Ag	$AgNO_3$	Spherical/ Hexahedral/ Triangular/ Semi-pentagonal	RT	ND	24	10–60	Extracellular	Saha et al. (2010)
Candida albicans	Au	$HAuCl_4$	Spherical	RT	ND	24	20–40	Extracellular	Chauhan et al. (2011)
	Au	$HAuCl_4$	Non Spherical				60–80		
Candida guilliermondii	Au	$HAuCl_4$	Near spherical	30	ND	48	50–70	Extracellular	Mishra et al. (2011)
	Au	$HAuCl_4$	Spherical	35	3	24	<10	Intracellular	Gericke and Pinches (2006)
			small spherical/ Triangles/ Hexagons/ Spheres/Rod		5		<10		
	Ag	$AgNO_3$	Spherical	27	ND	78	10–100	Extracellular	Balaji et al. (2009)
	Au	$HAuCl_4$	FCC	RT	ND	48	100	Extracellular	Joshi et al. (2017)
Cryphonectria sp.	Ag	$AgNO_3$	ND	25	ND	24	30–70	Extracellular	Dar et al. (2013)
cylindrocladium floridanum	Au	$HAuCl_4$	Spherical	30	ND	168	5–35	Intracellular	Narayanan and Sakthivel (2011)

Microorganism	Nano	Substrate	Shape	Reaction condition			Size (nm)	Mode of biosynthesis	Reference
				Temp (°C)	pH	Time (h)			
Epicoccum nigrum	Au	$HAuCl_4$	Spherical/Rod	27–29	2.5	72	5–50	Intracellular/ Extracellular	Sheikhloo et al. (2011)
Extremophilic yeast	Ag	$AgNO_3$	Spherical	22	ND	24	~20	Extracellular	Mourato et al. (2011)
Fusarium oxysporum	Ag	$AgNO_3$	Spherical/ Triangular	ND	ND	72	5–15	Extracellular	Ahmad et al. (2003c)
	Au	$HAuCl_4$	Spherical/ Triangular	RT	ND	72	8–40	Extracellular	Mukherjee et al. (2002)
	Au–Ag Alloy	$HAuCl_4 + AgNO_3$	Spherical	RT	ND	96	8–14	Extracellular	Senapati et al. (2005)
	$BaTiO_3$	$(CH_3COO)_2Ba + K2TiF_6$	Quasi-Spherical	RT (27)	Neutral	24	4–5	Extracellular	Bansal et al. (2006)
	Bi_2O_3	$Bi(NO_3)_3$	Quasi-Spherical	RT	ND	96	5–8	Extracellular	Uddin et al. (2008)
	CdS	$CdSO_4$	Hexagonal	28	5.5–6.0	288	5–20	Extracellular	Ahmad et al. (2002)
	CdSe	$CdCl_2 + SeCl_4$	Spherical	RT	ND	96	9–15	Extracellular	Kumar et al. (2007)
Fusarium oxysporum	Fe_3O_4	$K_3Fe(CN)_6 + K_4Fe(CN)_6$	Quasi-spherical	RT	Neutral	24	20–50	Extracellular	Bharde et al. (2006)
	$PbCO_3$	Pb(NO3)2	Spherical	27	ND	24	120–200	Extracellular	Sanyal et al. (2005)
	Si/SiO_2	K_2SiF_6	Quasi-spherical	27	3.1	24	5–15	Extracellular	Bansal et al. (2005)

(continued)

Table 7.2 (continued)

Microorganism	Nano	Substrate	Shape	Reaction condition Temp (°C)	pH	Time (h)	Size (nm)	Mode of biosynthesis	Reference
	$SrCO_3$	$SrCl_2$	Needle-like	27	ND	72	10–50	Extracellular	Rautaray et al. (2004)
	TiO_2	K_2TiF_6	Spherical	27	3.5	24	6–13	Extracellular	Bansal et al. (2005)
	ZrO_2	K_2ZrF_6	Quasi-spherical	27	3.6	24	3–11	Extracellular	Bansal et al. (2004)
Fusarium oxysporum f.sp. lycopersici	Pt	H_2PtCl_6	Circles/ Hexagons/ Pentagons/ Squares/ Rectangles	35	9	72	10–100	Intracellular/ Extracellular	Riddin et al. (2006)
Fusarium semitectum	Ag	$AgNO_3$	Spherical	27	ND	48	10–60	Extracellular	Basavaraja et al. (2008)
	Au	$HAuCl_4$	Spherical	RT	ND	24	18–80	Extracellular	Sawle et al. (2008)
	Au–Ag alloy	$HAuCl_4$ + AgNO3					10–35		
Fusarium solani	Ag	$AgNO_3$	Spherical	RT	ND	2	5–35	Extracellular	Ingle et al. (2009)
	Au	$HAuCl_4$	Spherical	30	8.5	24	20 to 50	Extracellular	Gopinath and Arumugam (2014)
Guignardia mangiferae	Ag	$AgNO_3$	Spherical	RT	7	12	5–30	Extracellular	Balakumaran et al. (2015)

Microorganism	Nano	Substrate	Shape	Reaction condition			Size (nm)	Mode of biosynthesis	Reference
				Temp (°C)	pH	Time (h)			
Helminthosporium solani	Au	$HAuCl_4$	Spheres/rods/triangles/pentagons/pyramids/stars	37 ± 1	ND	72	2–70	Extracellular	Kumar et al. (2008a)
Humicola sp.	Ag	$AgNO_3$	Spherical	50	9	96	5–25	Extracellular	Syed et al. (2013)
Hypocrea lixii	Cu	$CuCl_2$	Spherical	40	5	1	24.5	Extracellular	Salvadori et al. (2013)
	Ni/NiO	$NiCl_2$	Spherical	20–60	2–6	5	1.25	Intracellular	Salvadori et al. (2015)
							3.8	Extracellular	
Macrophomina phaseolina	Ag	$AgNO_3$	Spherical	28	ND	72	5–40	Extracellular	Chowdhury et al. (2014)
Magnusiomyces ingens	Au	$HAuCl_4$	Spherical/Pseudo-spherical	30	ND	48	20–30	Extracellular	Qu et al. (2018)
Microsporum canis	Ag	$AgNO_3$	Spherical	ND	ND	72	<50	Extracellular	Moazeni et al. (2012)
Neurospora crassa	Ag	$AgNO_3$	Spherical	28	ND	24	3–100	Intracellular	Castro-Longoria et al. (2011)
	Au	$HAuCl_4$							
Penicillium aurantiogriseum	Ag	$AgNO_3$	Spherical	25	4	72	12.7	Extracellular	Elshawy et al. (2016)

(continued)

Table 7.2 (continued)

Microorganism	Nano	Substrate	Shape	Reaction condition			Size (nm)	Mode of biosynthesis	Reference
				Temp (°C)	pH	Time (h)			
Penicillium brevicompactum	Ag	$AgNO_3$	ND	25	ND	72	23–105	Extracellular	Shaligram et al. (2009)
	Au	$HAuCl_4$	Spherical	30	5.0–8.0	12	25–60	Extracellular	Mishra et al. (2011)
Phoma glomerata	Ag	$AgNO_3$	Spherical	RT	ND	ND	60–80	Extracellular	Birla et al. (2009)
Phoma sp.	Ag	$AgNO_3$	ND	28	ND	50	71.06	Extracellular	Chen et al. (2003)
Rhizoctonia bataticola	Zn	ZnO	ND	28	ND	48	92	Extracellular	Raliya et al. (2013)
Rhizopus nigricans	Ag	$AgNO_3$	Round	RT	ND	72	35–38	Extracellular	Ravindra and Rajasab (2014)
Rhizopus oryzae	Au	$HAuCl_4$	Domain-like/ FCC	30	3	24	10	Extracellular	Das et al. (2009)
Rhizopus stolonifer	Ag	$AgNO_3$	Spherical	40	ND	48	2.86	Extracellular	AbdelRahim et al. (2017)
Rhodotorula glutinis	Ag	$AgNO_3$	ND	30	12	96	2.5–20	Extracellular	Zahran et al. (2013)
Rhodotorula mucilaginosa	Ag/Ag_2O	$AgNO_3$	Spherical	27	ND	20	11	Intracellular	Salvadori et al. (2017)
	Cu	$CuCl_2$	Spherical	30	5	1	10.5	Intracellular	Salvadori et al. (2014a)
	Ni/NiO	$NiCl_2$	Spherical	20–60	2–6	5	5.5	Extracellular	Salvadori et al. (2016)
Saccharomyces cerevisiae	Ag	$AgNO_3$	Spherical	60	ND	0.16–0.33	2–10	Intracellular	Jha et al. (2009b)

Microorganism	Nano	Substrate	Shape	Reaction condition			Size (nm)	Mode of biosynthesis	Reference
				Temp (°C)	pH	Time (h)			
	Sb_2O_3	$SbCl_3$	FCC/Spherical	RT		72–96			
Schizosaccharomyces pombe	CdS	$CdSO_4$	Hexagonal lattice	ND	5.6	36	2–2.5	Intracellular	Kowshik et al. (2002b)
Trichoderma asperellum	Ag	$AgNO_3$	FCC	25	ND	120	13–18	Extracellular	Mukherjee et al. (2008)
Trichoderma harzianum	Au	$HAuCl_4$	Spherical	28	ND	72	26–34	Intracellular	Tripathi et al. (2018)
Trichoderma koningiopsis	Cu	$CuCl_2$	Spherical	40	5	1	87.5	Extracellular	Salvadori et al. (2014b)
Trichothecium sp.	Au	$HAuCl_4$	Spherical/ Rod-like/ Triangular/ Hexagons	27	ND	48	5–200	Extracellular	Ahmad et al. (2005)
						72		Intracellular	
Trichoderma viride	Ag	$AgNO_3$	Plates	10	Neutral	24	80–100	Extracellular	Fayaz et al. (2009)
			Rod like and Spherical	27			10–40		
			Spherical	40			2–4		
Trichoderma reesei	Ag	$AgNO_3$	ND	25	ND	120	5–50	Extracellular	Vahabi et al. (2011)
Trichophyton rubrum	Ag	$AgNO_3$	Spherical	ND	ND	72	50–>100	Extracellular	Moazeni et al. (2012)
Trichophyton entagrophytes	Ag	$AgNO_3$	Spherical	ND	ND	72	<50	Extracellular	Moazeni et al. (2012)

(continued)

Table 7.2 (continued)

Microorganism	Nano	Substrate	Shape	Reaction condition			Size (nm)	Mode of biosynthesis	Reference
				Temp (°C)	pH	Time (h)			
Verticillium sp.	Ag	$AgNO_3$	Spherical	28	5.5–6.0	72	25	Intracellular	Mukherjee et al. (2001a)
	$Fe_3O_4 + \gamma\text{-}Fe_2O_3$	$K_3Fe(CN)_6 + K_4Fe(CN)_6$	Cubo-octahedrally	RT	Neutral	24	100–400	Extracellular	Bharde et al. (2006)
Yarrowia lipolytica	Ag	$AgNO_3$	FCC	20	ND	120	15	Extracellular	Apte et al. (2013)
	Au	$HAuCl_4$	Triangular/ Spherical/ Hexagonal	30	4.5	120	varying sizes	Intracellular/ Extracellular	Pimprikar et al. (2009)

ND Not determined, *FCC* Face centered cubic extracellular synthesis of silver NPs by a silver-tolerant yeast strain, MKY3, has been reported (Kowshik et al. 2002a).

Fungi have been recently added to the group of microorganisms able to synthesize NPs (Table 7.2). The fungi utilization is interesting, as they secrete huge quantities of enzymes with easier laboratorial management. Nevertheless, in comparison to prokaryotes, the genetic manipulation of eukaryotic organisms, as a means of overexpressing specific enzymes known in nanomaterial synthesis, seems to be more difficult.

Two genera are made as a result of a wide screening process, leading to huge amounts of metallic NPs either intracellularly (Mukherjee et al. 2001a, b) or extracellularly (Mukherjee et al. 2002; Ahmad et al. 2003a), upon being challenged with aqueous metal ions, for example, Ag^+ and $AuCl_4^-$. A distinctive purple color appears in the biomass of *Verticillium* following the exposure to the $HAuCl_4$ solution (10^{-4} M), showing the production of gold NPs intracellularly, observed in the UV–visible absorption spectrum associated with gold-loaded biomass (at ~550 nm) (Mukherjee et al. 2001b).

Considering the application point of view, harvesting the metal NPs produced inside the fungal biomass would be vital. The intracellular silver and gold NPs can be released through ultrasound treatment of the biomass, upon which NPs compose or react with appropriate detergents. Nevertheless, it can be much more plausible provided the fungus-exposed metal ions could be reduced outside the fungal biomass, as a consequence of which the metallic NPs are formed in the solution. It was quite surprising that the behavior of the plant pathogenic fungal strain *Fusarium oxysporum* was significantly different; the extracellular reduction of the metal ions happened, leading to the rapid formation of highly stable gold (Mukherjee et al. 2002) and silver (Ahmad et al. 2003a) NPs (with 2–50 nm diameters). Most possibly, the reduction of the $AuCl_4^-$ and Ag^+ ions happens because of the released reductases from the fungus into the solution, therefore introducing a new in vitro fungal/enzyme-based method for NPs synthesis. The stabilization of proteins, such as cysteine can bring about the long-term stability of the NPs in the solution (Gole et al. 2001). Unlike individual metal NPs, the bimetallic Au–Ag alloy is synthesized using *F. oxysporum*. Based on the recent papers, as a result of exposing the biomass of *F. oxysporum* to equimolar solutions of $HAuCl_4$ and $AgNO_3$, Au–Ag alloy NPs of various mole fractions can be obtained, which are highly stable (Senapati et al. 2005). Even more surprisingly, the exposure of *F. oxysporum* to the aqueous $CdSO_4$ solution ends in extracellular CdS quantum dots with sizes ranging from 5 to 20 nm (Ahmad et al. 2002). Another important use of this fungus is in the production of zirconia NPs (Bansal et al. 2004). The gold NPs of rod-like and prismatic morphology are produced via the exposure of an endophytic fungus (*Colletotrichum* sp.), growing in the geranium leaves, to aqueous chloroaurate ions (Shankar et al. 2003).

4.2 Synthesis of NPs by Algae

The green synthesis of NPs can be carried out utilizing algae. To date, there are not many reports about the alga-mediated synthesis of NPs (Table 7.3). Due to its global distribution, they can be used for the generation of eco-friendly and large-scale metallic NPs (Aziz et al. 2014, 2015; Sharma et al. 2018). Recently, the demand for silver and gold NPs generated by algae has risen extremely due to the presence of bioactive phytochemicals, the simple handling of raw material, and high stability. Some algae utilized to synthesize gold NPs are *Turbinaria conoides* (Rajeshkumar et al. 2013a), *Sargassum wightii* (Singaravelu et al. 2007), *Stoechospermum marginatum* (Rajathi et al. 2012), and *Laminaria japonica* (Ghodake and Lee 2011).

5 Significance of Bio-Based NPs for Green Application

The utilization of different microorganisms, for example, bacteria, thallophytes (fungi and algae), plant extracts, and waste materials, as eco-friendly precursors, for the synthesis of NPs with possible uses has been reported. The biological method, containing various kinds of microorganisms, has benefits compared to other chemical approaches, that is, it is greener, saves energy, and is nontoxic, while acting at room temperature and atmosphere with cheap materials and solvents, no expensive equipment, environmentally friendly and cost-effective technology (Sharma et al. 2019).

6 Summary and Perspective

The use of microorganisms like yeasts, bacteria, fungi, and algae in the biosynthesis of metal NPs has been reviewed. As an interdisciplinary field, bio-nanotechnology needs cooperation among chemists, physicists, engineers, and biologists. Microorganisms have been considered as a probable alternative to the presently common chemical and physical techniques. To develop rational microbial NPs synthesis methods, the explanation of biochemical pathways involved in metal ion reduction in the various kinds of microbes is essential. The surface chemistry of biogenic NPs ought to be correctly known. The particle properties can potentially be improved and their composition can be controlled using genetic engineering methods. The bacteria-to-fungi change, as a means of growing natural nanofactories, presents the extra benefits, that is, easier downstream processing and biomass handling. Presently, microbial procedures in the synthesis of nanomaterials of various compositions are restricted to some metallic sulfide, metal, and very few oxides. Hopefully, the microbial synthesis can be commercially feasible as a result of an extension of the techniques to enable the dependable synthesis of nanocrystals of other oxides (TiO_2, ZrO_2, etc.), nitrides, carbides, and so on.

Table 7.3 Biosynthesis of different NPs from algae and reaction conditions

Microorganism	Nano	Substrate	Shape	Reaction condition			Size (nm)	Mode of biosynthesis	Reference
				Temp (°C)	pH	Time (h)			
Scenedesmus sp.	Ag	$AgNO_3$	Spherical	28	ND	72	15–0	Intracellular	Jena et al. (2014)
				RT			5–20	Extracellular	
Spirulina platensis	Au	$HAuCl_4$	Spherical	RT	ND	48	2–8	Extracellular	Suganya et al. (2015)
	Pd	$PdCl_2$	Spherical	70	ND	0.33	10–20	Extracellular	Sayadi et al. (2018)
Tetraselmis kochinensis	Au	$HAuCl_4$	Spherical/Triangular	28–29	ND	48	5–35	Intracellular	Senapati et al. (2012)

ND not determined

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Chapter 8
Nanotechnology for Detection and Diagnosis of Plant Diseases

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1 Introduction

Nanotechnology is the science of building macromolecular or nano-materials, structures, devices, and even systems. It is also used for agriculture to make easy and better understanding of mechanisms of biological entities at cellular levels (Karunakaran and Jayas 2005). Diagnosing a plant disease by the use of nano-biotechnology is termed as nano-diagnostics. This chapter deals with how nanotechnology plays an important role in controlling plant diseases. Nanotechnology can also assist to study disease diagnostics/prevention. In fact, the most commonly used techniques viz., DNA/protein microarrays, enzyme-linked immune sorbent assay (ELISA), polymerase chain reaction (PCR), fluorescence resonance energy transfer (FRET)-based analysis, etc. (Shi et al. 2006), have or can benefit from nanotechnology.

Nano-phytopathology is an intensive science for the detection of plant diseases. There is a probability in the future to achieve some success that will be discussed. Nanotechnology provides better solutions to numerous problems in plant diseases (Abd-Elsalam and Prasad 2018, 2019). This chapter addresses the use of nanotechnology to fight plant diseases for a sustainable future. The nano-material solutions for the protection of plants from various pathogenic bacteria, fungi, nematodes, and viral agents are also emphasized here. Screening and diagnosis of diseases, treatment in-farming practices, including pest and detection and control of the vectors, which carries viruses, etc. (Karunakaran and Jayas 2005). Diagnosis of a disease in plants at very early stage can play a vital role in treatment. The nanoparticles which have been used in managing plant diseases include nanoforms of, carbon, silver, silica, and alumina–silicates (Sharma et al. 2012). Hydrogen has the smallest atoms in which they are nearly about quarter of nanometer diameter; therefore, nanotechnology must build its molecules and atoms in which the upper limit is more or less but around the size of the phenomenon that was not observed and can be made use in the field of nanoscience or nanodevice (Ganji and Kachapi 2015) (Fig. 8.1).

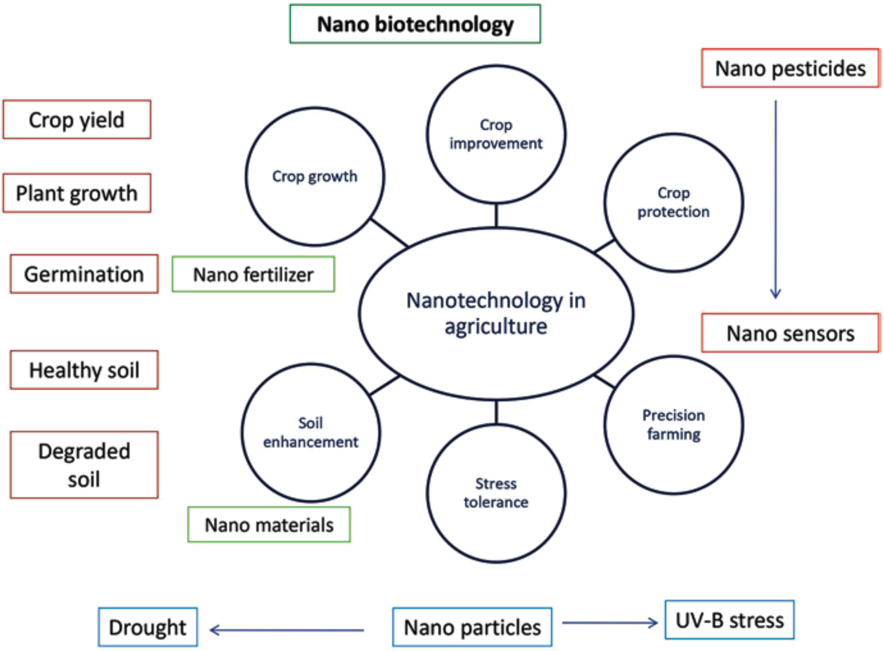

Fig. 8.1 Nanotechnology in agriculture

2 Nanotechnology in the Detection of Pathogens

It is notable that new techniques of disease detection involving nano-biosensors (Yalcin and Otles 2010) which is a fast and instant detection tool that can provide desired results within a few period of time (h). To identify the plant pathogens, the researcher needs prompt techniques and detection tools which can provide better results in short period of time. Detailed description of different detection techniques is discussed below (Fig. 8.2).

3 Tools of Nanotechnology

3.1 Nanodiagonastic Kit

A portable kit is used in the crops sown for the search of pathogens. This is a fast and accurate procedure to detect potential serious phytopathogens, which helps expert scientists in the prevention of epidemics of plant diseases from breaking out (Pimentel 2009). Very soon the plant pathologists are able to study the nanodiagnostic kit as a “lab in a box.” This refers to packaging of sophisticated measuring devices, reagents, power supply, and features that now take up the laboratory space

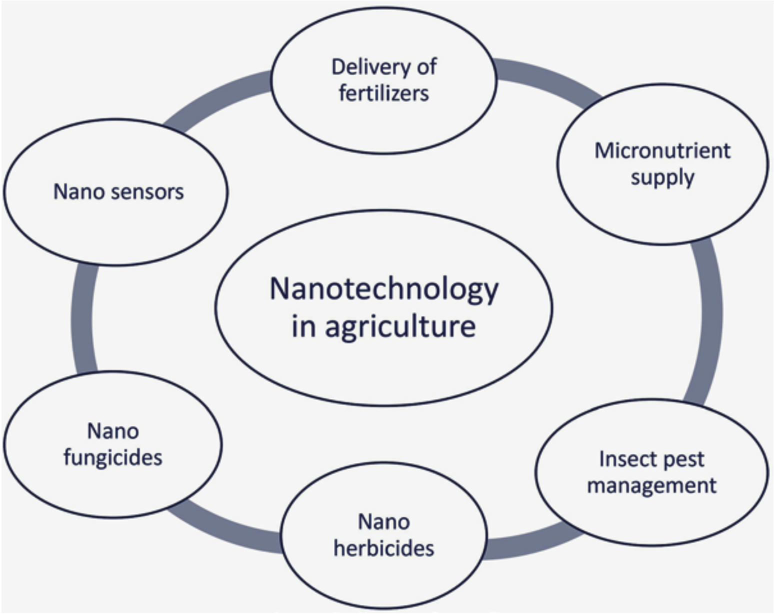

Fig. 8.2 Nanotechnology in agriculture

into a parcel no larger or heavier than a briefcase (Goluch et al. 2006). A briefcase kit is transferred to a field where the crops are growing to search for the pathogens that could infect and reduce the yield. This is a quick and precise procedure.

3.2 Nanoscale Biosensor

Some biological and chemical sensor points used to transmit nanoparticle data to the macroscopic world are nanosensors. Antibodies are flexible and are appropriate for varied immunosensing applications. It allows instant detection of a wide range of pathogens. In addition, it also gives numerous advantages viz., high sensitivity, potential for quantification, real-time analysis, pathogen detection in water, air, and seeds with different parameters. Biosensors are analytical device those used for detection and diagnosis of plant disease and their management an analytical device used for the detection of an analyze, the combines a biological component with a physicochemical detector. A highly sophisticated biological element such tissues of organisam and receptors sites like tissue, cell receptors, etc., is biologically derived material or biometric compound, which interacts or binds to analyze or under study (Turner et al. 1987; Singh et al. 2020).

3.3 Antibody Biosensor

Antibody-based biosensor plays a vital role in agricultural detection of plant pathogens. These biosensors enable the detection of plant pathogen in seeds, soil, air, and water with different principles in field conditions, greenhouses and as well as post-harvest storages along with the distributors of crops and fruits. Antibody biosensors have an efficient power in detecting the foodborne diseases and in which the techniques have already evolved for food safety monitoring. Besides, these biosensors provide various advantages such as improving in sensitivity, real-time analysis, fast detection, and potential of quantification. Antibody immune sensor lies in the specific antibody with a transducer that connects the binding event in which (the specific antibody can bind to specific antigen, e.g., interests of the pathogen) to that particular signal can be analyzed. Antibody biosensors mostly use only one type of electrochemical transducers such as impedimetric, conduct metric amperometric, and potentiometric). Impedimetric biosensors play an important role in the biomass detection based on the metabolic redox actions of microorganisms. On the other hand, the conduct metric On other hand conduct of metric and biosensors are used to detect the biological signal which is converted into an electrical signal through conductive polymer such as polypyrrole, polyacetylene, polyaniline, etc. The other types of transducers which are nonelectrochemicals that includes Quartz crystal microbalance (QCM), surface plasma resonance (SPR). Due to their attachment of the analytic on their metal surface, these SPR biosensors can change the measure of refractive index. On the other hand, mass variation per unit area can be detected through QCM by measuring the frequency change of a quartz resonator.

3.4 Gold Nanoparticles and Quantum Dots (QDs)

Gold nanoparticles based biosensors have been developed for finding the wheat disease viz. karnal bunt. For specific identification between the phytopathogen target cells and bifunctional nanomaterials, different techniques including adhesion receptor, antibody–antigen, and complementary DNA sequence can be recognized. Electrochemical procedures can be able to identify the pathogens by the use of gold nanoparticles which are having excellent markers that act as a biosensor. Besides these nanoparticles are also used along with the other biological materials for detecting antibody, for example, *Xanthomonas axonopodis* which causes bacterial spot disease. Several number of experiments have been conducted on nano-based particle to detect and develop the bimolecular DNA or protein-functionalized nanoparticles that have been used for specific target probes. In recent studies, various nano biosensors of agroterrorism and molecular diagnosis can be detected. QDs are semiconductor nanoparticles. QDs which are inorganic fluorophores having major advantages are used as markers also. In unicellular yeast, mycosynthesis of nanoparticles of semiconductor was first reported. For the biosynthesis, different microbes are used but, only few studies have been focused in luminescent properties. QDs are used as markers on proteins and nucleic acids for visual detection (Khiyami et al. 2014) as well as used for construction of biosensor designed for disease detection. Nanochips which are made of microarrays that contain fluorescent oligo probes which help in detecting single nucleotide change in viruses and bacteria. Many fluorescence resonance energy transfer (QD-FRET) sensors have been developed for disease detection in plants. For example, in *Rhizomania* disease, *Polymyxa betae* (Keskin) (Joshi et al. 2019) are the only known vector of BNYVV (Beet necrotic yellow vein virus) for the transmission of the virus to the beet plants, which were reported to be detected with QD-FRET-based sensor.

3.5 Nanofabrication

Nanofabrication is basically used for the development of artificial plant parts like xylem vessels and stomata. This process is helpful for the study of infection and behavior mechanism of plant pathogens inside host plant for example *Uromyces appendiculatus* (fungus causing rust disease of bean). *Colletotrichum graminicola* (fungus causing anthracnose in corn), and *Xylella fastidiosa* (xylem limited bacterium causing Pierce's disease of grapevine). All these pathogen infection mechanisms are studied by using nanofabrication tools.

3.6 Portable Nanopore Sequencing and Genome Sequence

Next-generation sequencing (NGS) technologies worked as key in recent decades to dramatically reduce the cost and time for pathogen identification with metagenomics strategies. Nano pore sequencing is also known as fourth-generation DNA sequencing technology. Application of external charges the electrolytes in the solution move from one side to another nanopore electrophoretically, due to which generates quantifiable ionic current. The first beta-testing of Minion can simplify the work by connecting to a USB port. As this device works with the flow of cells where the nana pore cells are mobilized; 5–10 Gb of sequencing information will be generated by each flow of cells. By the use of Minion, suitable work can be made in the remote location with small-sized particles (Quick and Choo 2017). Application of this device has also been tested in International Space Centre (NASA 2016). When the DNA strands move through biological nanopores by applying an electric field the Minion technology measures its rate, and also helps in detecting the translocation of DNA molecule (Jain 2003). It has been widely used to identify viruses without culturing, and using environmental samples directly, in the field of plant pathology (MacDiarmid et al. 2013; Boonham et al. 2014). However, till date the majority of the experiment on NGS assays are done in particular laboratories, require costly equipment, and complicated data algorithm (Feng et al. 2015). Nano pore technology is thought to be straight forward. The DNA passes into the nano pore and a direct electronic analysis is conducted. For the control of single standard DNA, an enzyme and a protein were designed. At the top of each micro well, this protein nano pore was inserted with a polymer bilayer membrane. A sensor chip has been inserted on each micro well in which the ionic current that has a single molecule passes through the nanopore.

3.7 *Portable PCR Systems and Portable Equipment*

Portable PCR is used for the amplification of DNA and agarose gel detection of pathogen which is efficiently used for amplification and detection of different types of samples plant pathogens. It will also not only simplify the detection techniques for the identification of plant diseases but also provides an effective way to do other tests at molecular levels. The amplified DNA is long enough to carry out agarose gel detection. This portable type of system provides an effective way to perform different types of PCR techniques for detection and diagnosis purposes. Comparing with the other techniques, the TWISTA quantitative and portable real-time fluorimeter provides a real-time analysis for examining the recombinase polymerase amplification. The advantages of portability and speed provide more efficiency in testing the DNAs for further analysis. Comparing with other traditional microbiological assays, Twista RPA fluorometer will supply instant fast diagnosis which requires a molecular assay in centralized equipment that can be done in the least hours (Fig. 8.3).

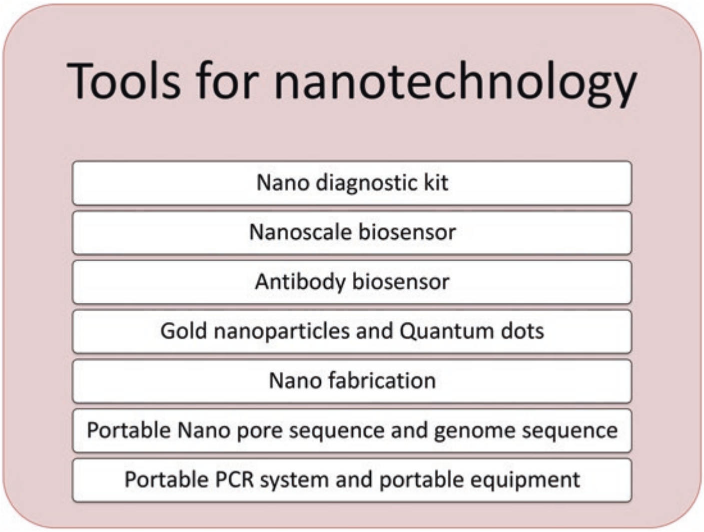

Fig. 8.3 Tools of nanotechnology

3.8 Nanotechnological Advancement of Plant Pathogen Identification and Diagnosis

Nanotechnology is an newly emerged science for identification of real cause of disease or disorder due to the biotic, mesobiotic, and abiotic factors, which is also useful for identification and elimination of latent types of symptoms of diseases or disorders such as viral and viroid diseases and nutrient-deficient expression of plant.

3.9 Fluorescent Silica Nanoparticles Merge with Antibody Molecules (FSNP)

Silica nanoparticles are used for detection and diagnosis of entity of several diseases of crop plants. Mostly fungal and bacterial are diagnosed with the help of Fluorescence silica nanoprobe that acts as a biomarker is used to detect *axonopodis* pv of *Xanthomonas.*

4 Modified Copper Nanoparticles with Gold Electrode

Copper nanoparticles with gold electrode with electrolytic oxidation help in the detection of fungal pathogen *Sclerotinia sclerotiorum* of rapeseed crop.

4.1 QD Cadmimumtelluride Thioglicolic Acid

Use of quantum dots (FRET) biosensors could detect *Polymyxa betae*, acting as a beet necrotic yellow virus (BNYVV) vector, in sugar beet *Rhizomania* disease and *Candidatus Phytoplasma aurantifolia*.

4.2 Nano Structural Layer of Biosensors and CuO Nanoparticles

CuO nanoparticles synthesis and manufacture of biosensors for nanostructural layers to detect the fungus *Aspergillus niger.*

4.3 Carboxylic Groups Contain Modified QD

Devise of the DNA biosensor based on the fluorescence energy resonance transfer (FRET) for detection of *Ganoderma boninense* synthetic oligonucleotide, a pathogen of the oil palm.

4.4 Nanoribbon and Nanorod

Nanoribbon polypyrrole chemiresistive immuno sensors are used for the detection of viral pathogen, whereas nano rod-based fiber is used for the detection of orchid virus.

4.5 Carbon Electrodes are Screen Printed by TiO_2 and SnO_2 Nanoparticles

By using oxide nanoparticles, the fungi-infected fruit can be detected with the help of electrochemical detection of p-ethylguaiacol.

4.6 Silver Nanoparticle and Nanowire

Plant diseases can be detected by the use of nanowire-based biosensor. Isothermic based amplification with combination of chip hybrids may be used for the detection of selected *Phytophthora species.*

4.7 Metal Diagnostics Nanoparticles

Biochemical sensors metal nanoparticles can be used as marker tags to replace enzymes as the name. Voltammetry striping can detect nanoparticles of metal directly making the test simple. The gold (AuNP) and silver nanoparticles (AgNP) can be used for analytical detection using these techniques, including various inorganic nanocrystals (ZnS, PbS, and CdS) (Upadhayayulva 2012). The last 15 nucleotides are in addition to a sequence of one half the target. Once objective DNA is inserted into the process, all AuNP forms bind to an aggregate DNA. Colloidal AuNPs are highly sensitive and selective than conventional strategies. They can be used to detect specific pathogen goals (Khan and Rizvi 2014). The AuNP system has two AuNP types: each covered with various thiol oligonucleotides. Oxanica

(UK) Quantum dots and MultiPlx Beads™ from Crystalplex Corporation, USA (Tothill 2011) are the various products which are available in the market. Nanoparticles can also be used in conductivity sensors in which a signal change can be caused upon the attachment of the antigen to the sensor surface with nanoparticles (Servin et al. 2015). Different strategies have been developed for accurate detection between the target phytopathogenic cells and biofunctionalized nanomaterials, including antimicrobial antibodies, adhesion receptor, antibiotic, and DNA complementary sequence recognition. Gold nanoparticles are good markers in biosensors because optical and electrical pathogens can be easily changed. Singh et al. (2010) exploited a plasma resonant (SPR) based on nanogold immunosensors capable of detecting karnal bunt disease of wheat (*Tilletia indica*). Gold nanoparticles "capacity to act as quenchers for fluorescent labeling at the end of 50 of DNA oligonucleotides and coupled with gold nanoparticles at 30" (Dubertret et al. 2001; Thakur et al. 2020). The treatment of phytoplasmas associated with grapevine dore'e flavescence (FD) demonstrated improvement in the application of these oligonucleotides (Firrao et al. 2005). Gold nanoparticles have opened new prospects for optical production of nano biotransducer quality for diagnostically purposes to quench fluorescence from light harvester polymer, such as polyfluorene (Fan et al. 2003). Oligo AuNP probes are hybridized with oligonucleotide-functionalized magnetic microparticle (MMP) probes in the case of oligonucleotide targets using the target sequence as a linker. Such complexes are then magnetically isolated from the oligo-AuNP probes for subsequent release of the oligonucleotides. The scan metrical studies evaluate these published biobarcodes quantitatively. The experiment allows rapid identification in engineered conditions (Goluch et al. 2006) of nuclear acids at high zeptomolar concentrations (Nam and Kim 2004) and protein targets at low molar values. In combination with on-chip hybridization in order to detect plants and *Phytophthora*, Schwenkbier et al. (2015) developed a helicase-dependent isothermal amplification (HDA). This method enables an effective amplification of the GTP (Ypt1) target gene region of the yeast in a miniaturized heating system at a constant temperature. DNA hybridization in chips and subsequent silver nanoparticles deposition were used to determine the specificity of the sample. This is a step toward onsite and simultaneous detection of several types of plant pathogens. It is a sign of the silver deposits that enables both visual and electrical readout. The use of nanostructures, due to its high surface-to-volume ratio, size-dependent electric properties, and possibilities for device miniaturization, has been expanded in the advancement of nanotechnology and biotechnology as a new platform diagnosis (Prieto-Simon et al. 2007; Sertova 2015). The design of pathogen-sensing platforms and mycotoxin determination platforms is based on nanoparticles, such as carbon nanomaterials (carbon nanotubes and graphene), nanocomposites, and nanostructured nano metal oxide nanoparticles (Abu Salah et al. 2015). The large format and potential to detect interesting compounds in timely sample volumes at high speed are a major benefit of such systems (García Alvarez et al. 2010). The set of thousands of nanoparticles developed by Bhattacharya et al. (2007) was visualized in different colors in contact with food pathogens. The micronutrients are other types of nanostructure platforms, which can also efficiently and highly sensitively detect pathogens in real time (Baeummer and Dhawan 2004).

4.8 miRNA Expression Pattern in Diseased State

Different biological processes such as cell growth and growth, biogenesis, transduction of signal, and apoptosis are involved with miRNAs. Genetic alterations are often caused by miRNA genes because it is found in fragile region of the genome. Horseradish peroxidase (HRP) biosensors were also used for the detection in spiking beer and roasted coffee without any pretreatment. For the detection of ultratrace amounts of aflatoxinM1 (AFM1 (up to 0.01 ppb) produced by *Aspergillus flavus*, Paniel et al. (2010) used magnetic nanoparticles to improve the electrochemical immune sensor. Hervas-Stubbs et al. (2011) described the "lab on chip" strategy for the fast, sensitive, and discriminatory quantification of *Fusarium* sp generated zearalenone by means of an electrokinetic magnet-based electrochemical immunoassay in a microfluidic chip. Ansari and Raghava (2010) have shown that solgel-based nanoZnO film can be used to block rIgG or BSA for detecting 0.0060.01 nM OTArange detection from unspecific binding sites of r-IgG. Kaushik (2013) have developed a film-based immunosense nanostructuring cerium oxide detective method for foodborne mycotoxins. Rabbit immunoglobulin anti-conservation and BSA are immobilized on a cerium oxide film synthesized with a soil-free nanostructure on an indium oxide plate to detect ochratoxins. Mak et al. (2012) stated that for the detection of more than one mycotoxin ultrasensitive magnetic nanoparticle is used.

The gap between the clay layers has been extended ten times by the use of nanosized clay and nanoclay can therefore bind the entire mycotoxin family. In combination with smaller water molecules and smaller mycotoxins, as aflatoxin and ochratoxin, silica, and clay are most efficient. Moreover, clays are less active in binding large mycotoxins, including fumonisin and vomitoxin, since there is not enough space between the layers of clay to accommodation in larger molecules (Jaynes et al. 2007). The use of superparamagnetic nanoparticles enhances a simple enzyme-connected immune sorbent assay (ELISA) (Radoi et al. 2008). A 4-mercaptobenzoic acid-based monolayer on a gold electrode (ABA/Au) to produce the BSA/aAFB1CAuNP/MBA/Au immune electrode was immobilized for cysteamine functional gold nanoparticles (C-AuNP) together with aflatoxin-B1 anticorps (aAFB1). Such electrodes have been used to detect AFB1 between 10 and 100 ng L^1 (Sharma et al. 2010). A moving machine has recently been developed which can at the same time identify different bacterial, fungal, and pathogenic toxins in stored food (Biswal 2012; Yalcin and Otles 2010).

From all these studies, nanostructured platforms seem to be a promising alternative to traditional mycotoxin and pathogen detection techniques which ruin foodstuffs and farm crops.

4.9 Nanobiosensor Diagnostics

Nanosensors selective for target analyte molecules with immobilized bioreceptor samples are called nano biosensors. They are highly sensitive, accurate, quantorial, precise, reproducible, and reliable and thus can be used for minute quantification and identification in agriculture and food systems for the use of pollutants such as viruses, bacteria, fungi, toxins, and other biohazardous substances (Srinivasan and Tung 2015; Singh et al. 2020). Such sensors can be connected to GPS and distributed in the field to track diseases, soil conditions, and plant health in precise agriculture in real time (Nezhad 2014). Nanosensors allow us to recognize diseases of plants prior to visible symptoms and thereby improve diseases and farm production and productivity (Rai and Ingle 2012). Dubas and Pimpan (2008) found that silver nanoparticles in a solution were prone to increased ammonia concentrations and caused a color variance from yellow to orange red and, finally, violet. This can be used to develop nanosensors to detect contamination from food, plants, and the environment as organic pollutants and microbial toxins (Dubertret et al. 2001). Fluorescent silicon nanoparticles, together with anticorps pathogens *Xanthomonas axonopodis* pv, are successfully observed. Bacterial spot conditions in tomatoes and peppers are caused by Vesicatoria (Yao et al. 2009).

Nanoparticles and nanolayers of copper oxide (CuO), which consist of nanowires, such as DNA molecules, polypeptides, fibrin proteins, and filamentous bacterial phages, have been synthesized using the sol gel and spray process, of which major sensing elements are composed. Since the surfaces of the nanowire are easily modified, almost every possible chemical or molecular biological detector unit can be used to decorate nanowires, making the wires autonomous.

Nanomaterials are extremely sensible, in real time and quantitatively to the nanowire conductance on their surface to express the chemical-binding activity. Ariffin et al. (2014) have used nanowire to detect cucumber mosaic virus and papaya ring spot virus as biosensor for this theory. Remote nanowires have been shown to be an excellent material for the development of nanoscale biosensors for further applications in plant health care, diagnosis of diseases, and environmental monitoring, for *Aspergillus niger* fungi detection. Nanowire biosensors are a category of nano biosensors which need more work to be used on a wide range of soil.

5 Use of Nano Carbon as a Sensor

In our research lab at nsnRc we work on Carbon Nano Material Selection for electrochemical sensors by measuring the electrochemical properties of different CNM from several different raw materials as a result of different pesticides. Electrochemical analysis already includes carbon as an electrode (Sharon 2008; Kareem et al. 2019). Residual pesticides are not just detrimental to human consumption in animals, but also less beneficial for crops. In order to provide the correct oxidation/reduction possible values for a specific analytic, it is important to prepare electrochemical cell having CNM as an electrode in this sensor. Nanosensors are small enough for traps and measures of individual proteins or little molecules that use carbon nanotubes or nano-cantilevers.

Many nanosensors operate by initiating enzyme reactions or by using nano-generated molecules called dendrimers to bind chemicals and proteins. Nanoparticles or nano surface elements trigger electric or chemical signal. For increased sensitivity and a lower response time due to nanosensors, pathogens and contaminant detection are possible.

5.1 Plant Disease Control Nano-Particles

Nano forms of carbon, gold, silica, and aluminum silicates are some of the nanoparticles in the field of managing plant diseases.

5.2 Nano Carbon, Silver, and Aluminosilicate

Nanosciences, in which completely different materials, new technologies, and new expectations exist for existing challenges concerning the regulation and use of agrochemicals, pesticides, and herbicides (Prasad et al. 2014, 2017). Focus is given to research in carbon nanoparticle production to reinforce, for example, natural fibers from coconuts, sisal, or nanoparticles containing or regulated by pesticides. Brazilian Agriculture Research Company (Embraga) is responsible for the production. Through developing agricultural nanotechnologies, Brazil is seeking to improve the quality of its exports. Most scientists focus on carbon nanotubes (CNTs). Carbon nanotubes are carbon allotropes whose cylindrical shapes are nanostructure. Such nanotubes are used in many ways, in particular in nanotechnology, electronics, and architecture. Frequently used as thermal conductors, such nanotubes contain special and surprisingly strong electrical properties.

Nanosilver nanoparticle for the bio-system is the most studied and used. Silver nanoparticles have a high surface area and a high proportion of the surface atoms relative to bulk gold. For a long time, significant inhibitory and bactericidal effects and a wide range of antimicrobial activities have been identified. Kim et al. (2008) reported that antifungal effectiveness of the *Sphaerotheca pannosa Var rosae* solution of colloidal nanosilver (1.5 nm average diameter) in powdery mildew. Greenhouse and outdoor roses are very prevalent and commonly known. It distorts the leaves, causes the leaves to curl, defoliates early, and reduces flowering. The chemical reaction of silver ion using physical method, reduction agent, and stabilizers was used to produce double capsulized nanosilver. In aqueous solution, they were very stable and very well dispersed. The 5000 ppm concentration nanosilver colloidal solution was diluted in 10 ppm of 500 kg and sprayed at an area of 3306 m^2 contaminated with rose powdery mildew. During 2 days, more than 95% of rose-powdery mildew was sprayed. Colloid nano silver is a well spread and stable solution for silver nanoparticle and is more resistant for bacteria and fungi, hence stronger fungicide. It is no wonder that "silver nano for the preservation and treatment of agricultural diseases" has been filed with maximum patents. Nanosilver was very common because of its control and identification of nanosilver as a pesticide (Anderson 2009).

Another such initiative is the use of active ingredient alumina silicate nanotubes. The benefit is that nanotubes sprayed from alumina silicate on plant surfaces are quickly collected in insect hair. The insects purposefully grow and eat nanotubes filled with pesticides.

5.3 Association Nanostructures Colloidal Forms for the Supply of Functional Ingredients

The ideal nanomaterials for nanodispersions and nano capsulation for the delivery of functional ingredients were found to be surfactant micelles, vesicles, bilayers, reverse micelles, and liquid crystals etc. Colloid is a stable system of small particulate matter that is scattered throughout a liquid. Colloids associated with polar, non-polar, and amphiphilic functional components have been used for many years to deliver. Nanoparticle size ranges from 5 to 100 nm in colloids. The biggest disadvantage is that colloids can dissociate spontaneously when diluted (Flanagan and Singh 2006; Chaudhari et al. 2020).

5.4 Nano-Emulsion Ingredients

Nanoemulsions can encapsulate functional ingredients in outlets that can reduce chemical degradation. It is a combination that doesn't blend easily two and more liquid (such as oil and water). The dispersed droplets have diameters of 500 nm or lower in nanoemulsion (Clements and Decker 2000; Youssef and Elamawi 2020).

6 Conclusion

Nanotechnology is the trending after biotechnology for groundbreaking research. However, in plant pathogen detection, the nanotechnological application is still in its infancy. Finding out new strategies to handle diseases would help further bio-nano technological research, particularly with regard to physiology, infection mechanisms, and disease diagnostics.

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Chapter 9
Microbial Nanotechnology in Life Sciences: An Opportunity for Green Applications

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Contents

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1 Introduction: Mechanisms of NPs Production by Microorganisms

Various microorganisms have different mechanisms for NPs production. Nonetheless, NPs are generally formed according to the following approach: first, the metallic ions are trapped on the surface or inside the microbial cells. After that, the trapped metal ions are reduced to NPs in the presence of enzymes. Generally, microorganisms influence the formation of the mineral through two different methods: they can change the solution's composition until it becomes supersaturated or more supersaturated than it formerly was regarding a particular phase. They can also affect mineral formation via the manufacturing of organic polymers; in turn, influencing the nucleation by preferring (or inhibiting) the stabilization of the first mineral seeds (Benzerara et al. 2011). Some feasible formation mechanism for some usual NPs: silver and gold NPs, heavy metal NPs, magnetic NPs, and sulfide NPs are reviewed in this part (Li et al. 2011).

The intracellular formation of the NPs of silver and gold using *Verticillium* sp. or algal biomass was not comprehended precisely. However, the formation of NPs on the surface of the mycelia advocates the following theory: the silver or gold ions were first trapped on the surface of fungal cells through electrostatic interaction among the ions and negatively charged cell wall from the carboxylate groups in the enzymes. Then, the metallic ions were reduced by enzymes, producing silver or gold nuclei, which then grew via further reduction and accumulation (Sneha et al. 2010; Prasad 2016, 2017; Prasad et al. 2018; Srivastava et al. 2021). Kalishwaralal et al. (2008) suggested that the enzyme of nitrate reductase is engaged in the production of NPs of silver in *Bacillus licheniformis*. The nitrate ions activate this enzyme and reduce silver ions to metallic silver. The electron shuttle enzymatic metal reduction process is considered as a probable mechanism probably involving the reduction of silver ions. In the biosynthesis of metallic NPs, NADH and NADH-dependent nitrate reductase enzymes are significant factors. *B. licheniformis* is reported to secrete the cofactor NADH and NADH-dependent enzymes, particularly nitrate reductase, probably responsible for the bioreduction of Ag^+ to Ag^0 and the consequent formation of silver NPs (Husseiny et al. 2007).

The heavy metallic NPs are formed, probably because the metallophilic microorganisms develop proteomic and genetic responses to poisonous environments (Reith et al. 2007). Besides, heavy metal ions, such as Cd^{2+}, Ag^+, Hg^{2+}, Cu^{2+}, Ni^{2+}, CrO_4^{2+}, Co_2^+, Zn^{2+}, and Pb^{2+}, have toxic effects on microorganisms' survival. To address these impacts, microorganisms have developed proteomic and genetic responses to strictly regulate metallic homeostasis (Nies 1999). In addition, they possess many metal resistance gene clusters making cell detoxification possible through a variety of mechanisms like reductive precipitation, efflux, or complexation. Therefore, metallophilic bacteria grow in the presence of high concentrations of heavy metallic ions, like mine waste rock piles, efflux streams of metallic processing plants, and naturally mineralized zones (Mergeay et al. 2003). A multistep process is used for the molecular mechanism of bacterial magnetic particles biomineralization (Arakaki et al. 2008). In the first step, the cytoplasmic membrane is investigated and the formed vesicle serves as the precursor of the bacterial magnetic particle membrane. However, the envelope formation mechanism yet remains unknown. According to most reports, the mechanisms mentioned for the vesicle formation for magnetotactic bacteria are similar to most eukaryotes and the priming of the invagination is mediated by a particular guanosine triphosphatase. Then, the assembling of produced vesicles is done into a linear chain along with cytoskeletal filaments. Ferrous ions are accumulated into the vesicles by the transmembrane iron transporters in the second step of bacterial magnetic particles biomineralization. The transport proteins and siderophores are used to internalize the external iron. The strict control of interior iron is run utilizing an oxidation–reduction system. Finally, in the third step, tightly bound bacterial magnetic particle proteins trigger magnetite crystal nucleation and/or regulate morphology. Different proteins related to the bacterial magnetic particle membrane could have fundamental roles in magnetite production, namely the upkeep of reductive conditions, the oxidation of iron to induce mineralization, accumulation of supersaturating iron concentrations, or the partial reduction and dehydration of ferrihydrite to magnetite (Arakaki et al. 2008). Recently, Perez-Gonzalez et al. (2010) recommended another plausible mechanism for synthesizing magnetite by *Shewanella oneidensis*, containing both active and passive mechanisms. First, when ferrihydrite is applied by bacteria as a terminal electron acceptor, the active generation of Fe^{2+} happens, and the pH value surrounding the cells increases, likely because of the bacterial metabolism of amino acids. After that, via a passive mechanism, the concentration of Fe^{2+} and Fe^{3+} localized at the net negatively charged cell wall, cell structures, and/or cell debris causes a locally increased supersaturation of the system for magnetite, leading to the precipitation of the magnetite phase. Furthermore, the formation of CdS NPs is via disulfide (cystine) bridges, attributable to the cleavage of S–H bonds and formation of a novel bond, that is, –S–Cd bond of Cd–thiolate ($Cd{-}S{-}CH_2COOH$) complex on the NPs surface (Sanghi and Verma 2009). Hence, as stated by Tang et al. (2005), the capped CdS NPs are bonded via hydrogen bonds to $-NH_2$ groups.

2 Uses of Microbial Nanotechnology

NPs of microbial sources have diverse uses in various fields, for example, medicines, anticancer and antitumor agents, antimicrobial agents, diagnostics, drug delivery, agriculture, environmental, bioremediation, food and beverages, cosmetics, coatings, packaging, electronics, catalysis, and so on (Prasad et al. 2016; Prasad and Aranda 2018; Prasad 2019a, b; Maddela et al. 2021). This section discusses some of these uses.

2.1 Uses of Microbial Nanotechnology in the Medicine

Nano-medicine refers to the application of structures with nanoscale for diagnosis, treatment, and disease prevention, contributing to human health improvement (Patil et al. 2008; Grasso et al. 2020; Maddela et al. 2021). Nanomaterials are comparable with cell organelles containing nano-size proteins; therefore, they can be utilized to goal sites without interfering with other cell machinery (Salata 2004). Different chemical and physical approaches are widely utilized for synthesizing NPs. Although they yield higher production rates and better control of size in the produced NPs, they are considered undesirable because of using poisonous reagents and producing hazardous wastes, raising production cost, and required energy. Furthermore, the NPs synthesized chemically are less biocompatible and the usage of poisonous chemicals for synthesis plus lack of stability has restricted their utilization in clinical uses (Hosseini and Sarvi 2015; Fariq et al. 2017). Hence, biocompatible and affordable approaches are required for the synthesis of NPs. Synthesis of NPs through biological sources suggests a nontoxic, cheap, and eco-compatible alternative, compared with chemical and physical techniques (Ahmed and Ikram 2016; Prasad et al. 2016). The microbial synthesis of NPs has combined different sciences such as microbiology, biotechnology, and nanotechnology into a novel field entitled nano-biotechnology. It is at its early stages, but due to its numerous advantages, it may have promising uses in nano-medicine (Narayanan and Sakthivel 2010).

2.1.1 Biosynthesized NPs as Antimicrobial Agents

The emergence of antibiotic-resistant pathogenic strains has prompted an increment in the rate of infective diseases related to these microorganisms. Successive exposure of microbes to antibiotics for several generations increases their resistance. Microbes have developed complicated mechanisms to resist antibiotics such as inactivating them, altering the target site, changing the metabolic pathways, and so on (Seil and Webster 2012; Koch et al. 2021). Thus, researchers should look for alternative antibiotics with potent bactericidal and bacteriostatic abilities.

Microbial NPs are reported to show potent antibacterial activities. NPs' effectiveness may be because of their greater surface area, enhancing their interaction with the microorganisms. After adhering to the cell membrane, they interact with DNA and penetrate inside, thus interfering with the replication process or attacking the respiratory chain of pathogens (Aziz et al. 2014, 2015, 2016, 2019). Besides, a similar bactericidal mechanism was observed for the silver NPs obtained from endophytic bacterium *Bacillus cereus* versus pathogenic bacteria such as *Escherichia coli*, *Staphylococcus aureus*, *Salmonella typhi*, *Klebsiella pneumoniae,* and *Pseudomonas aeruginosa* (Sunkar and Nachiyar 2012). There is a different probable mechanism of antimicrobial activity of NPs including the structural damage to cell membranes, leading to the formation of pits and subsequent degradation of cel-

Table 9.1 Antimicrobial activities of biosynthesized NPs of silver

Source of Ag NPs	Antimicrobial activities	References
Alternaria alternata	*Pterolepis glomerata*, *Trichoderma* sp., *Candida albicans*	Gajbhiye et al. (2009)
Cryphonectria	*Staphylococcus aureus*, *Escherichia coli*, *Salmonella typhi*, *Candida albicans*	Dar et al. (2013)
Klebsiella pneumoniae	*E. coli*, *S. aureus*	Shahverdi et al. (2007a, b)
Lysinibacillus varians	*P. aeruginosa*, *E. coli*, *S. aureus*, *C. albicans*, *Bacillus subtilis*	Bhatia et al. (2016)
Ochrobactrum anhtropi	*Salmonella typhi*, *Salmonella paratyphi*, *Vibrio cholera*, *Staphylococcus aureus*	Thomas et al. (2014)
Streptacidiphilus durhamensis	*Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Proteus mirabilis*, *Escherichia coli*, *Klebsiella pneumoniae*, *Bacillus subtilis*	Buszewski et al. (2018)
Staphylococcus aureus	*Staphylococcus epidermidis*, *S. aureus*, *Streptococcus pyogenes*, *Klebsiella pneumoniae*, *Salmonella typhi*	Nanda and Saravanan (2009)
Trichoderma viride	Different Gram-positive and Gram-negative microbes	Fayaz et al. (2010a, b)

lular constituents, and lastly their death (Sondi and Salopek-Sondi 2004). Malarkodi et al. (2013) biosynthesized TiO_2 NPs using *Planomicrobium* sp. and assessed their antimicrobial effect versus *B. Subtilis*, *A. niger*, and *K. planticola*. Abdeen and Praseetha (2013) described that iron NPs synthesized with *Fusarium oxysporum* showed antimicrobial features versus *Bacillus, E. coli*, and *Staphylococcus* sp. Iron NPs with small sizes restricted oxygen supply, and as a result, disrupt the respiration process of pathogenic microorganisms. Antimicrobial activities of biosynthesized silver NPs versus pathogenic microorganisms are described well (Table 9.1). Nevertheless, antimicrobial properties of other NPs synthesized biologically and their action mechanisms are yet to be known.

2.1.2 Biosynthesized NPs as Antitumor and Anticancer Agents

In recent years, cancer all over the world is becoming one of the major reasons for mortality. Customary cancer treatment approaches including surgery, radiation, or chemotherapy have known side effects. Furthermore, in-time diagnostics and localized drug delivery to the targeted organ are yet not well known (Jabir et al. 2012). Because of these restrictions, the numbers and variety of cancers (blood, lung, breast, colon, and so forth) are increasing day by day, highlighting the necessity of logical alternatives to address these problems.

Nano-medicine has been efficiently experienced for detecting tumor, targeted delivery of drugs, and treatment (Sutradhar and Amin 2014). Anticancer activities of *Saccharomyces boulardii* biosynthesized platinum NPs were assessed versus A431 and MCF-7 cell lines (Borse et al. 2015). The Ag NPs gained from

Cryptococcus laurentii were efficient for antitumor activity versus both normal breast cell lines and cancer cell lines. Moreover, the effectiveness of Ag NPs was reported to be dependent on the cancer cells' endocytosis activity (Ortega et al. 2015). Noticeably, selenium nanorods, biologically produced from *Streptomyces bikiniensis* showed considerable anticancer activity via induction of death in MCF-7 and Hep-G2 human cancer cells. Ahmad et al. (2015) suggested a mechanism for their anticancer activity, including mobilization of chromatin-bound copper followed by prooxidant action and consequent death of Hep-G2 and MCF-7 cells. Furthermore, gold NPs produced by *Streptomyces cyaneus* were examined in vitro in terms of anticancer activity versus human breast carcinoma and liver cells, for example, MCF7 and HEPG-2, respectively. The stimulation of mitochondrial apoptosis and localization of nuclei of cells by Au NPs caused DNA impairment, also inducing cytokinesis detention (El-Batal et al. 2015).

2.1.3 Biosynthesized NPs in Drug Delivery Systems

NPs are reported to have considerable applications in targeted drug delivery, drug bioactivity bioavailability, and stability (Prasad et al. 2017). As outlined by researchers (Salouti and Ahangari 2014; Omlor et al. 2015; Brakmane et al. 2012), the drug delivery nano-vehicles of different types contain a water-soluble polymer like synthetic polymers and natural antibodies, liposome composed of the vesicle with bilayer wall, nanosphere of natural or synthetic polymers, polymeric micelles and emulsions stabilized by amphipathic surface coatings. Since NPs have surface properties and small sizes, they contribute to the proper reaching of pharmacologically active compounds inside all the cell compartments of the human body at the optimal rate. Besides, the formation of conjugates between drugs and NPs by encapsulation or via various linker molecules can lead to the control of toxicokinetics. They decrease the poisonous side effects of drug carrier systems whilst preserving therapeutic impacts on the patients. Compared to conventional drug delivery systems, NPs have numerous advantages such as specific targeting and bio-distribution, biocompatibility, and safety (De Jong and Borm 2008). The conjugation of multi-shaped gold NPs derived from fungus *Helminthosporum solani* to anticancer drug doxorubicin was reported. The conjugated drug was more easily taken into HEK293 cells with cytotoxicity comparable to doxorubicin (Kumar et al. 2008). Furthermore, Khan et al. (2014) synthesized gadolinium oxide NPs using thermophilic fungus *Humicola* sp. and bioconjugated it with anticancer drug taxol, aiming at incrementing its potency versus antitumor cells via utilizing these NPs as drug delivery.

2.1.4 Biosynthesized NPs in Diagnostics

The incidence of infectious illnesses is one of the main reasons for mortality in developing countries. They can spread rapidly from one region to another and could become a worldwide epidemic. For quick detection of illnesses, new technologies of diagnostics are necessary (Hauck et al. 2010). Traditional approaches to the diagnosis of the disease include microscopy, culturing of microorganisms, immunoassays, and molecular diagnostics, and biochemical tests. However, these approaches are boring, time-consuming, and difficult. Nanomaterials suggest quick, specific, exact, ultrasensitive, and easy-to-utilize diagnostic tools for pathogen detection. Although fluorescent NPs (quantum dots and dye-loaded NPs), metallic NPs, and magnetic NPs have been efficiently applied to the image, track, and recognize various pathogens (Tallury et al. 2010), the role of biosynthesized nanomaterials in diagnostics is not completely known. The potential of *Candida albicans*-mediated biosynthesized gold NPs was assessed to probe liver cancer cells through their binding with liver cancer cell surface-specific antibodies. According to obtained results, the antibody-conjugated gold particles bonded clearly to the surface antigens of affected cells, enabling the unambiguous to distinguish of normal cells from cancer cells (Chauhan et al. 2011).

2.1.5 Conclusion

Although microbes showed the secure, eco-friendly, and economical method of NPs synthesis, in contrast with their chemical alternates, the absence of monodispersity beside uncontrolled size, and time-consuming production process have restricted their usage on a commercial scale. Thanks to the nontoxicity of biosynthesized NPs, they indicated favorable potential in nano-medicine; however, their use in drug delivery and diagnostics is still has a long path ahead. Furthermore, more research is necessary to comprehend the mechanisms of NPs synthesis to obtain higher production rates and desired morphology. Moreover, the scale-up of their production is much required for therapeutic uses in the future.

2.2 Uses of Microbial Nanotechnology in the Agriculture

The effective utilization of nanotechnology in various fields has pulled in extensive consideration of agricultural researchers to modernize the agricultural part toward agri-nanotechnology (Nair et al. 2010; Ghahari et al. 2018; Usman et al. 2020). This new technology has a vast array of applications, for example, enhanced nutrient uptake, better plant disease control, sustained release of agrochemicals, and improved plant growth (Salamanca-Buentello et al. 2005; Mishra et al. 2014b; Mishra and Singh 2015a, b; Prasad et al. 2014).

2.2.1 Uses of Nanotechnology in Agriculture

There is a conspicuous need to raise crop production via using traditional and advanced technologies whilst simultaneously keeping up maintainability in the agroecosystems. The most important challenges facing the agricultural sector are biotic and abiotic stresses, which impede total agricultural production. Therefore, the development of agricultural technology becomes essential for these challenges to be coped. Over the previous decade, the use of nanotechnology in the agricultural sector has obtained momentum by delivering strong applications (Kah and Hofmann 2014). These contain nanotechnological uses in resistance to plant disease and plant growth (Ghormade et al. 2011; Chowdappa and Gowda 2013).

During the 1970s, the use of chemical pesticides for plant disease management came into existence after the promotion of the green revolution, changing the overall picture of the agricultural sector. Utilization of chemical pesticides led to successful control over plant diseases, however, at the same time, it resulted in numerous environmental and health hazards including development of pesticide-resistant pathogens, a decrease in soil fertility, and accumulation of pesticide residues in the food chain (Tilman et al. 2002; Sangeetha et al. 2017a, b, c).

There has been a growing demand for biopesticides in the last few decades because of rising awareness of the health and environmental risks caused by chemical pesticides. Biopesticides are a useful, environmentally friendly way of controlling plant diseases. Currently, the main worldwide market portion is occupied with chemical pesticides, whilst biopesticides are just in their early stages (Glare et al. 2012; Rana et al. 2020). Recently, the pioneering method of harnessing nanotechnology and its uses in agriculture is obtaining significant importance and it is known that this technology may be capable of tackling a number of the main concerns associated with the use of biopesticides (e.g., on-field stability, shelf life, coverage area, and required dose) (Ghormade et al. 2011; Singh 2014; Mishra et al. 2014a; Mishra and Singh 2015a; Bhattacharyya et al. 2016).

NPs produced via nanotechnology in the size range of 100 nm or less have exclusive physical, biological, and chemical specifications, contributing to promising uses in agriculture. These NPs with a broad surface area are extremely stable and offer size-dependent characteristics (Nair et al. 2010). Synthesis of NPs is done via chemical and physical approaches and until now numerous organic and inorganic materials have been produced utilizing these approaches. Although, the materials produced via these techniques are costly, unstable, and environmentally dangerous. Hence, at present, the synthesis of NPs via biological methods, either of microbial or plant origin, are gaining popularity as they are non-toxic, low cost, and eco-friendly (Gardea-Torresdey et al. 2002; Raut Rajesh et al. 2009; Mishra et al. 2014b; Prasad 2014, 2019c).

It is evident from prior reviews that biosynthesized silver NPs act as a potent fungicide versus different phytopathogens and have effectively controlled plant diseases caused by them (Jaidev and Narasimha 2010; Mala et al. 2012; Gopinath and

Table 9.2 Varied role of biosynthesized NPs in agriculture

Microbial sources	NPs	Applications	Reference
Aspergillus niger	Silver (Ag)	Antifungal and antibacterial activity	Jaidev and Narasimha (2010)
Aspergillus fumigatus	Zinc oxide (ZnO)	Enhanced native phosphorus-mobilizing enzymes and gum production in cluster bean	Raliya and Tarafdar (2013)
Brassica juncea	Copper (Cu)	Antifungal activity against phytopathogens	Umer et al. (2012)
Brassica rapa	Ag	Antifungal activity against wood-rotting pathogens	Narayanan and Park (2014)
Bacillus sp.	Ag	Antifungal activity toward *Fusarium oxysporum*	Gopinath and Velusamy (2013)
Cow's milk	Ag	Antifungal activity against phytopathogens	Lee et al. (2013)
Calotropis procera	Ag	Antimicrobial activity	Mohamed et al. (2014)
Serratia sp.	Ag	Antifungal activity toward *Bipolaris sorokiniana*	Mishra et al. (2014b)
Spirulina platensis	Ag	Bactericidal activity against phytopathogens	Mala et al. (2012)
Trichoderma viride	Ag	Vegetable and fruit preservation	Fayaz et al. (2010a)

Velusamy 2013; Mishra et al. 2014b). Moreover, they are also reported to have promising uses in fruit and vegetable protection (Fayaz et al. 2010a). Furthermore, the use of biosynthesized zinc oxide NPs improves Zn nutritional status and helps to the secretion of phosphorus-mobilizing enzymes that would eventually result in the uptake of phosphorus as a nutrient (Raliya and Tarafdar 2013). These reports propose the robust applicability of NPs in agriculture; however, because the continuous research examines are based in the lab, more research needs to be performed to strengthen these findings. Some roles of biosynthesized NPs in agriculture are listed in Table 9.2.

Main uses of nanotechnology in agriculture contain:

1. Improved seed germination of rain-fed crops mediated using carbon nanotubes;
2. Formulation of nano-fertilizers for balanced crop nutrition;
3. Development of effective nanoformulations including mostly AgNPs for control of plant diseases;
4. Development of nano-herbicides for weed control;
5. Management of postharvest diseases by an NP-based strategy;
6. Diagnostic devices based on nano-sensors for monitoring agroecosystems; and.
7. Improved agricultural engineering by nanotechnology in the field of agricultural machinery.

2.2.2 Role of Different Microbes in the Synthesis of NPs

The biosynthesis of NPs utilizing biological methods has attracted considerable attention because of a growing need to develop environmentally safe, trustworthy, and nontoxic approaches in material synthesis (Kalishwaralal et al. 2008; Srivastava et al. 2021). The idea for the biogenic synthesis of NPs by microbes was first given while doing the experiments on bio-sorption of metals with Gram-negative and Gram-positive bacteria. The introduction of the enzymatic process put an end to the usage of costly chemicals and the green route synthesis was more supported by the fact that most of the bacterial species inhabit ambient situations of differing temperature, pressure, and pH. Thus, the particles produced through these techniques have higher catalytic reactivity, vaster specific surface area, and better contact among the enzyme and metal salt because of the bacterial carrier matrix (Bhattacharya and Mukherjee 2008). The Ag NPs were first synthesized by *Pseudomonas stutzeri* AG259, a bacterial strain initially isolated from a silver mine (Haefeli et al. 1984). Biological synthesis of NPs with the different microbes needs the resistance of the organism to silver ions themselves, as numerous studies have indicated that, on the one hand, the lower concentration of silver nitrate triggers the synthesis of Ag NPs; on the other hand, greater concentrations can kill the organism inside in minutes (Kalimuthu et al. 2008; Pandian et al. 2010). To date, several microorganisms have been effectively hired for the synthesis of different kinds of NPs. Some of them are stated in Table 9.3.

Table 9.3 Some microorganisms utilized for the synthesis of NPs

Microorganisms	Reference
Bacillus megaterium	Fu et al. (1999)
Cladosporium cladosporioides	Balaji et al. (2009)
Candida utilis	Gericke and Pinches (2006)
Escherichia coli	Gurunathan et al. (2009)
Fusarium semitectum	Basavaraja et al. (2008)
Geobacter sulfurreducens	Law et al. (2008)
Lactobacillus spp.	Nair and Pradeep (2002)
Morganella sp.	Parikh et al. (2008)
Neurospora crassa	Castro-Longoria et al. (2011)
Proteus mirabilis	Samadi et al. (2009)
Pseudomonas aeruginosa	Jeyaraj et al. (2013)
Plectonema boryanum	Lengke et al. (2006)
Rhodococcus species	Ahmad et al. (2003c)
Staphylococcus aureus	Nanda and Saravanan (2009)
Stenotrophomonas maltophilia	Oves et al. (2013)
Trichoderma asperellum	Mukherjee et al. (2008)
Verticillium sp.	Ahmad et al. (2003b)

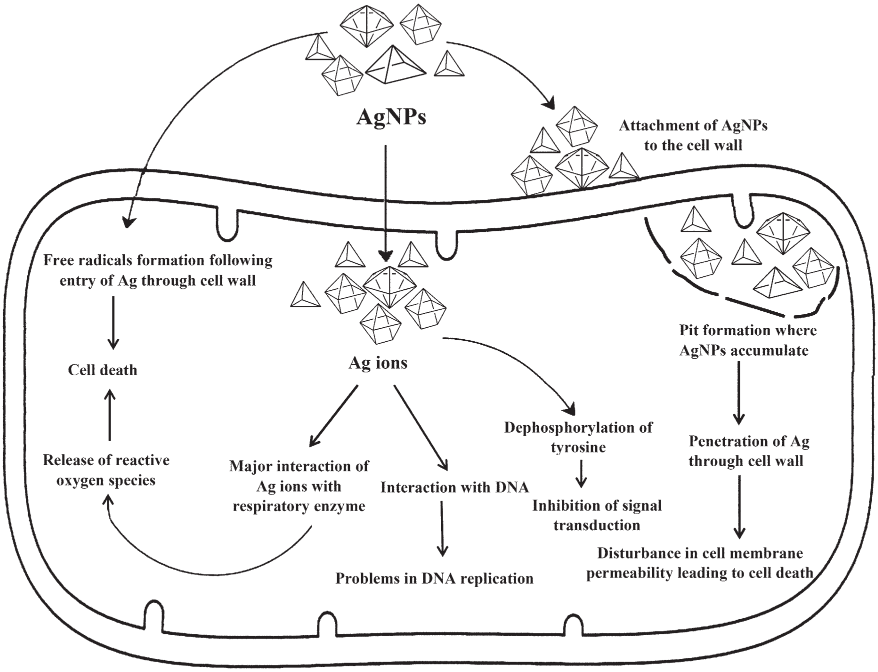

Fig. 9.1 Possible mechanisms of antimicrobial action of Ag NPS

2.2.3 Possible Mechanisms for Antimicrobial Action of NPs Versus Plant Pathogens

With the growth in microbial organisms resistant to multiple pesticides and antibiotics, various researchers have regarded nanotechnology for developing novel and efficient antimicrobial reagents free of resistance and low price. Between the various types of NPs, Ag NPs have been most worked upon. Silver and its compounds have been reported to indicate potent inhibitory and antimicrobial activities against bacteria, fungi, and viruses and when contrasted with other metals, silver is reported to show greater toxicity to microorganisms than to mammalian cells. The precise mechanism used by NPs to kill a microbe is not obviously recognized and to date, this is a subject of debate. However, there are different theories in the public domain to describe the most probable mode of action adopted through NPs. The Ag^+ ions' antimicrobial modes of action have been shown in some details (Fig. 9.1) (Mishra et al. 2016). According to the first theory, Ag NPs can join and break through the bacterial cell wall, thus bringing about structural changes in the cell membrane that cause cell membrane penetrability and cell death. Sondi and Salopek-Sondi (2004) observed this by the formation of pits on the cell surface, where NPs gather in huge numbers on the cell surface. The second theory considers the free radicals formation with the silver as the mechanism responsible for cell demise (Kim et al. 2007). According to the third theory, the release of silver ions with the aid of NPs can lead to the interaction of the ions with the thiol groups of numerous essential enzymes, thereby inactivating the enzymes (Matsumura et al. 2003). The fourth theory proposes that reaction among NPs and sulfur/phosphorus or both results in troubles in DNA replication of the bacteria, hence killing the microbes (Hatchett and White 1996; Prasad and Swamy 2013). According to another group of researchers, dephosphorylation of the peptide substrates on tyrosine residues via NPs can result in inhibition of signal transduction, halting the growth of the microorganism. Lately, a group of researchers recognized the accumulation of envelope protein precursors via proteomic analyzes, showing that NPs of Ag could have targeted the bacterial membrane, resulting in a dissipation of the proton motive force (Lok et al. 2006). Since most of the mechanisms have been studied on pathogens causing human diseases, it is unclear whether or not these mechanisms can also provide an explanation for the antimicrobial action versus plant pathogens. Nevertheless, since the cellular machinery is nearly the same, it is expected that these theories could be of use for exploring the mechanism adopted by NPs in inhibiting plant pathogens.

2.2.4 Conclusion

In spite of the numerous challenges confronting the acceptance of biopesticides, they are yet to be considered as appropriate alternatives to ordinary pesticides. The usage of synthetic chemicals has caused serious worries because of their destructive impacts on human health, the environment, natural enemies, and ecosystem balance. Moreover, since synthetic pesticides have some active carcinogenic elements, they threaten human life. Biopesticides seem to be a better alternative to synthetic pesticides, because of their biodegradability, low toxicity, and low persistence in the environment. Biopesticides are easily accessible and have cheap base materials.

2.3 Uses of Microbial Nanotechnology in the Environment

As a dark side of the increasing rate of urbanization, industrialization, and agriculture, the environment becomes contaminated extraordinarily by the pollutants disposed into nature. The undesired results of such pollution are the contamination of air, soil, and water, ending in terrible deforestation, lost biodiversity, degraded soil, and damaged human health. Samples of stated contaminants are chlorofluorocarbons (CFCs), carbon monoxide (CO), hydrocarbons, heavy metals (lead, arsenic, chromium, mercury, cadmium, and zinc), organic compounds (dioxins and volatile organic compounds), nitrogen oxides, sulfur dioxide, and particulates (Bhandari 2018). Numerous of these contaminants are recognized or suspected as carcinogens and mutagens, which may alter ecosystem function. Therefore, various environmental cleanup techniques have been introduced, utilizing physical and chemical remediation, phytoremediation, and bioremediation. The conventional techniques of treatment (e.g., isolation, disposal to landfill, and pump-and-treat) are not sustainably resulted in a significant rise in the development of alternative treatment methods for environmental remediation (Cundy et al. 2008). It is critically important to develop novel and more effective techniques for the remediation of pollution, targeting at holding and repairing the integrity of natural habitats (Prasad 2017, 2018).

Three main uses of nanotechnology in the environmental fields can be classified namely as restoration (remediation) and purification of polluted material (Yunus et al. 2012), contamination identification (sensing and detection) (Krantzberg et al. 2010), and contamination prevention (Yunus et al. 2012). With the fast increase of contaminant species and concentration, the development of instruments capable of treating and preventing them is essential (Yunus et al. 2012).

Until now, the long-standing treatment regimens for remediation of heavy metals ions contain techniques such as chemical precipitation, coagulation, electrodialysis, floatation, flocculation, ion exchange, evaporative recovery, nanofiltration, ultrafiltration, reverse osmosis, and so forth (Gupta and Diwan 2017). Although effective, these techniques are generally costly because of high energy and reagent requirements. Furthermore, they produce a great number of poisonous muds and byproducts, contaminating the environment. Many times they may lead to incomplete and unpredictable removal of metal ion (Barakat 2011; Gavrilescu 2004). Therefore, there is a vital necessity to find efficient, effective, economical, and environmentally safe techniques able to minimize the concentration of heavy metal ion from toxic to safe limits in an environment (Gupta and Diwan 2017). In order to perform in situ and ex situ remediation of metal pollutions and wastes, microbial metal reduction can be a proper technique. In addition, aiming at discovering the relationship between NPs synthesis and metallic reduction as well as the bio-recovery of heavy metals and bioremediation of toxic ones, researchers have evaluated the mechanisms of nanoparticle synthesis and bioreduction, focusing on reducing agents in bacteria (e.g., enzymes and proteins) and biochemical pathways involved in metal ion reduction. Furthermore, these microorganisms were able to mobilize and immobilize metals, and occasionally; the bacteria that ought to reduce metal ions indicated the capability to precipitate metals at the nanometer scale (Stephen and Macnaughtont 1999; Iravani 2014; Prasad et al. 2016).

The transformation or degradation of pollutants into undangerous or less dangerous materials, mediated by microorganisms is called bioremediation. The application of different organisms such as plants, fungi, bacteria, and algae for effective bioremediation of contaminants has been studied (Vidali 2001; Prasad and Aranda 2018). Indeed, the bioremediation procedure is a very slow procedure. Only some species of bacteria and fungi have been confirmed as strong contaminant degraders. Numerous strains are recognized as effective bioremediation agents, but only under laboratory conditions. The growth of bacteria is dependent on temperature, pH, moisture, oxygen, soil structure, as well as poor bioavailability of pollutants, a suitable level of nutrients, and the presence of other toxic compounds. Notwithstanding the existence of microorganisms in an extreme environment, most of them prefer optimal conditions, difficult to achieve outside the laboratory (Vidali 2001; Bernhard-Reversat and Schwartz 1997; Dua et al. 2002; Karigar and Rao 2011).

Besides, despite the operation of most bioremediation systems under aerobic conditions, the anaerobic environments might also allow microbial degradation of recalcitrant molecules. Based on the results of a study carried out by Vidali (2001) and Karigar and Rao (2011) both bacteria and fungi do the remediation of recalcitrant and lignin and organo-contaminants, respectively, with the participation of various intracellular and extracellular enzymes.

2.3.1 Application of Environmental Cleaning Processes

Enormous quantities of harmful chemicals are disposed into the surroundings, either deliberate release of material like pesticides, or inadvertent disposal like the case of oil spills (Ezezika and Singer 2010). The isolation or engineering of some microorganisms capable of effective degradation of toxins and xenobiotics have been carried out. Nevertheless, the real utilization of these microorganisms in bioremediation has not advanced compared to their discovery, or different developments in the biotechnology field (Ezezika and Singer 2010). The degradation or conversion of hazardous organic compounds into nontoxic substances by microorganisms is run through a process named microbial bioremediation. These dangerous substances contain toluene, benzene, dioxins, nitro-aromatics, and polychlorinated biphenyl (PCBs) (Ezezika and Singer 2010; Thakare et al. 2021).

The selection of the most appropriate remediating technology for any use is generally dependent on the site properties and the task’s goals. Despite the considerable variety, remediation technologies can in general be classified into in situ and ex situ techniques. In situ technologies include, yet are not restricted to Vitrification, Stabilization and Solidification, Soil flushing, Electrokinetic remediation, Phytoextraction, Chemical stabilization, and Phytostabilization (Martin and Ruby 2004). Ex situ techniques, on the other hand, consist of excavating the affected soils, following treating at the surface and extracting the polluted groundwater and treating at the surface. Ex situ remediation technologies contain Pump-and-Treat, Dig-and-Dump (Landfills and Engineered Landfills), Oxidation, Incineration, Adsorption, Pyrolysis, Ion-Exchange, Dehalogenation, and Soil Washing (Kuppusamy et al. 2016).

2.3.2 Use for Degradation of Emerging Contaminants

2.3.2.1 Degradation of 4-Nitrophenol

As a known nitro-aromatic pollutant present in dyes and synthetic pesticides, 4-nitrophenol is capable of inhibiting and stimulating the central nervous system as well as different nerve endings in humans. Its degradation has been utilized as a common test for assessing the catalytic affectivity of NPs, given the simplicity of measuring its degradation using UV–vis spectroscopy (Hosseinpour et al. 2018;

Zhang and Hu 2017). Zhang and Hu (2018) utilized the marine bacterium *Bacillus* sp. GP to synthesize Pd/Au NPs, the catalytic activity of which was assessed for the reduction of 4-nitrophenol. However, they reported that it was weaker compared to that of the chemically synthesized NPs. Hence, a number of metal oxides were tried to boost the catalytic efficiency, like Al_2O_3, Fe_3O_4, and SiO_2. The increased resultant from these metal oxides is dose-dependent, attributable to the metal ions, and alloy formation: (1) Metal ions associated with metallic oxides behaved as Lewis acids, promoting the reaction. (2) The probable formation of an alloy perturbed the activity of noble metallic sites. The biosynthesis of Au NPs was done with *Shewanella oneidensis* MR-1 on rGO at both ambient and culture conditions. Unlike its chemical equivalent, the bio-Au-NPs/rGO not only promoted the microbial reduction of 4-nitrophenol more sufficiently but also showed greater catalytic efficiency and reusability to the degradation of other pollutants, including nitrobenzene (Cumbal et al. 2003). After ten reduction cycles, the catalytic activity was yet kept up at 72% of the primary value. The proper catalytic activity and reusability of these materials might be attributed to the synergistic impacts of rGO and Au NPs considering the following: (1) rGO provided the template for preventing the Au NPs from aggregation, leading to the higher concentration of 4-nitrophenol around the Au NPs on rGO. (2) The electron transport was improved by the conductivity of rGO (Dong et al. 2015).

2.3.2.2 Degradation of Aromatic Hydrocarbons

Considered as a type of organic molecules, aromatic compounds contain, for example, one or more aromatic rings, particularly benzene rings. In petroleum refining and distillation sites, various aromatic compounds coexist as complex mixtures. There are three main groups: polycyclic aromatic hydrocarbons (PAHs), heterocyclics, and substituted aromatics (Seo et al. 2009).

Polycyclic aromatic hydrocarbons (PAHs) have two or more benzene rings. Owing to their toxic, genotoxic, mutagenic, and/or carcinogenic features, their abundance, and recalcitrance, they contain a category of hazardous contaminants with serious effects on the environment and public health (Hassanshahian et al. 2015). They can undergo volatilization, photolysis, adsorption, and chemical oxidation; however, changing through microorganisms is the main neutralization procedure of PAH-polluted sites in an environmentally accepted approach. A variety of environmental factors affect PAHs' microbial degradation, such as kind and number of the microorganisms, nutrients, nature, and chemical property of the PAH being degraded (Ghosal et al. 2016).

Naphthalene-degrading bacteria are abundant in nature. A myriad of researchers have tried to document the bacterial degradation of naphthalene, such as studying the genetic regulations, enzymatic mechanisms, and the elucidation of the biochemical paths (Ghosal et al. 2016). Among the isolated bacteria which use naphthalene, as the only carbon and energy source, are genera *Burkholderia*, *Alcaligenes*, *Polaromonas*, *Mycobacterium*, *Ralstonia*, *Pseudomonas*, *Sphingomonas*, *Rhodococcus*, and *Streptomyces* (Seo et al. 2009). With three rings, fluorene is the key component of both fossil fuels and coal derivatives. The isolation of a number of bacteria whose sole source of carbon and energy was fluorene has been carried out, confirming their genera to be *Brevibacterium*, *Arthrobacter*, *Mycobacterium*, *Burkholderia*, *Sphingomonas*, and *Pseudomonas* (Seo et al. 2009). As a three aromatic ring system, phenanthrene is highly concentrated in waste sites, surface soils, and PAH-polluted sediments (Seo et al. 2009). The bacterial strains isolated in *Arthrobacter*, *Pseudomonas*, *Acidovorax*, *Burkholderia*, *Brevibacterium*, *Comamonas*, *Mycobacterium*, and *Sphingomonas* showed the ability to utilize phenanthrene as a sole carbon and energy source (Seo et al. 2009). In addition, the degradation of phenanthrene by *ochrobactrum* sp. strain PWTJD through 2-hydroxy-1-naphthoic acid, salicylic acid, and catechol was reported (Ghosal et al. 2010). Along with naphthalene, several studies on phenanthrene degradation using a variety of Gram-negative and Gram-positive bacterial species have been reported (Ghosal et al. 2016). Having four rings, fluoranthene is among the most dominant PAHs in nature. The exhaustively studied *mycobacterium* is a popular genus capable of mineralizing high molecular weight PAHs like fluoranthene, benzo[*a*]pyrene, and pyrene (Seo et al. 2009). Furthermore, strains in the genera *Pasteurella*, *Burkholderia*, *Sphingomonas*, *Stenotrophomonas*, and *Rhodococcus* have been isolated to degrade fluoranthene, with fluoranthene, as a sole carbon and energy sources (Seo et al. 2009).

Recently, fungi have been extensively used in the biodegradation of PAHs and the ability of plenty of fungal species to metabolize different PAHs has been confirmed (Ghosal et al. 2016).

Unlike bacteria and fungi, the biodegradation of PAHs by microalgae (cyanobacteria, diatoms, etc.) has not received enough attention. Microalgae are among the essential primary producers in aquatic ecosystems, affecting PAHs drastically in those environments. Myriad strains of microalgae metabolize/transform PAHs such as naphthalene, phenanthrene, anthracene, and so on (Ghosal et al. 2016).

Found in different kinds in the environment, heterocycles consist of oxygen, nitrogen, and sulfur and originated from anthropogenic or natural sources. Guo et al. (2008) could isolate a stable carbazole-degrading microbial consortium containing *Chryseobacterium* sp. NCY and *Achromobacter* sp. NCW.

Furthermore, when alkanes were degraded, monocarboxylic acid intermediates were yielded, whilst the degradation of polycyclic aromatic hydrocarbon pyrene, found in the acidic oily sludge, resulted in the oxygenated intermediate pyrenol. The proficient on-site degradation of the acidic oily sludge by strain *Candida digboiensis* was reported, probably owing to its strong nature that can be evolved via extended exposure to the pollutants. Therefore, *C. digboiensis* TERI ASN6 has a high capability for bioremediating hydrocarbons. Elliott et al. (2008) suggested a method utilizing zero-valent iron NPs for the treatment of water polluted with Hexachlorocyclohexanes.

2.3.2.3 Toxic Organic Degradation

Considered as a main study area in the environmental sciences, bioremediation is referred to as the use of microbial methods to deal with contamination. Upon bioremediation, microbes are acclimatized to the toxic wastes, leading to the natural development of new resistant strains, ultimately transforming different toxic chemicals into less dangerous forms. It is worth notifying that the action of the biotransformation enzymes is the basis of the biodegradation mechanism of recalcitrant combinations in the microbial system (Saratale et al. 2011). Some scientists pointed to the degradation of complex organic substances such as tyrosinase (Zhang and Flurkey 1997), aminopyrine-*N*-demethylase (Salokhe and Govindwar 1999), lignin peroxidase (Duran and Esposito 2000), laccase (Hatvani and Mécs 2001), NADH-DCIP reductase (Bhosale et al. 2006), and hexane oxidase (Saratale et al. 2007) via enzymatic mechanisms.

Candida digboiensis TERI ASN6 proceeded the fungal degradation of oily sludge-polluted soil, degrading 40 mg of eicosane in 50 mL of minimal salts medium in 10 days and 72% of heneicosane in 192 h at pH = 3 (Sood et al. 2010).

Organophosphorous pesticides are extensively utilized in agriculture. Although they are biodegradable in nature, some are acutely toxic and their residues are found in the environment. Different traditional physicochemical methods are utilized to detoxify these chemicals such as incineration, landfilling excavation, and so on. But due to their tedious method and high expenditure cost, they are not utilized frequently. Microbial degradation is considered to be the main factor determining the fate of organophosphorus insecticides in the environment in a cost-effective way. Early studies provided evidence that microorganisms played an essential role in enhancing the degradation of methyl parathion (Mishra and Jamaluddin 2017). Siddaramappa et al. (1973) reported two bacterial species, *Bacillus sp.* and *Pseudomonas sp.* capable of hydrolyzing methyl parathion, by the hydrolysis product para-nitro phenol as a sole source of carbon. Rosenberg and Alexander (1979) isolated two *Pseudomonas sp.* capable of hydrolyzing several organophosphorus compounds containing parathion, which used the ionic cleavage products as a sole source of carbon. Misra et al. (1992) isolated a *Flavobacterium sp.* Strain, for which MP was the sole source of carbon.

Huge attention has been paid to the variety of biotechnological methods, thanks to their capability of removing azo dye contamination in an eco-efficient manner, mainly using bacteria and often combined with physicochemical methods. Azo dyes are xenobiotic in nature and recalcitrant to biodegradation. In addition, it is advantageous to use microbial or enzymatic treatment methods for their complete decolorization and degradation from textile effluent since (1) they are environmentally-friendly, (2) they present cost-competitive properties, (3) they produce less sludge, (4) they yield end products that are nontoxic or have complete mineralization; and (5) they require less water consumption in contrast to physicochemical approaches (Saratale et al. 2011). Depending on the adaptability and the activity of the selected microorganisms, the microbial decolorization has different levels of efficiency. Therefore, numerous species have been studied for the decolorization and mineralization of different dyes recently (Saratale et al. 2011). Among the most intriguing biological aspects of effluent treatment is the isolation of potent species and their degradation (Saratale et al. 2011). A vast array of microorganisms can decolorize plenty of dyes containing; bacteria, fungi, actinomycetes, algae, and plants (phytoremediation) (Saratale et al. 2011). Besides, they can entirely mineralize many azo dyes under certain environmental conditions (Saratale et al. 2011).

2.4 Uses of Microbial Nanotechnology in Biosensor

A biosensor is a tool to identify, transmit, and record information with respect to a physiological or biochemical change. As a result of combining biological component with an electronic transducer, it transforms a biochemical signal into a quantifiable electrical reaction. It utilizes a variety of transducers, including electrochemical, optical, electronic, and acoustic (D'souza 2001). Besides, a biosensor's function relies on the biochemical specificity of the biologically active material. The selection of the biological material is done considering several attributes, namely the storage, specificity as well as operational and environmental stability. The choice is also dependent on the analyte to be identified, for example, antigens, chemical compounds, hormones, microbes, nucleic acids, or any subjective parameters such as taste and smell. Among the most well-known biological sensing elements are antibodies, enzymes, DNA, organelles, microorganisms, receptors as well as animal and plant cells or tissues. Some of the main features of a proper biosensing system are its easy operation, sensitivity, portability, specificity, reliability, the capability to function even in optically opaque solutions, and real-time analysis (D'souza 2001).

NPs have fascinating electronic and optical properties, justifying their utilization in biosensors. The formation of spherical selenium NPs by the *Bacillus subtilis* (with diameters 50–400 nm diameters) was reported (Yunus et al. 2012). A day after their synthesis, these spherical monoclinic Se NPs can be converted into extremely anisotropic, one-dimensional (1D) trigonal shape at room temperature. Moreover, owing to the great surface-to-volume proportion of Se nanomaterial crystals as well as their sufficient adhesive capability and biocompatibility, they were utilized to enhance and settle materials for constructing HRP (horseradish peroxidase) biosensor. Furthermore, they demonstrated acceptable electrocatalytic activity toward the reduction of H_2O_2 because of the Se nanomaterials' suitable adhesive capability and biocompatibility. Noticeably, these H_2O_2 biosensors showed sensitivity and affinity for H_2O_2 with a detection limit of 8×10^{-8} M. In addition, various crystals of Se nanomaterials had no considerable difference in electrochemical uses. Therefore, the electrode modified with Se nanomaterials is hoped to be promising for a wide range of uses associated with the H_2O_2 identification in food, clinical, pharmaceutical, industrial, and environmental analyses. Moreover, yeast-biosynthesized Au–Ag alloy NPs were used to produce a sensitive electrochemical vanillin sensor (Zheng et al. 2010b). According to the electrochemical studies, the vanillin sensor based on

Au–Ag alloy NPs-modified glassy carbon electrode could increase vanillin's electrochemical response for at least five times. This vanillin sensor was effectively utilized to determine the vanillin from the vanilla bean and vanilla tea sample, recommending that it might have pragmatic uses in vanillin-monitoring systems. Furthermore, AuNP-based glucose oxidase (GOx) biosensors were introduced following the observations that AuNPs are capable of increasing the enzyme activity of GOx (Zheng et al. 2010a). This kind of biosensor was effectively utilized to measure the content of glucose in commercial glucose injections.

2.5 Uses of Nanotechnology in Food Science

Nanotechnology is considered an attractive technology revolutionizing the food sector. The increasing consumer concerns about food quality and health-related issues are the main driving force of scientists to find effective methods for increasing food quality, yet preserving the product's nutritional value. In the food industry, the popularity of nanoparticles-based materials has witnessed an increase, as many of them include vital elements and are additionally discovered to be nontoxic (Roselli et al. 2003; Shafiq et al. 2020). Their stability at high temperatures and pressures was proven (Sawai 2003). From food production, processing to packaging, nanotechnology provides whole food solutions. Not only do nanomaterials promote food quality and safety but they also boost the health advantages of foods, underscoring the need for new techniques, methods, and products with more efficient use of nanotechnology (Dasgupta et al. 2015; Prasad et al. 2017a).

Food nanostructured ingredients and food nanosensing are two main food areas enjoying nanotechnology the most. Food nanostructured ingredients cover a vast area ranging from food processing to food packaging. In food processing, nanostructures can act as food additives, antimicrobial agents, anticaking agents, carriers for smart delivery of nutrients, fillers for improving mechanical strength and durability of the packaging material, and so on, while the main purpose of utilizing food nanosensing is to achieve better food quality and safety evaluation (Ezhilarasi et al. 2013, Fig. 9.2).

Numerous nanomaterials are utilized for various food uses on an industrial scale (Alfadul and Elneshwy 2010). With a particle size of less than 100 nm, titanium dioxide is extensively utilized as a food additive and antimicrobial agent for food packaging and storing containers (Long et al. 2006). Likewise, silver NPs are vastly utilized as antimicrobial agents in food packaging, storage containers, refrigerators, and chopping boards as well as a health supplement (Wang et al. 2008). Besides, zinc and zinc oxide serve as nutritional additives and antimicrobial agents in food packaging (Brunner et al. 2006). With particles of a few 100 nm in size, silicon dioxide and carbon are hired as food additives and for food packaging (Chen and von Mikecz 2005). Platinum and gold nano-wires are utilized as biosensors in order to improve the food analysis (Wang et al. 2008).

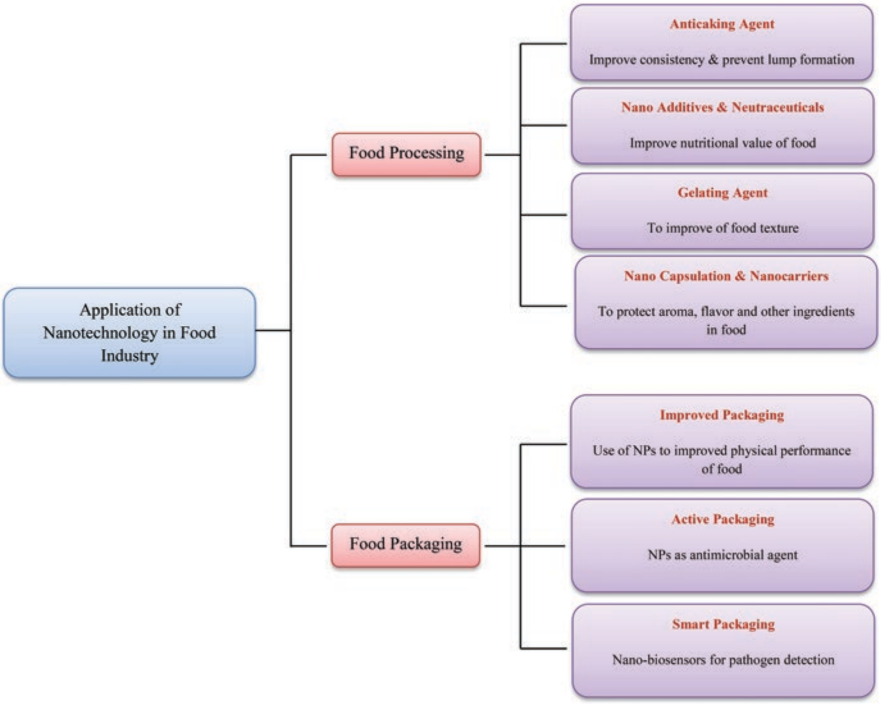

Fig. 9.2 Schematic diagram presenting the role of nanotechnology in different aspects of food sectors

2.5.1 Antimicrobial Effect of NPs for Food Packaging Uses

Food packaging systems are established to protect food versus environmental factors such as chemical pollutants, microorganisms, oxygen, and water vapor, extend food shelf life, and improve food safety. The conventional food packaging systems protect the food in an inactive way, that is, they do not interact with the food; instead, they act solely as a hindrance among the food and the environment (de Azeredo 2012). In contrast, active food packaging systems play some other roles than acting as an inert barrier to the surroundings (de Azeredo 2012). As the most well-known active packaging system, the antimicrobial type releases antimicrobial agents into the food surface, where microbial growth predominates, resulting in the inhibition or retard of microbial growth and spoilage (de Azeredo 2012).

The higher effectivity of nanocomposite antimicrobial systems is particularly owing to the high surface-to-volume proportion and increased surface reactivity of the nano-sized antimicrobial agents, enabling them to inactivate more microbial molecules and cells in contrast to larger-scale counterparts (Luo and Stutzenberger 2008). The antimicrobial activity of the materials in nanoscale has been investigated as growth inhibitors, killing agents, or antimicrobial carriers (de Azeredo 2012).

Antimicrobial food packaging systems effectively hinder the growth of post-processing pollutant microorganisms, leading to increased food shelf life, and enhanced food safety.

2.5.2 Silver NPs

Most nanocomposites utilized as antimicrobial food packaging are based on silver NPs (Ag NPs), efficient antimicrobials even bigger than the biggest silver particles, due to their greater surface area accessible for interaction with microbial cells (de Azeredo 2012).

Ag NPs antimicrobial activity relies on the release of Ag^+ ions (Morones et al. 2005). Kumar and Münstedt (2005) indicated the binding of Ag^+ to electron donor groups in biological molecules including oxygen, nitrogen, or sulfur. Besides, the interactions of Ag^+ ions with thiol groups in proteins might inactivate the bacterial enzymes; since as a reaction to the protein denaturation impacts of Ag^+ ions, DNA molecules might become condensed and could not replicate (Feng et al. 2000; Prasad et al. 2012; Swamy and Prasad 2012; Prasad et al. 2020). Another mechanism recommended for Ag NPs' antimicrobial activity was given considering its adhesion to the cell surface, lipopolysaccharides degradation and pits' formation in the membranes, drastically boosting permeability (Sondi and Salopek-Sondi 2004). According to Mohammed Fayaz et al. (2009), the biosynthesized highly stable Ag NPs utilized the fungus *Trichoderma viride* and incorporated them into sodium alginate for the preservation of fruit and vegetables. The nano bio-composite film indicated good antibacterial activity versus test strains and raised carrot and pear shelf life compared to uncoated controls. Besides their antimicrobial activity, Ag NPs can absorb and decompose ethylene, extending the shelf life of fruits and vegetables (de Azeredo 2012). Furthermore, Ag NPs can improve the thermal and tensile properties of polymers utilized in food packaging. When Ag NPs were incorporated into polyvinyl alcohol films, they could improve thermal stability, increase glass transition temperature, and improve tensile properties (tensile strength and Young's modulus) (Mbhele et al. 2003).

2.6 Uses of Nanotechnology in the Cosmetics

In the cosmetic industry, the NPs are available in shampoos, anti-wrinkle creams, conditioners, toothpaste, anti-cellulite creams, whitening skin, aftershave lotions, moisturizing, face powders, deodorants, soaps, sunscreens, makeup in general, perfumes, and nail polishes (Baril et al. 2012; Melo et al. 2015).

New nanocarriers such as nanostructured lipid carrier, nanoemulsions, liposomes, solid lipid NPs, nanocapsules, and so on, are utilized as cosmeceuticals to condition the hair, skin, and nail as well as lip care, aging, and hyperpigmentation, thanks to their self-cleansing, antimicrobial, biocompatible, skin-compatible, and dermatological behavior (Singh et al. 2016). In general, with a wavelength beneath the critical wavelength of light, NPs are transparent, making them appropriate for use in the cosmeceutical industry (Purohit et al. 2019). Metal NPs, such as zinc and titanium oxide NPs, are utilized in sunscreens, due to being transparent to visible light and absorbing and reflecting UV rays encountered in their way (Morganti 2010). These properties of nanoscale materials in cosmetics agents justify their extensive use in personal care industries (Purohit et al. 2019).

3 Conclusion

Clean, nontoxic, and eco-friendly techniques have been focused considerably on the synthesis and assembly of NPs. The biological organisms such as fungi, bacteria, and yeasts are mostly preferred to be utilized in NPs synthesis, due to their quick growth rate, easy cultivation, and capability to grow at ambient temperature, pH, and pressure. Microbial-based NPs possess myriad potential uses in various fields such as coatings, electronics, cosmetics, packaging, antimicrobial agent, agriculture, environment, food and beverages, drug delivery, bioremediation, diagnostics, and biomedicines. Presently, bio-based methods are still in the early stages of development, since still the stability and aggregation of the biosynthesized NPs, controlling the crystal growth, shape, and size distribution are the most frequently encountered problems. Moreover, NPs synthesized biologically are more polydisperse compared to the ones synthesized chemically. It is possible to control the NPs' properties via optimizing the effective parameters controlling the growth condition of organisms, cellular activities, and enzymatic processes. The aim of this chapter is, therefore, to highlight the green approaches of nanomaterials synthesis using microbes, current status, and future prospects of NPs of microbial origin in various mentioned fields.

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Part II
Nanotechnology for Biomedical Applications

Chapter 10
Organic Carbon Dots for Mitigating Neurodegenerative Diseases

Jyoti Ahlawat and Mahesh Narayan

Contents

1 Introduction

Neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) are debilitating neurological disorders with no available disease-modifying therapies present for the patient despite the intensive research going on in this area (Iadanza et al., 2018; Brown and Wobst, 2019). AD is cognitive neurodegeneration afflicting more than a million people and accounts for more than 50% of dementia cases in the United States alone. The standard presentation of the disease includes a decline in thinking, behavioral, and social skills, making an individual incapable of functioning independently and ultimately results in death. In comparison, PD is an illustrative example of neurodegenerative movement disorders. It is clinically characterized by tremors on one or both sides of the body, bradykinesia, rigidity, and

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postural instability are affecting more than half a million people in the United States alone (Brown and Wobst, 2019; Goldsmith et al., 2014; Uversky, 2011).

The word neurodegeneration derives its origin from the Greek prefix *néuro,* meaning *"nerval"* and the Latin verb *dēgenerāre* meaning *"decline."* The term "Neurodegenerative diseases" is a broad class of diseases that includes a range of conditions, all arising from the progressive degeneration and destruction of the neurons leading to the dysfunction, disabilities, and ultimately death of an organism (Brown and Wobst, 2019; Goldsmith et al., 2014; Uversky, 2011). As the amount of dead neuronal cells increases, it eventually results in deterioration of the affected brain regions of the nervous system, which then begins to shrink: hippocampal region in AD and *substantia nigra* in PD (Brown and Wobst, 2019; Goldsmith et al., 2014; Uversky, 2011). This destruction of the nerve cells can either result in ataxia (e.g., PD) or dementia (e.g., AD) (Brown and Wobst, 2019; Goldsmith et al., 2014; Uversky, 2011). According to a recent report published by the World Health Organization (WHO), the neurodegenerative diseases will be the second leading cause of death around the world after the cardiovascular diseases in the upcoming 20 years (Brown and Wobst, 2019; Goldsmith et al., 2014; Uversky, 2011). Hence, pointing toward the urgent need for the development of novel drugs with the potential to ameliorate the course of these neurological disorders (Brown and Wobst, 2019; Goldsmith et al., 2014; Uversky, 2011).

2 Molecular Mechanisms of AD and PD

These neurological diseases share common mechanisms and phenotypes, and at the molecular level, various factors can induce neuronal death. Some of these factors are aberrant protein misfolding, oxidative damage, compromised autophagic flux, impaired bioenergetics, and mitochondrial dysfunction, to name a few (Brown and Wobst, 2019; Goldsmith et al., 2014; Uversky, 2011). This section will highlight these molecular outcomes of AD and PD in detail.

2.1 Aberrant Protein Misfolding

The misfolding of amyloidogenic proteins into fibrillar aggregates and their extracellular deposition as plaques or as intracellular inclusions inside the cells is the molecular hallmark of amyloid-related disorders such as AD and PD. These as-formed plaques act as the accumulation site for various proteinaceous and non-proteinaceous elements (e.g., metal ions) present inside the organ. Whereas, the intracellular inclusions interfere with the cellular physiology by either disrupting the calcium homeostasis or by interfering with the intracellular protein or RNA transport or sequestering the chaperone proteins. These amyloid depositions of functional protein precursors into aggregates are collectively termed as amyloido-

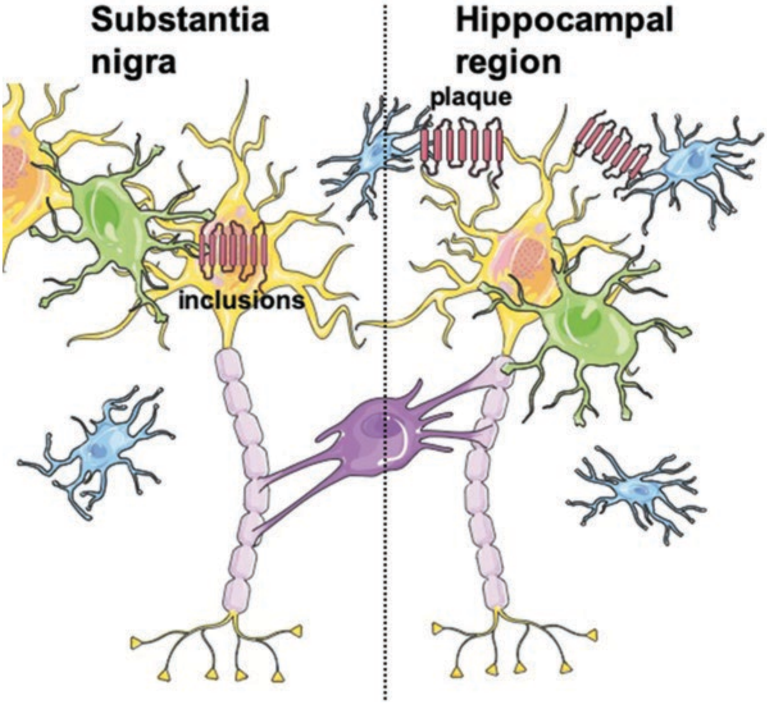

Fig. 10.1 Schematic representation of neuronal cells displaying molecular hallmarks of PD (inclusions) and AD (plaques). Drawn with the help of Servier Medical Art by Servier

sis. These misfolded proteins are associated with various neuropathological conditions such as AD and PD (Iadanza et al., 2018; Brown and Wobst, 2019; Goldsmith et al., 2014; Uversky, 2011) (Fig. 10.1).

The amyloid fibrillates through three kinetic phases, namely nucleation, elongation, and saturation in the primary nucleation (Fig. 10.2). This trend can be visualized over time using the fluorescent dyes such as Thioflavin T (ThT). Comparatively, the lag phase is considered as the rate-limiting step as it requires bypassing one or more free energy barriers. The outcomes of these kinetic transitions are unusual oligomers, protofibrils, and amyloid fibrils, which are pathogenic (Brown and Wobst, 2019; Goldsmith et al., 2014; Uversky, 2011).

These fibrillar assemblies are an outcome of protein misfolding–refolding, which results in the formation of insoluble amyloid fibrils via the nucleation–extension growth process (Fig. 10.2) (Li and Mezzenga, 2013). The apparent consequences of this protein misfolding are protein aggregation, loss of biological function, and onset of toxicity (Li and Mezzenga, 2013).

This misfolding can originate from a point mutation(s) or interaction with external or internal toxins, oxidative damage, impaired posttranslational modifications of the protein, or impaired trafficking (Uversky, 2011). All these factors can affect protein folding independently or together. The fibrils from different pathologies

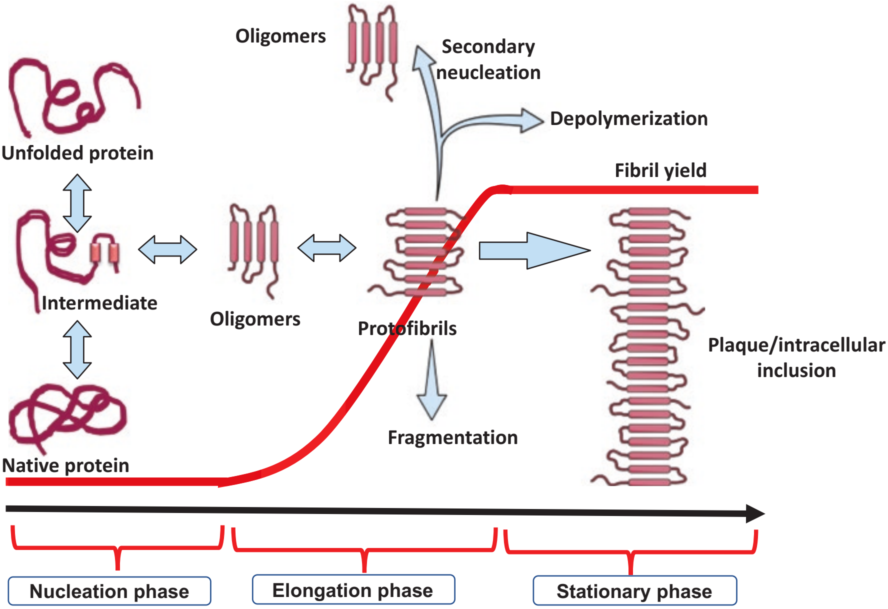

Fig. 10.2 The different stages of amyloid folding. Drawn with the help of Servier Medical Art by Servier

such as AD and PD share some common properties such as a core cross beta-sheet rich secondary structure in which continuous beta sheet are present, with each beta strand running perpendicular to the long axis of the fibrils. This beta-sheet rich structure is responsible for the fibrillar insolubility, resulting in deposition of the misfolded protein (plaques and inclusions) (Uversky, 2011; Li and Mezzenga, 2013).

Plenty of studies have shown that oligomers and protofilaments are more toxic than the insoluble fibrillar aggregates. For example, in the case of alpha-synuclein, which is responsible for the onset of PD, three different mechanisms of neurotoxicity have been proposed (Brown and Wobst, 2019; Goldsmith et al., 2014; Uversky, 2011). An increase in the monomeric form due to duplication or triplication of the alpha-synuclein gene is an example of a familial form of PD. It is associated with the intracellular elevation of monomeric species. This intracellular abundance is associated with neurotoxicity (Brown and Wobst, 2019; Goldsmith et al., 2014; Uversky, 2011). Whereas other studies have shown that oligomers can form pores and intracellular membranes, increasing the cations permeability inside the neurons. Further, studies have also demonstrated that fibrils can cause neuronal dysfunction and death by affecting proteasome functions, disrupting ER and Golgi apparatus, impairing axonal transport, and disrupting the cell membrane. However, a complete understanding of the exact nature of amyloid toxicity is still a far-fetched dream and yet to be realized (Uversky, 2011; Zhang et al., 2013).

2.2 Oxidative Stress

The oxidative stress is a causative agent of various pathophysiological conditions such as neurodegenerative diseases. The cellular response is altered under such oxidative stress conditions resulting in a diseased state. Some of the reasons responsible for the brain to experience more considerable oxidative damage is the high consumption of oxygen (20% of the total), accumulation of metals with age, high levels of iron and ascorbate, comparatively low levels of natural antioxidants (catalase), and low regenerative capabilities (Uversky, 2011). Furthermore, microglia and astrocytes in the brain produce cytokines that have been studied to generate ROS (e.g., NO), thus acting as the mediators of the inflammatory process along with the P450s in specific brain regions. Also, the human body produces free radicals, such as reactive oxygen species (ROS) and reactive nitrogen species (RNS) as part of the normal biochemical reactions (Uversky, 2011; Nimse and Pal, 2015).

To maintain the level of free radicals under control and to avoid their harmful effects, our bodies have evolved to bear self-defense mechanisms in the form of various enzymes such as glutathione, catalase, and superoxide dismutase (SOD) which can effectively "neutralize" these free radicals by enhancing cellular defense mechanisms (Uversky, 2011; Nimse and Pal, 2015). However, the problem arises when this balance is perturbed, which results in the elevation of free radicals generating oxidative stress inside the affected tissue. This elevation in ROS level results in the oxidative damage to the major biomacromolecules (protein, DNA, and lipid) (Uversky, 2011; Nimse and Pal, 2015). Another important target of these free radicals is the powerhouse of the cell, "the mitochondria," resulting in its dysfunction (Fig. 10.3). Therefore, it is not surprising that although AD and PD differ in etiology, symptoms, and brain regions affected, the oxidative stress is one of the main culprits responsible for neuronal death in both the diseases (Uversky, 2011; Nimse and Pal, 2015).

2.3 Mitochondrial Dysfunction

Mitochondria is the powerhouse of the cell and takes part in the pivotal biochemical reactions happening inside the cell (Iadanza et al., 2018; Brown and Wobst, 2019; Goldsmith et al., 2014; Uversky, 2011). Therefore, its dysfunction is associated with impaired bioenergetics resulting in intracellular death signals. In the case of AD, disruption of the morphology of mitochondria, hampered activity of three Krebs cycle enzymes (pyruvate dehydrogenase, isocitrate dehydrogenase, and alpha-ketoglutarate dehydrogenase), and impaired activity of electron transport cycle (ETC) complexes (complex I, III & IV) has been observed (Iadanza et al., 2018; Brown and Wobst, 2019; Goldsmith et al., 2014; Uversky, 2011). Whereas, in the case of PD, impairment of the activity of complex III of the ETC by alpha-synuclein toxicity and elevated level of ROS, impairment in mitochondrial

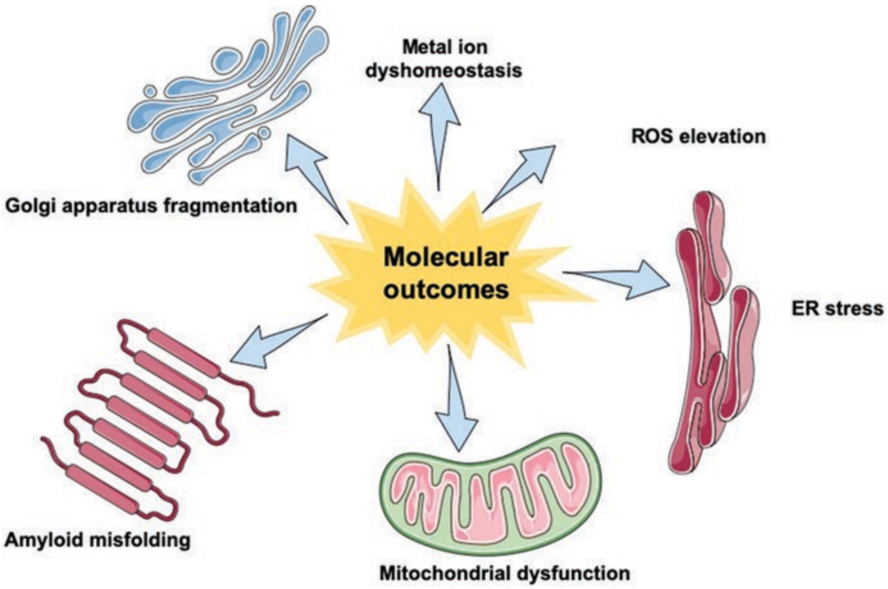

Fig. 10.3 Schematic representation of the molecular outcomes of oxidative stress inside the brain. Drawn with the help of Servier Medical Art by Servier

morphology, and calcium buffering has been observed which results in neuronal death (Iadanza et al., 2018; Brown and Wobst, 2019; Goldsmith et al., 2014; Uversky, 2011).

2.4 *Endoplasmic Reticulum (ER) Stress and Golgi Apparatus Fragmentation*

ER is an essential cellular organelle that is involved in protein folding, posttranslational modification of the protein, calcium homeostasis, synthesis of lipid and sterols, and redox control (Iadanza et al., 2018; Brown and Wobst, 2019; Goldsmith et al., 2014; Uversky, 2011). Therefore, ER stress has been observed to induce oxidative stress, deposition of misfolded proteins, and metabolic disturbances inside the nerve cells, indicating how various cellular events play an important role toward the onset of neurodegenerative diseases (Iadanza et al., 2018; Brown and Wobst, 2019; Goldsmith et al., 2014; Uversky, 2011).

Golgi apparatus, on the other hand, is involved in protein sorting, packaging, and transportation (Iadanza et al., 2018; Brown and Wobst, 2019; Goldsmith et al., 2014; Uversky, 2011). Therefore, the interaction of the misfolded amyloid protein with any protein of the Golgi apparatus involved in maintaining its structure can result in Golgi apparatus fragmentation, as reported in AD and PD (Iadanza et al., 2018; Brown and Wobst, 2019; Goldsmith et al., 2014; Uversky, 2011).

To summarize, the molecular outcomes of AD and PD include protein misfolding and aggregation, ER stress, Golgi apparatus fragmentation, oxidative stress, and mitochondrial dysfunction. Various studies related to AD and PD are focused on either inhibiting the formation of protein fibrils or their disruption in case the fibrillar aggregates are formed. Therefore, this book chapter describes the applicability of CDs as prophylactic and/or therapeutic drugs to mitigate neurodegenerative diseases such as AD and PD.

3 Carbon Dots: Nano-Drugs

The rapid development of nanomaterials has resulted in numerous benefits to many sciences and engineering fields, which includes the introduction of a new class of fluorescent carbon nanomaterials. These nanomaterials are zero-dimensional nanosized carbon particles (size less than 10 nm) with inherent strong fluorescence characteristics (Fig. 10.4) (Wang et al., 2019). These are mono-dispersed spherical nanoparticles with a carbon-based skeleton and a large amount of oxygen-containing (–OH and –COOH) and amine-bearing (–NH_2) surface functionalities. The structure of CDs is composed of sp^2 hybridized carbon interior and an amorphous shell containing functional groups on the edges (Semeniuk et al., 2019). The CDs can be divided into three main categories, namely graphene quantum dots (GQDs; composed of one or few layers of graphene connected to above-mentioned functional moieties at the edges), carbon nanodots (CNDs; spherical nanoparticles with no crystal lattice), carbon quantum dots (CQDs; bear crystal lattice with an interlayer distance of 0.34 nm), and polymer dots (PDs; bear a carbon core with aggregated polymers attached) (Semeniuk et al., 2019). Currently, a wide variety of synthetic methods have been developed to produce fluorescent CDs, such as hydrothermal or solvothermal synthesis, electrochemical method, microwave-assisted synthesis, and electron-beam lithography (Wang et al., 2019).

The CDs can be synthesized via a "top-down approach" or "bottom-up approach." The "top-down" method involves breaking down of larger carbon-rich structures (Zhang et al., 2017; Yang et al., 2012; Peng et al., 2012). This process is done chem-

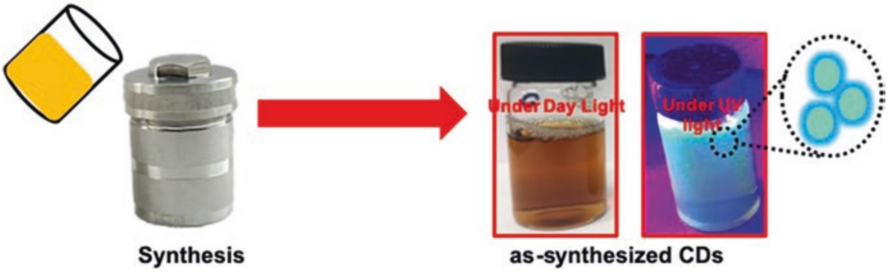

Fig. 10.4 Schematic representation of CDs synthesis

ically, electrochemically, and physically. The bigger carbon structures are oxidized and broken down into smaller carbon nanoparticles by S- and N-rich molecules such as H_2SO_4 and HNO_3. Zhu's group made yellow–green light-emitting GQDs (graphene quantum dots) by breaking down graphene oxide (GO) with an acidic agent through microwave treatment (Deng et al., 2014). The GQDs were further reduced into blue-light emitting GQDs with $NaBH_4$.

In contrast, the "bottom-up approach" involves the building of carbon molecules. This process occurs in four stages: condensation, polymerization, carbonization, and passivation. The small molecules may form structures through a condensation reaction like amidation (Zhu et al., 2013; Liu et al., 2019a, b; Kudr et al., 2017), aldol condensation (De and Karak, 2013; Chen et al., 2017), Schiff base condensation (Chen et al., 2016; Liu et al., 2017; Chen et al., 2017; Gao et al., 2013), and radical reaction (Yang et al., 2016; Gao et al., 2015). They are then formed into carbon clusters, a carbon core forms at high temperatures, and eventually surface passivation happens. Liu's group had five stages: decomposition, self-polymerization, aggregation, carbonization, and surface passivation (Song et al., 2016).

Some of the exciting chemical and physical properties of these nanomaterials include high aqueous dispersibility, excellent biocompatibility, chemical inertness, large surface-to-volume ratio, low toxicity, tunable photoluminescence, unique optical properties, chemical stability, ease of surface modification, resistance to photobleaching, and feasible and facile synthesis methods. Since their accidental discovery in 2004 during electrophoretic purification of SWCNTs, these newcomers of nanomaterials have attracted a lot of great attention of scientific community worldwide as an environmentally friendly replacement of traditional toxic inorganic quantum dots (QDs) or noble, metal nanoclusters, in the biomedical field such as bioimaging, chemical sensing, disease detection, and nanomedicine (Das et al., 2018; Ehtesabi et al., 2020; Yan et al., 2019; Sharma and Das, 2019; Xu et al., 2015).

4 Application of Carbon Dots to Mitigate Protein Aggregation in AD and PD (Nanodrug)

In a study, Liu et al. (2019a, b) described the regulatory effects of GQDs on Aβ aggregation. The GQDs were prepared by the incision of graphene oxide (GO) via the oxidation chemistry. The as-synthesized GQDs were analyzed using microscopic and spectroscopic techniques. The average size of GQDs was observed to be ~4 nm via TEM. The GQDs displayed excitation-dependent emission with a redshift in photoluminescence spectra from 360 to 520 nm. The FTIR and XPS revealed oxygen dominated surface of the GQDs. The circular dichroism (CD) spectra of GQD/$A\beta_{1-42}$ revealed retention of the β-turn secondary structure of Aβ after 8 h of incubation. In comparison, the $A\beta_{1-42}$ alone displayed a β-sheet dominated secondary structure at the end of 8 h. Furthermore, the Thioflavin T (ThT) data revealed the influence of GQDs on the Aβ aggregation. The images obtained from TEM were in

Table 10.1 A comprehensive table summarizing the application of organic CDs in neurodegenerative diseases

S. No.	CDs	Activity	Reference
1.	GQDs	Interaction of GQD with Aβ peptide prevented or slowed down aggregation of Aβ peptide.	Liu et al., 2019a, b
2.	GQDs	Detection of monomeric species of Aβ.	Huang et al. (2017)
3.	gCNQD	Determination of monomeric Aβ species concentration as low as ng/mL.	Zhang et al. (2019)
4.	OPCDs	Chelate Cu(II) ions, mitigate Aβ aggregation and photooxygenate Aβ peptides.	Chung et al. (2019)
5.	CDs	Inhibit BACE1 enzyme activity and delay amyloid-beta fibrillation	Han et al. (2017)
6.	L-CDs & D-CDs	Chiral modulation of $A\beta_{42}$ fibrillation using enantiomeric CDs	Malishev et al. (2018)
7.	GQDs	Inhibition of Aβ aggregation.	Liu et al. (2015)
8.	CDs	CDs displayed intrinsic affinity and photoinduced disintegration capabilities against amyloid species	Chung et al. (2017)
9.	GQDs	GQDs can act as therapeutics against α-synucleopathy in PD	Kim et al. (2018)
10.	Y-CDs	Nanocarrier to delivery drug across the BBB, bypass BBB and inhibit Aβ aggregation.	Zhou et al. (2019)

alignment with the CD and ThT assay. The DLS data also displayed interaction between the Aβ peptide and aggregates. The interaction of GQD with Aβ peptide prevented or slowed down the aggregation of Aβ peptide. Whereas, the GQDs had little or no impact on the fibrillar Aβ aggregates. GQD was not observed to dissolve or disintegrate these fibrillar assemblies (Liu et al., 2019a, b) (Table 10.1).

In a different study, Huang et al. (2017) proposed the use of GQDs for detecting monomeric species of Aβ. The GQDs were synthesized by the oxidation cutting of the graphite. The as-synthesized GQDs displayed a lateral dimension of ~5 nm and an average height of ~2 nm, as evident by transmission electron microscopy (TEM) and atomic force microscopy (AFM) images. The emission spectra of GQDs displayed excitation-dependent emission behavior. The X-ray diffraction (XRD), XPS (X-ray photon spectroscopy), and FTIR (Fourier transform infrared spectroscopy) data revealed oxygen-rich surface of GQDs. After the careful analysis of the morphology and surface chemistry of the GQDs, the feasibility of using GQDs to monitor $A\beta_{1-42}$ was examined. The photoluminescence (PL) data revealed the capability of GQDs to track fibrillization as a linear decrease in PL was observed in the presence of monomeric $A\beta_{1-42}$ peptides. In contrast, a linear increase in PL of GQD (as the concentration of GQD was increased) was observed in the presence of the fibrillar $A\beta_{1-42}$. Similar results were obtained from the ThT assay revealing the feasibility of monitoring monomeric $A\beta_{1-42}$ fibrillization. To explore the interaction between the GQD and $A\beta_{1-42}$, the PL readings were taken at high pH (pH 10). Interestingly, recovery in fluorescence of GQD was observed in the presence of monomeric $A\beta_{1-42}$

peptides, suggesting the interactions were affected by pH. The proposed interactions between the monomeric species and GQD were H-bonding and electrostatic interactions, which could be easily altered by the changes in pH. Thus, this work provides new inroads in the applicability of GQDs for the diagnosis of amyloid-associated diseases (Huang et al., 2017) (Table 10.1).

In a recent study, graphitic carbon nitride quantum dots (gCNQD) were developed for the determination of monomeric Aβ species concentration as low as ng/mL (Zhang et al., 2019). High-resolution transmission electron microscopy (HRTEM) displayed monodisperse gCNQDs with a lateral dimension of 2.7 nm, spherical morphology, and a d-spacing of 0.34 nm. The FTIR and XPS data showed an abundance of $–NH_2$, –COOH, and –OH on the surface of gCNQDs. Also, the fluorescence data displayed excitation-dependent emission behavior of the gCNQDs. Furthermore, the affinity of gCNQDs against various biologically relevant metal ions such as Cu^{2+}, Zn^{2+}, and Fe^{3+} was tested using fluorescence studies. Compared to Cu^{2+}, the fluorescence quenching of gCNQDs observed in the presence of Zn^{2+}, and Fe^{3+} was weak, indicating the selectivity and sensitivity of gCNQDs toward Cu^{2+}. Thus, gCNQDs–Cu^{2+} was used as a nanoprobe for further Aβ determination experiments. Various monomeric species of Aβ peptide are found in the cerebral system of the rat such as $Aβ_{1–11}$, $Aβ_{1–16}$, $Aβ_{1–38}$, $Aβ_{1–40}$, and $Aβ_{1–42}$. Therefore, the affinity of all these fragments against gCNQDs– Cu $^{2+}$ was monitored using fluorescence studies. Introduction of $Aβ_{1–40}$ and $Aβ_{1–42}$ into the nanoprobe induced more changes in fluorescence intensity compared to the $Aβ_{1–11}$, $Aβ_{1–16}$, $Aβ_{1–38}$. Furthermore, to validate the proposed mechanism of fluorescence quenching in the presence of the Aβ fragments, TEM images were obtained. The data showed variation in the morphology of gCNQDs, gCNQDs– Cu $^{2+}$, and after additions of $Aβ_{1–42}$ to the nanoprobe. Interestingly, in the presence of $Aβ_{1–42}$, the nanoprobe showed interconnected particles that arouse from the aggregation of the gCNQDs. Furthermore, this nanoprobe was used for the monitoring of $Aβ_{1–42}$ in the cortex of the AD rats. Hence, the obtained results point toward the applicability of gCNQDs, fluorescence sensing systems for the selective and sensitive detection of $Aβ_{1–42}$ in the aqueous solution (Zhang et al., 2019) (Table 10.1).

In another study, polymerized o-phenylenediamine (pOPD)-derived CDs (OPCDs) with an inherent ability to chelate Cu (II) ions, mitigate Aβ aggregation by breaking β-sheets, and photooxygenate Aβ peptides were developed as a therapeutic drug (Chung et al., 2019). The as-synthesized OPCDs were characterized using various analytical techniques such as TEM, fluorescence, FTIR, and XPS. The obtained data showed spherical OPCDs with an average size of ~7.3 nm and $–NH_2$, –OH, and –COOH-rich surface. The CD and ThT assay were performed to explore the effect of OPCDs on the secondary structure of the Aβ. The obtained results displayed the ability of OPCDs to chelate Cu (II) ions and interrupt β-sheet stacking within Aβ–Cu (II) complex, thus preventing amyloid aggregation. The data were further validated by the HRTEM images of Aβ-Cu (II) ions complex in the presence and absence of the OPCDs. Finally, the ability of OPCDs to photooxygenate Aβ–Cu (II) complex in the presence and absence of light was studied. The obtained data from MALDI-TOF mass spectrometer, CD, and AFM images, in the dark and in the presence of light, suggested modulation of Aβ oxygenation is irradiation time-dependent. Also, it pointed toward the inhibitory efficacy of OPCDs against Aβ–Cu (II) complex-mediated aggregation. Hence, this work points toward the potential of OPCDs as a therapeutic drug to treat metal associated amyloid diseases (Chung et al., 2019) (Table 10.1).

In a study, Han et al. (2017) synthesized CDs that displayed blood–brain barrier (BBB) permeability with the ability to target and inhibit beta-secretase 1 (BACE1) enzyme activity and delay amyloid-beta fibrillation and associated in vitro toxicity. The inhibition activity was followed using ThT assay, CD, and AFM using four different concentrations of the CDs. The CDs were able to delay or inhibit fibrillation at a concentration of 10 μg/mL. The human transferrin (HT) conjugated CDs were able to bypass the BBB and enter the forebrain area of the zebrafish. Hence, it can be claimed that these HT-functionalized CDs can be used for the effective treatment of AD (Han et al., 2017) (Table 10.1).

In another study, Malishev et al. (2018) studied the ability of enantiomeric CDs (synthesized from L- or D-lysine) on the modulation of amyloid-beta fibrillation and associated toxicity. The results showed that L-lysine-CDs displayed a higher affinity toward $A\beta_{42}$ compared to D-lysine-CDs. This higher affinity resulted in modulation of the $A\beta_{42}$ fibrillar assembly process and the impact of CDs on reducing the associated cytotoxicity. This work was the first demonstration of chiral modulation of $A\beta_{42}$ fibrillation using enantiomeric CDs (Malishev et al., 2018) (Table 10.1).

In a different study, Liu et al. (2015) synthesized biocompatible GQD for the inhibition of Aβ aggregation. The AFM and TEM images displayed an average size of less than 1.3 nm, suggesting that the GQDs could possibly cross the blood–brain barrier (BBB). The ThT assay and AFM data revealed the prophylactic activity of these GQDs as the fibril formation was delayed in the presence of the GQDs (Liu et al., 2015). Whereas, the MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay displayed rescuing activity of the cells by the GQDs from amyloid insult suggesting the prophylactic capabilities of this nanosystem (Liu et al., 2015) (Table 10.1).

In another study, photoluminescent CDs were synthesized via hydrothermal method using ammonium citrate as the starting material (Chung et al., 2017). CDs with an average size of ~4.4 nm were synthesized. These CDs were surface passivated with branched polyethyleneimine (b-PEI) exhibiting cationic surface. The hydrophilic surface allows interactions with the negatively charged residues of the Aβ fibrils resulting in its disintegration. The bPEI-CDs hindered Aβ aggregation via electrostatic interaction with the Aβ residues. The light-triggered enhancement in Aβ aggregation inhibition and dissociation of the β-sheet rich structure was observed. Thus, it can be concluded that these CDs displayed intrinsic affinity and photoinduced disintegration capabilities against amyloid species (Chung et al., 2017) (Table 10.1).

In a different study, GQDs were tested for their ability to prevent α-synucleinopathy in PD. These GQDs were developed from carbon fiber dissolved in strong acids at 80 °C for 24 h (Kim et al., 2018). The study showed the capability of GQDs to inhibit fibril formation and trigger their disintegration by directly interacting with the α-synuclein, as evident by TEM, ThT, and turbidity assays. Moreover, in vivo studies showed the ability of GQDs to bypass the BBB and prevent dopaminergic neuronal loss induced by α-synuclein fibrils, Lewy bodies, and mitochondrial dysfunction. Therefore, it can be concluded that these as-synthesized GQDs can act as therapeutics against α-synucleinopathy in PD (Kim et al., 2018) (Table 10.1).

In a recent study, the applicability of citric acid and OPD derived CDs (Y-CDs) as a nanocarrier was examined (Zhou et al., 2019). The as-synthesized Y-CDs were amphiphilic, as evidenced by the zeta potential results. The TEM images displayed spherical CDs with an average size of 3.4 nm. The FTIR spectrum showed an abundance of $–NH_2$, –COOH, and –OH on the surface of Y-CDs, responsible for the water dispersibility of the CDs. The Y-CDs displayed excitation-dependent emission pattern of fluorescence. To examine the ability of Y-CDs to bypass the BBB, zebrafish was used as the model organism. The obtained data revealed the ability of CDs to cross the BBB via passive diffusion. It could be attributed to the amphiphilic nature of the CDs and its ability to disperse in various organic solvents without any evident effect on the PL intensity. The cytotoxicity results against various cell lines (HEK293, SJGBM2, and CHLA200) revealed the nontoxic nature of Y-CDs, thus confirming its safety to use for biological applications. Furthermore, the cellular imaging capability of Y-CDs was tested in SJGBM2 and HEK293 cell lines. Both the cell lines showed bright yellow fluorescence compared to the control. The fluorescence was localized in the cytoplasm of the cells. Hence, passive diffusion was proposed as the mechanism of Y-CDs entry inside the cells. Finally, the applicability of Y-CDs to inhibit amyloid precursor protein (APP) and Aβ was examined. The obtained data revealed the potential of these CDs to inhibit APP and Aβ owing to their amphiphilic surface. Thus, it can be claimed that these CDs can be used as a nanocarrier to deliver drugs across the BBB (owing to its amphiphilic surface), bypass BBB, and inhibit Aβ aggregation. Hence, it can be used for the treatment of AD in the near future (Zhou et al., 2019) (Table 10.1).

5 Conclusion

The self-assembly of amyloid fibrils into a highly organized and conserved structure that is composed of β-sheet aggregates is a molecular hallmark of neurodegenerative diseases such as AD and PD. These structures are stabilized via H-bonding, Vander Waals interactions, hydrophobic interactions, and π–π stacking interactions resulting in the formation of insoluble amyloid aggregates. Such aggregation induces pathophysiological conditions associated with the gravest of human diseases such as AD and PD. Hence, it is crucial to attenuate these amyloid aggregates to avoid or overcome amyloid-associated neurotoxicity. Therefore, in the present study, the ability of CDs as nanodrug with therapeutic capability was summarized because of their low cytotoxicity, nanosizing, large surface area to volume ratio, low cost of production, and superior optical properties. Further research in this area is needed, but the future of CDs in this field looks promising, and hopefully, the next decade will present massive scope for developing and delivering these nanodrugs to mitigate neurodegenerative diseases such as AD and PD.

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Chapter 11
Characterization and Biocompatibility of a Polylactic Acid (PLA) 3D/Printed Scaffold

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1 Introduction

Tissue engineering, also called regenerative medicine, is the application of the principles and methods of engineering and the biological sciences, to understand the relationship between the structure and function of tissues; and thus, to develop biological substitutes that restore, maintain, or improve the function of damaged or lost tissues. The tissue engineering triad is composed of the scaffolds, the cells and growth factors, or functionalization molecules (Gupte and Ma 2012; Ou and Hosseinkhani 2014).

All the main components must interact to present a scaffold that will be capable of replacing the damaged or missed tissue, without generating an immune response or creating new side effects in the receiving organ. By definition, a scaffold is a biomaterial that provides support as a biological platform to facilitates the proper repair and restoration of physiological–histological characteristics of damaged tissues during the healing process (Ceccarelli et al. 2017). The scaffolds incorporate cells that must carry out in vitro biological functions, to offer possible in vivo guided bone tissue regeneration. Briefly, the ideal characteristics of a scaffold are summarized in Fig. 11.1.

The scaffolds must facilitate the location and distribution of the cells to specific sites of the body to be restored, maintaining a three-dimensional (3D) architecture that allows the formation of new tissues with a proper function. Thus, the scaffolds should have different characteristics such as being biocompatible, nontoxic, and must offer optimal physicochemical properties. Moreover, allow mimicking the nanometric and micrometric attributes of the native tissue structure. For this, the 3D scaffolds play a fundamental role in tissue engineering, by acting as a temporary shelter for cells that attach, grow, and secrete its own matrix, that eventually will

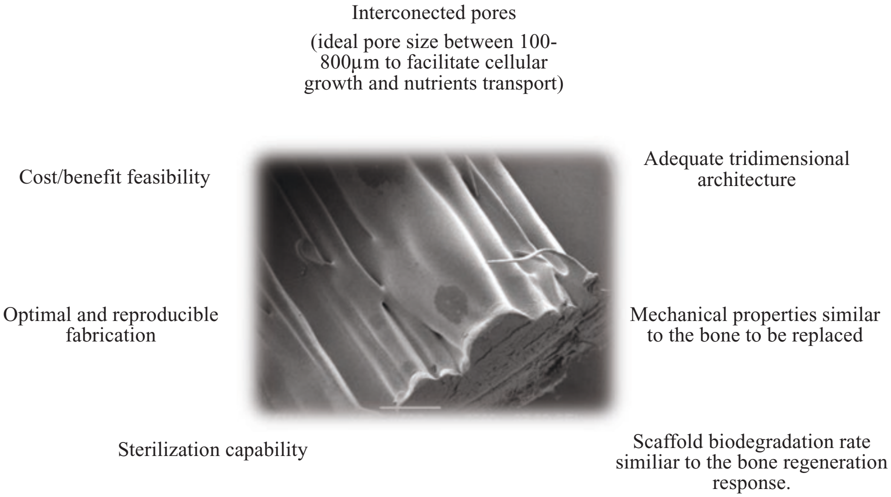

Fig. 11.1 Characteristics of the “ideal” scaffold

form an organized tissue system. Cells cannot grow in 3D orientations on their own; thus, scaffolds can give the anatomical shape of the tissue and guide the regenerative process.

2 Bone Tissue Engineering

Bone is a metabolically active tissue that is capable of adapting its structure to mechanical stimuli and to repair the structural damage through the process of bone remodeling. It is a very sophisticated type of mineralized vascular connective tissue, which can provide exceptional rigidity and hardness to support strong forces, facilitating at the same time psychochemical and mechanical signals to maintain the bioactivity of the cells. However, in the case of a severe injury or illness such as arthritis, trauma, or infection, the bone tissue loses its capacity for self-regenerate, creating the need to use substitutes such as implants, prothesis, or bone substitutes. Since the first definition offered by Langer in 1993, tissue engineering had focused on the use of artificial biomaterials to the regeneration of damaged or diseased tissues (Li et al. 2007).

There are four different ways of how a biomaterial can favor the bone regeneration, briefly:

1. A biomaterial with an appropriate composition may provide continuous nutrition to the bone to improve the mineralization process.
2. The nanometric properties of the biomaterials could mediate the cellular behavior (such as proliferation and cell adhesion), as well as the osseointegration of cells. Nanostructures themselves will have the capacity to improve the resistance of the new bone.
3. Biomaterials must have a hierarchical architecture that encompasses a macro-, micro-, and nano-porous structure, allowing cellular permeability, the nutrient and waste transport, bone growth, and vascularization.
4. The use of nanostructures may facilitate how growth factors are released and interchanged, allowing the scaffolds to accelerate the formation of bone and healthy vessels.

Not only the nanometric surfaces provide a larger surface area to promote cellular adhesion and protein affinity, but the surface patterns have an impact on cell differentiation and cell distribution on the scaffolds. Therefore, the 3D structure must imitate as good as possible, the real conditions in the size and shape of the defect. It is intended to generate the appropriate microenvironment for the exchange of nutrients, waste disposal, cell migration, proliferation, differentiation, angiogenesis, and vascularization. In this matter, the design is as crucial as the construction of the scaffolds. Interconnected macroporosity with a diameter >100 μm is a prerequisite for bone growth, cell migration, and nutrient transport, and those with pores between sized 200 and 300 μm have favored the extension and elongation of cells. Therefore, the incorporation of macro, micro, and nanostructures creates a synergistic effect to play specific roles in the regenerative process. By manipulating the hierarchical architecture of the biomaterial, complementary microenvironments will play particular roles that allow an adequate composition, structure, and biological functions with the bone regenerative process (Li et al. 2017).

Bone grafts are classified as autologous, allograft, xenograft, and alloplastic. Autologous bone is the gold standard in bone regeneration. It consists of obtaining healthy bone tissue from the same person to be grafted onto the defect, which minimizes the rate of rejection. It has a cortical bone (excellent structural support and decreased resorption, but slow revascularization) and medullary bone (early revascularization, therefore less risk of infection, and less waiting time in case of dental implant placement) (Kao and Scott 2007; Benic 2014). Allografts are those derived from donor sites of the same species (also called "*bone banks*"), but because of their manipulation (sterilization and decellularization) to minimize rejection or transmission of disease, they lose many of the characteristics, so they end up being only osteoconductive. Xenografts are derived from different species, such as bovine bone. The survival is comparable to the autologous bone, offers osteoconductive properties, and cost less than allografts. Allografts and autografts have proven successful in restoring bone form and function; however, they still carry significant risks. One of the risks associated with the use of autologous grafts is the morbidity of the donor site. At the same time, allografts may involve the transmission of disease, which is compromised by the sterilization process (Ceccarelli et al. 2017; Kao and Scott 2007; Benic 2014; Zizzari et al. 2016).

3 3D Printing of Synthetic Scaffolds

Even when the current synthetic printed scaffolds lack osteogenic and osteoconductive intrinsic properties, some advantages such as the control on the structural composition and design, a minimum chance of biological contamination, and the avoidance of a donor site manipulation, and its possible complications make these biomaterials an attractive alternative. Due to these reasons, the last two decades are full of new studies focused on the development of synthetic biomaterials that may act as scaffolds for bone regeneration (Masaeli et al. 2019). Although the first steps were considered expensive or even unfeasible, currently 3D printers are part of almost all the laboratories (Fairag et al. 2019); and to create new functional scaffolds is now a part of the daily routine.

3.1 The 3D Printing Process

3D printing is one of the tools that tissue engineering offers as a promising solution to fulfill the demand for tissue substitutes. Using a layer-by-layer deposition technique, 3D printing can create novel biomaterials by incorporating materials and biomolecules in a precise way to resembles the extracellular matrix of tissues (Masaeli et al. 2019). This is an additive manufacturing method that considers the equipment itself (also called "printers"), printing materials, and predesigning with advanced software (Serra et al. 2013). It was first described in 1984, and since then, this technology is considered essential when body substitutes are needed (Choi et al. 2015). The 3D printing method becomes a more predictable technique, as it creates a precise micro-architecture, which achieves the ideal environment for cell growth (Feng et al. 2018; Behera et al. 2020). This method makes the manufacture of a specific scaffold design in a more controlled and reproducible manner compared to other scaffold manufacturing techniques (Guvendiren et al. 2016). This is important because the properties of the scaffold are essential to favor cell migration, influence its morphology and cytoskeletal structure, and to determine gene expression and lineage (Markovic et al. 2015; Hutmacher et al. 2014).

3D printing is divided into three general categories: forming technique, subtractive technique, and additive technique. The forming technique consists of shaping a workpiece without reducing or adding material. The subtractive technique usually requires cutting materials to achieve the desired shape (i.e., computed numerical control) contouring a precise part. Finally, the additive technique involves adding material layer by layer with a thickness that varies in proportion to the diameter of the output nozzle of the chosen printer (Hutmacher et al. 2014; Stansbury and Idacavage 2016).

More specifically, Guvendiren et al. (2016) presented a complete classification. These authors reported that printing technologies can be subclassified as the extrusion-based method (which include fused deposition modeling and direct ink writing), particle fusion-based methods (including selective laser-sintering method and particle-binding method), light-induced methods (also known as light-assisted 3D printing or stereolithography), and inkjet printing (Guvendiren et al. 2016; Hutmacher et al. 2014; Stansbury and Idacavage 2016; Zhu et al. 2015). What differentiates the 3D printing method from others is that it can be controlled, from the design (size, architecture, walls, and pore interconnectivity) to the manufacturing depending on each specific method. In this sense, scaffolds can be manufactured to provide an adequate temporary load resistance during regeneration, fulfilling specific biological requirements. However, there are always possible surgical complications associated with the fact that the interaction between extracellular matrix and cell, the standardization of biological systems, and the technical capacity to manufacture them is still unclear (Luo et al. 2007).

There are important challenges of 3D printing, such as to optimize the mechanical strength, to mimic the complexity of the design of the structures, the manage the porosity, and to favor further anatomical vascularization. Many efforts have been made to improve the resistance of 3D bone scaffolds through chemical and structural optimization of the material, both considered during the synthesis and printing processes. The 3D printing has the advantage of modulating the printing parameters and to obtain hierarchical scaffolds with macropores in a range of 250 μm and micropores in the range of 5–30 μm, allowing resistance to compression similar to that of the trabecular bones (Masaeli et al. 2019). Pores are a particular aspect to consider, not only its single size but their number and distribution. Several studies have shown a high degree of osteoblastic infiltration and proliferation in scaffolds with larger pores (600 μm) than those with smaller pores (40 μm). Increasing the number of pores also favors the diffusion of nutrients and proliferation of the cells, improving the deposition of proteins and formation of tissues (Hutmacher et al. 2014; Jafari et al. 2017). On the other hand, during the manufacture of a scaffold, the design is essential so that neither mechanical nor biological properties are affected. If the pore size is increased, the mechanical properties can be impaired, since the 3D structure is weakened by favoring the presence of voids.

3.2 3D Printing Materials

To choose the ideal material to create a scaffold is an important issue (Serra et al. 2013). 3D printing considers different biomaterials both natural or synthetic. Natural materials such as gelatine, alginate, collagen, fibrin, or hyaluronic acid have been used to print scaffolds; however, synthetic polymeric biomaterials are usually preferred. Selecting a polymer to be printed as a scaffold is not an easy task. Beyond ensuring biocompatibility and host acceptance, polymeric scaffolds must be biodegradable, have excellent mechanical properties, and ideally be bioactive. Besides, their porosity and surface topography should be attractive to cells. As mentioned before, the polymeric matrix should try to mimic the structure of an extracellular matrix (Guvendiren et al. 2016; Hutmacher et al. 2014). Another type of classification given to polymeric scaffolds is by their topographic properties, such as roughness, hydrophilicity, and their microstructure (pore size, porosity, interconnectivity, and architecture of the pore and fiber) (Jafari et al. 2017).

Aliphatic polyesters are the most attractive family of synthetic polymers for research (Chiulan et al. 2018). They are poly (α-hydroxy acid) represented by the formula –(–0–CHR–CO)–n. Among the aliphatic polyesters, we can mention polyglycolic acid (PGA) (the simplest polymer synthesized in 1930 by William Carothers, the father of nylon); polycaprolactone (PCL) (one of the first polymers synthesized by Carothers in the 1930s) and polylactic acid (PLA).

3.3 PLA: A Versatile Printing Material

PLA is the most widely used biodegradable synthetic polymer in health sciences and is accepted by both the FDA (US Food and Drugs Administration) and the EMA (European Medicines Agency) (Fairag et al. 2019). This is a chiral molecule, two stereoisomeric forms that give rise to four morphologically distinct polymers: Poly (D-lactide), poly (L-lactide), its mixture poly (D, L-lactide), and a final form poly (meso-lactide) (Hutmacher et al. 1996; Mohammadi et al. 2014; Asti and Gioglio 2014; Kundu et al. 2013). It is more hydrophobic than PGA due to the presence of an extra methyl group and more soluble in organic solvents, that is why copolymers have been developed to combine the advantages of both biomaterials, such as polylactic co-glycolic acid (PLGA) (Ko et al. 2008; Jeong et al. 2008; Jafari et al. 2017). Its mechanical properties (modulus of elasticity 1.5–2.7 GPa) and a 60 °C glass transition temperature, make it easy to handle (Carrow et al. 2015). It is commercially available for STL and molten deposition modeling. Table 11.1 summarizes some of the chemical and physical properties of PLA.

A synthetic polymer such as PLA has enormous potential mainly because of its known biocompatibility. Its degradation products can be reabsorbed by the body, allowing biological spaces for tissue extension. However, PLA alone is not sufficient to act directly on bone formation. It has low bioactivity, so it only mediates bone formation by promoting cell adhesion and proliferation. Despite the benefits of PLA and its versatility in applications in medicine, its real biocompatibility is still under debate. The degradation products can lower the pH of the surrounding tissue, favoring inflammation or foreign body reactions, and thus inhibiting the formation of hydroxyapatite (HA) crystals, compromising the osseointegration process. The hydrophobic properties of resorbable polyesters can negatively influence cell adhesion, so different bioinductive particles have been added to scaffolds such as titanium nanoparticles, demineralized bone particles, bioactive nanoparticles, fibronectin, bioactive glass, HA, tricalcium phosphate, tetracalcium phosphate, or biphasic calcium phosphate. By adding these macromolecules as well as biological growth factors, the problem of the bone induction can be partially compensated (Masaeli et al. 2019; Virlan et al. 2015). As for PLA microparticles, these are used to maintain drug concentrations for prolonged periods used in a genetic release,

Table 11.1 Physical and thermal properties of PLA

	Values	Units
Viscosity	0.265–0.467	Pa*s
Density	1.25	g/cm^3 @ 21.5 °C
Thermal conductivity	0.13	W/(m*K)
Thermal diffusivity	0.056	m^2/s
Specific heat	1800	J/(kg*K)
Feed rate	2.247–2.67	m/s
Tensile yield strength	53	MPa
Elongation at yield	10–100	%
Flexural modulus	345–450	MPa
Melting temperature	145–186	°C
Glass transition temperature	50–64	°C
Shear modulus	2.4	GPa
Melt flow rate	4.3–2.4	g/10 min
Yellowness index	20–60	(YI) ASTM
Tensile strange	28–50	MPa
Young's modulus	1.3–3	GPa
Elongation at break	2–6	%

cancer therapy, and vaccines. The use of nanoparticles is also considered, with the advantage that this size can facilitate the penetration of cells, increasing the release of drugs and reducing the inhibitory and the possible bacterial concentration. However, these last two still need further evidence to confirm their clinical applicability (Jafari et al. 2017; Virlan et al. 2015; Woodard et al. 2007).

4 Nanotechnology and Nanomaterials for Bone Regeneration

Tissue engineering goal is to achieve tissue repair when the applied material is fully integrated with surrounding tissues, replicating the functionality of the native tissue, while showing no adverse effects (Manoukian et al. 2018). Nowadays, nanotechnology is part of most biological research, specially in development phases of new products. Nanotechnology works to characterize, manipulate, and organize matter systematically at the nanometre scale, with a dimension sized from 1 to 100 nm (Gusić et al. 2014; Pryjmaková et al. 2020). Recent advances in the fields of nanotechnology, biomaterials sciences, tissue engineering, and the biomanufacturing technologies have generated a great promise to find treatments for bone defects, specially creating bone graft substitutes (Mohammadi et al. 2018). Research in nanotechnology for tissue regeneration includes nanoparticle-based scaffold manufacturing, designing nanoscaffolds to mimic extracellular matrix function (Funda et al. 2020). By adding nanoscale modifications to polymeric scaffolds, the surface and mechanical properties necessary for support can be improved, as well as cellular adhesion, differentiation, and integration into the surrounding environment (Walmsley et al. 2015).

Nanotechnology can play different roles, depending on the scope of each research. First, the process can be concibed to analyze nanometrically a bone substitute or an scaffold, expanding the already known information about the biomaterial, specially in terms of porosity and biological response (Wang et al. 2020). A second option, will be to use the nanotechnological tools to understand a certain response of the material once submitted to mechanical, biological, or chemical agents. The third option is not to work on available materials, but to create a new one with nanometric properties. Of course, to obtain a real nanomaterial for bone regeneration will represent a special challenge. Nanomaterials are undergoing rapid development, and compared with bulk materials, its decreased size leads to an exponential increase in effective stiffness, surface area, and surface area to volume ratio (Li et al. 2017). Their size enhances protein adsorption, cell adhesion, proliferation, and differentiation, resulting in increased biocompatibility (McMahon et al. 2013). Nanomaterials also possess features like macroscopic quantum tunneling or quantum size, causing altered physicochemical properties, such as wettability, charge, and roughness modification. As an example, aqueous contact angles become three times smaller, leading to increased adhesion of the osteoblasts in comparison with micro-sized materials (Zakrzewski et al. 2020). As a possibility to obtain nanoscaffolds, 3D printing increased the economic feasibility of low volume production

(Cubo-Mateo and Rodríguez-Lorenzo 2020) by using layer-by-layer deposition of biomaterials as described before (Qasim et al. 2019). These scaffolds with controllable pore architecture, excellent mechanical strength, and mineralization ability for bone regeneration are an accessible revolutionary option for bone regeneration (Gu et al. 2013). By combining 3D printing, nanotechnology, cell biology, and materials science; bone tissue engineering exhibits enormous prospects for future development (Wang et al. 2020). If it is necessary, additional nanoparticles can be added to be designed scaffold to enhance biological responses. Ceramic nanomaterials such as HA and bioactive glass, carbon-based materials, graphene, or metallic nanoparticles (such as gold and titanium oxide) have been widely investigated (Hill et al. 2019; Vieira et al. 2017). Nanoparticles had been applied in bone tissue engineering to augment tissue regeneration or even to prevent infections in the integration process (Walmsley et al. 2015). By including new characterization or functionalization alternatives into the process, researchers understand that to make “nano-modifications” will turn into “micro-changes” and finally “macro-transformations”; so, even the smallest variable cannot be underestimated. So, nanotechnology is not only a matter of size, it represents the compilation of all aspects of science taken to a new level. Even with these new alternatives that recognize the great potential of nanobiotechnology in bone repair, many steps are still needed to recreate the next bone hierarchical structure, and further research is always welcome (Gusić et al. 2014).

5 PLA 3D/Printed Scaffold Characterization

In the scope of this chapter, we present the design and basic characterization of a cubic PLA scaffold obtained by 3D printing. Scaffold designs can also be cylindrical and pyramidal (Tan et al. 2014; Senatov et al. 2016). However, scaffolds can also be classified according to the basic PLA structure as orthogonal structures (exhibiting a 0/90° pattern), diagonal structures (with a 45/135° or 60/120° pattern), and cylindrical porous structures (Souness et al. 2018). This specific scaffold was designed using the fused deposition modeling method in a modular 3D printer MM1 MakerMex (Mexico City, Mexico) at a temperature of 204 °C in a flexible module. A PLA filament cartridge was used, with a thickness of 3.0 mm diameter. This filament passes through a nozzle where the material is melted and using a layer-by-layer deposition, following the designed structure. The design was introduced in modeling and animation software or computer-aided design (CAD) and consisted of a three-dimensional cubic model of 2 cm × 1 cm × 2 cm (Fig. 11.2). The inner pattern allowed empty prisms interconnected by thin layers of PLA.

The scaffolds were sterilized for 30 min with 75% ethanol preparation and an antibiotic solution (penicillin (100 IU/mL), streptomycin (100 μg/mL), and fungisone (0.3 μg/mL)), and 1 h exposure to UV light at a constant temperature of 37 °C. The obtained biomaterials were sealed and stored. The basic characterization of a 3D-printed scaffold may vary from study to study, depending on the scope or

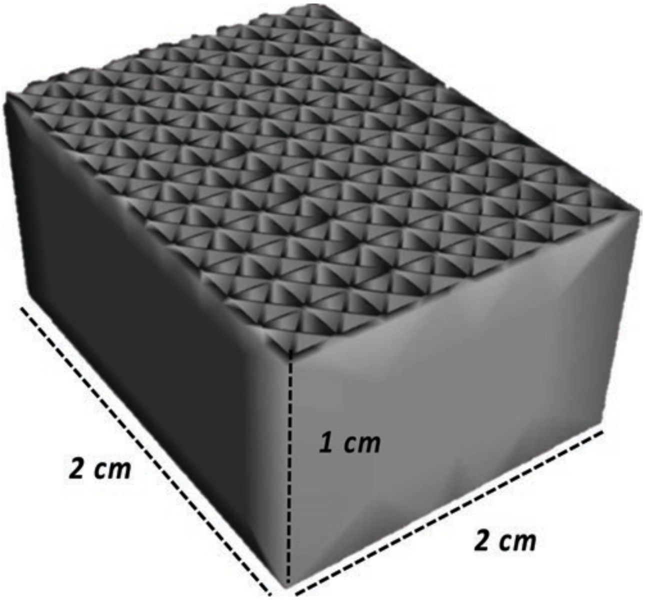

Fig. 11.2 3D design of the cubic scaffold

the main aim to be analyzed to an specific material. However, basic stages are proposed to determine if the obtained scaffold offers some of the ideal desired characteristics. Correspondingly, this chapter discusses the physical, thermodynamic, and biological tests performed on the 3D PLA scaffold.

5.1 Physical Characterization

5.1.1 Scanning Electron Microscopy (SEM)

The scanning electron microscope (SEM) is one of the most versatile instruments available to analyze the morphology of the microstructure of polymeric materials (Sun et al. 2016). The SEM uses a focused electron beam to systematically scan the surface, producing a large number of signals that finally become a visual sign displayed on a cathode ray tube. The SEM image formation depends on the acquisition of signals generated from the interaction of the electron beam and the sample (Zhou et al. 2006). The signal emitted by the secondary electrons is the one generally used to obtain an image of the sample. It is considered a secondary electron to the one that emerges with an energy lower than 50 electron volts (eV). In comparison, the backscattered electron signal is composed of those electrons that emerge from the sample with an energy higher than 50 eV. The emission of electrons is one of the basic forms of SEM that provides a 3D image of the structures. This phenomenon is

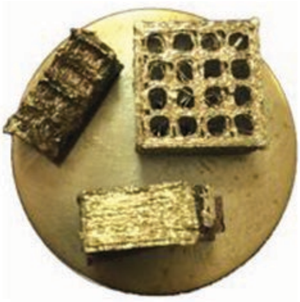

Fig. 11.3 3D-printed cubic scaffold prepared for SEM analysis

possible after the coating of the polymeric sample with a nanometric metallic layer to prevent or reduce the electric charge effect caused by the beam of electrons. The most common metals used for this purpose are gold, palladium, carbon, or different combinations of these. However, gold is the most widely used due to its easy acquisition in pure form (Fig. 11.3).

For this scaffold, a SEM equipment (ASEM Microscopy JEOL JSM-6390LV, USA) was selected, and samples were coated with a 5 nm gold layer (EMS 150R equipment, Quorum, USA). The three surfaces of each scaffold (upper, lateral, and inner surfaces) were analyzed at 5 kV at three different magnifications (45×, 200×, 1000×). At 45×, the inner surface showed interconnected pores in a polymer matrix structure with lattice pattern. This kind of surface may be favorable for vascularization to occur and may guide an adequate cell adhesion and proliferation. Due to the design and the printing pattern, the lateral surface showed less porous surface than the inner one; however, it still showed scarce pores presence. On the upper surface, some prolongations emerge from pores. At 200× and 1000×, all surfaces showed irregular roughness and the presence of different sizes of pores. Especially at 1000×, the pores are visible in the inner and lateral surfaces (Fig. 11.4).

5.1.2 Profilometry Analysis

The roughness is determined by techniques that explore a determined area of the surface to obtain a two- or three-dimensional profile. The use of low-resolution magnification can create a preliminary subjective perception of roughness; however, this analysis will depend on many circumstances of the observer. Roughness can be more accurately analyzed by the use of profilometers (contact or noncontact devices) or even by atomic force microscopy when nanometric data are needed.

For this specific scaffold, topographic images were obtained with a contact profiler (Bruker Dextak XT, USA). A needlepoint from 2 μm radio was used, and the scanning axis was taken with an applied force of 4 mg, with a resolution of 0.033 μm/point (which corresponds to a needlepoint speed of 10 μm/s covering a total area of 500 × 500 μm). The image was constructed by merging 500 scans. Roughness values were evaluated using the entire measured area, determining average roughness

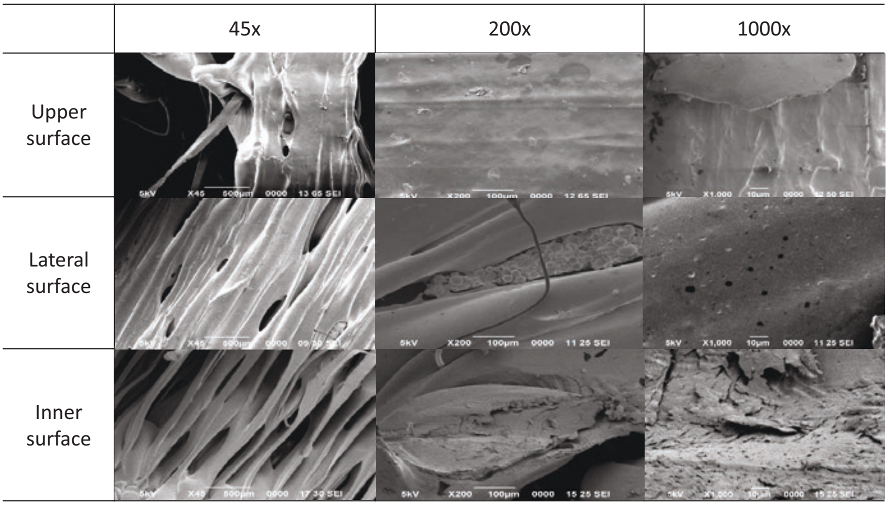

Fig. 11.4 3D-printed cubic scaffold SEM analysis

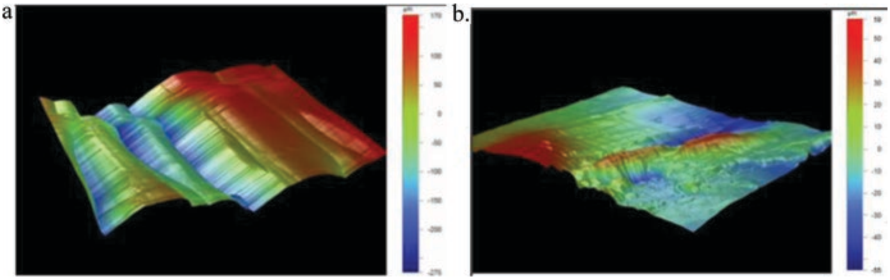

Fig. 11.5 Profilometry analysis. (**a**) Upper surface. (**b**) Lateral surface

(Ra), average maximum heights (Rv), and average maximum depressions (Rq). Also, a 3D image was obtained from a specific area (Fig. 11.5).

The average roughness was greater in the lateral surface than in the upper one (Fig. 11.6). This difference is the result of the layer-by-layer printing method that progressively deposits the material. The scaffold–cell interaction is influenced not only by the type of material but also by its topography. Several studies support that cell adhesion and proliferation depend on the architecture of the scaffold. If the average roughness of a surface is greater than the individual size of an osteoblast, for example, this surface can be perceived as smooth, since the distance between peaks is too large to be detected (Hayes et al. 2011). The orientation of the cells along the scaffold and the degree of the direction of the cells depend on the roughness of the material (Saltzman and Kyriakides 2000), so extraordinarily smooth and pore-free surfaces are not recommended when looking to enhance a biological response.

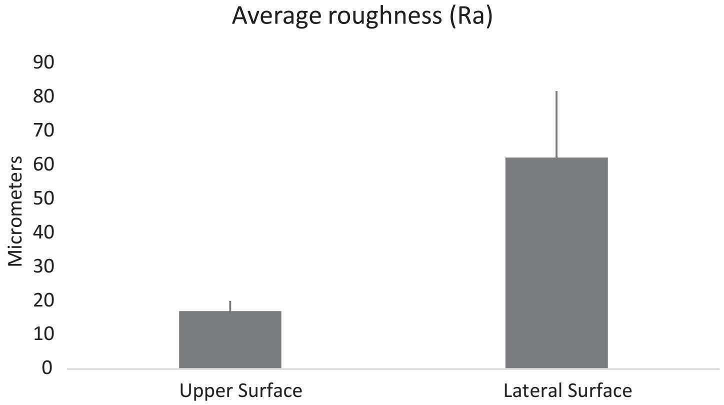

Fig. 11.6 Profilometry analysis. Average roughness results

5.2 *Thermodynamic Characterization*

5.2.1 Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry (DSC) had shown to be an important technique in the field of materials science due to its high degree of sensitivity and the short duration of the analysis. In most cases, it allows us to identify the physical state changes that take place at a certain temperature, obtaining important data like melting point (Tm), glass transition temperature (Tg), and crystallization temperature (Tc). In the particular case of polymers, DSC is advantageous to establish the thermal stability of the amorphous phase. Since our scaffold used a printing method based on the organized deposition of melted PLA, it is essential to consider DSC as part of the characterization. 3D printing requires the use of thermoplastic materials with good melting and viscosity properties, which can be modified or even affected depending on the temperature manipulation (Stansbury and Idacavage 2016; Hutmacher et al. 2014; Zhu et al. 2015; Kundu et al. 2013).

A DSC equipment (TA Instruments, model DSC Q200) was used to analyze different samples of the scaffold and pure PLA fiber. A nitrogen flow of 50 mL/min as purge gas was used, and a ramp from 25 to 250 °C was programmed, with a heating rate of 10 °C/min. It was observed that when the PLA scaffold is printed, the polymer did not lose its properties, since both thermal scans are similar. The PLA (pure and printed) showed comparable results, i.e., the Tg (57.78 °C pure PLA, 55.65 °C 3D PLA) and the Tm (169.02 °C pure PLA and 168.98 °C 3D PLA) are very similar, so that the nature and conditions of the polymer are still maintained after the construction of the scaffold through the printing temperature (204 °C) (Fig. 11.7). Also, it was shown that during the manufacturing process, no impurities or detectable contaminations are added to the scaffold.

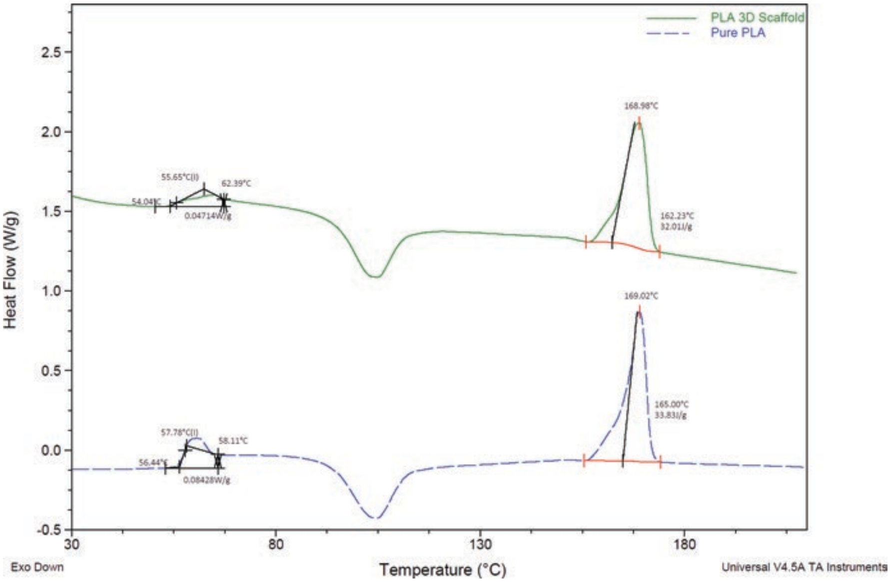

Fig. 11.7 Comparative DSC analysis

5.2.2 Thermogravimetric Analysis (TGA)

To characterize the scaffolds and to confirm that the working temperature of the polymer does not compromise the integrity of the scaffold, not only DSC but TGA may be needed (Brown et al. 2010). TGA is part of a set of thermal analyses that have been developed to identify and measure the physical changes in the materials when exposed to controlled temperature variations. These analyses have been designed specifically for the study of initial reactions in the decomposition of solid materials and liquids. The analysis consists of continuously recording the variation of mass of the material as the temperature is varied at a constant rate (linear temperature change). This type of thermogravimetric procedure is known as dynamic analysis.

The scaffold was analyzed in TGA equipment (TA Instruments TGA Q500). The analyses were carried out with a thermal ramp of 25–1000 °C under nitrogen control (heating speed 20 °C/min). The analyzed properties were the point of beginning mass loss, known as Onset Point (To) and the inflection point (Tp) (maximum mass loss rate calculated by the first derivate of the curve (Derivate of % weight/temperature)).

The printing temperature did not affect the properties of the polymer, compared to pure PLA scaffold. The To for the pure polymer was 328.36 °C and the 3D PLA scaffold was 325.47 °C. Also, both Tp were very similar (pure PLA showed a Tp of 340.81 °C and 3D PLA scaffold 346.16 °C) (Fig. 11.8). As it was observed in the TGA analysis, the printing temperature didn’t affect the mass of the PLA. Table 11.2 shows a comparison of the thermodynamic properties of the 3D PLA scaffold.

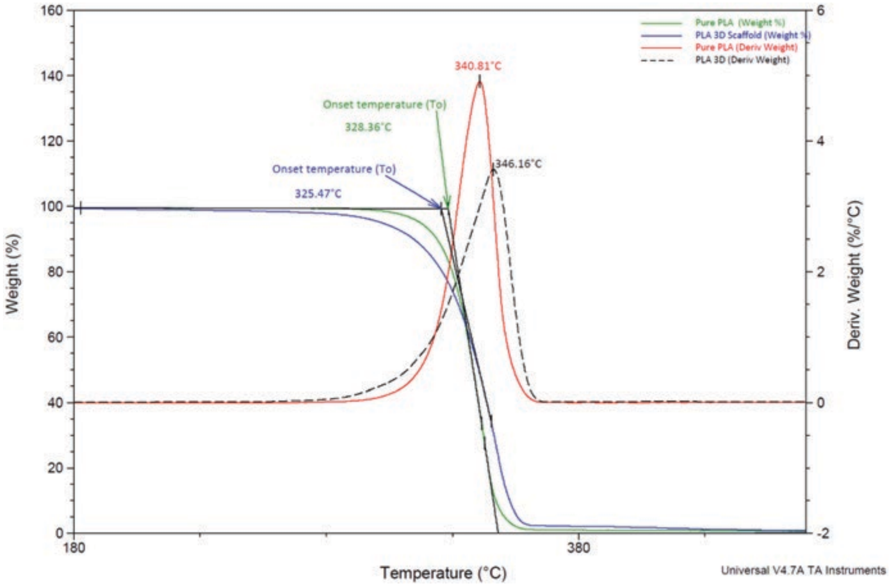

Fig. 11.8 Comparative TGA analysis

Table 11.2 Comparison of the thermodynamic properties of the 3D PLA scaffold

	DSC		TGA	
	Tg (°C)	Tm (°C)	To (°C)	Tp (°C)
Pure PLA	57.78	169.02	328.36	340.81
3D PLA	55.65	168.98	325.47	346.16

5.3 *Biological Characterization*

The biological characterization will be considered just when the scaffold demonstrates to be a suitable option for bone regeneration. Although the ideal tests will include in vivo experiments (i.e., biological response in laboratory animals), the first steps to analyze biocompatibility and cell behavior will be done in vitro with cell culture. For this stage, fetal osteoblasts from the Tissue Bioengineering Laboratory of the Faculty of Dentistry, UNAM México, were used. The cells were cultured and expanded in alpha-MEM culture medium supplemented with 10% fetal bovine serum (FBS), a solution of antibiotics (penicillin (100 IU/mL), streptomycin (100 μg/mL), and fungisone (0.3 μg/mL)), and 100 mM of glutamine. The cultures were kept at a temperature of 37 °C and in an atmosphere of 95% air and 5% CO_2 in an environment with 100% humidity.

5.3.1 Cell Adhesion Assay

To analyze the effect of 3D PLA scaffolds on cell adhesion, the cells were grown on 2 cm × 2 cm × 1 cm cubic scaffolds. Cells were plated in 15-well culture plates, with a cell density of 1×10^5 cells/mL with 500 μL of alpha-MEM medium and cultured for 4 and 24 h at a temperature of 37 °C and in an atmosphere of 95% air and 5% CO_2 in an environment with 100% humidity. After the time of sowing, the cells that did not adhere to the surfaces were removed by three washes with PBS. The cells attached to the scaffolds were fixed with 4% paraformaldehyde. Cell adhesion was evaluated according to the violet crystal method. The fixed cells were incubated with 500 μL of the 0.1% crystal violet solution for 15 min, washed three times with bidistilled water to remove the nonspecific dye. Then, the color was extracted with 500 μL of 1% sodium dodecyl sulfate (SDS). From the obtained solution, 200 μL were taken and placed in a well of a 96-well plate for ELISA assays and read in a plate reader (ChroMate Plate Reader, AWARENESS Technology) at an absorbance of 545 nm. The control cultures were the cells seeded on the same plastic plates over a 6% PLA membrane. The absorbance values obtained were extrapolated according to the standard curve to determine the number of cells or the percentage of cells adhered to the scaffolds. Cell adhesion experiments were performed in triplicate, repeating at least three times. The adhesion assay showed that the 3D PLA scaffold had a better interaction with cells. After 24 hours, there is an increase in cell adhesion, maybe related to the surface variations previously described (Fig. 11.9).

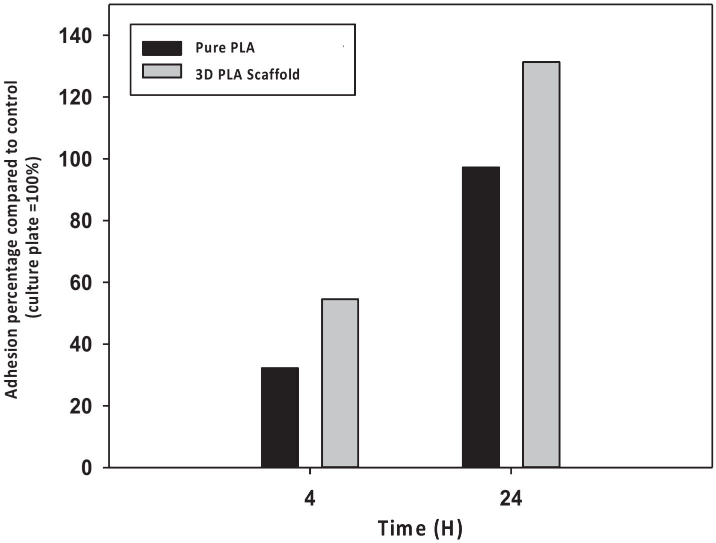

Fig. 11.9 Cell adhesion assay (4 and 24 h analysis)

5.3.2 Cell Viability Assay (Proliferation)

To evaluate the effect of 3D PLA scaffolds on cell viability, the triazole blue (MTT) test was carried out based on the ability of mitochondrial dehydrogenase enzyme to oxidize a tetrazolium salt to an insoluble product of blue color. The cells were cultured at a cell density of 1 × 10^5 cells/mL in the alpha-MEM medium at a temperature of 37 °C and in an atmosphere of 95% air and 5% CO_2 in an environment with 100% humidity. They were triplicated by 1, 3, 5, 7, and 9 days of culture. After each experimental period, the cells were incubated with MTT (50 mg/mL) at 37 °C for 4 h. After this time, the supernatant was removed, and a solution with 0.2% dimethyl sulfoxide (DMSO) was added and allowed to act for 30 min. From the obtained solution, 200 μL were taken and placed in wells of a 96-well plate for ELISA tests, taken to a plate reader (ChroMate Plate Reader, AWARENESS Technology) to obtain the optical density at a wavelength of 545 nm. The experiments were performed by triplicate. The test showed increased cell proliferation in the 3D PLA scaffold at the period when compared with pure PLA and the control (Fig. 11.10). The best behavior of the scaffold was observed by day 7. Cellular proliferation is an essential phenomenon for tissue engineering since it supports the enhanced biological response of living tissues once exposed to the designed scaffold (Saltzman and Kyriakides 2000), and the modified topography is considered as one of the most important features affecting the biological response of a scaffold (Serra et al. 2013). Our results coincided with previous reports who demonstrated that human osteoblastic cells dynamically seeded on hierarchical scaffolds, showed significantly

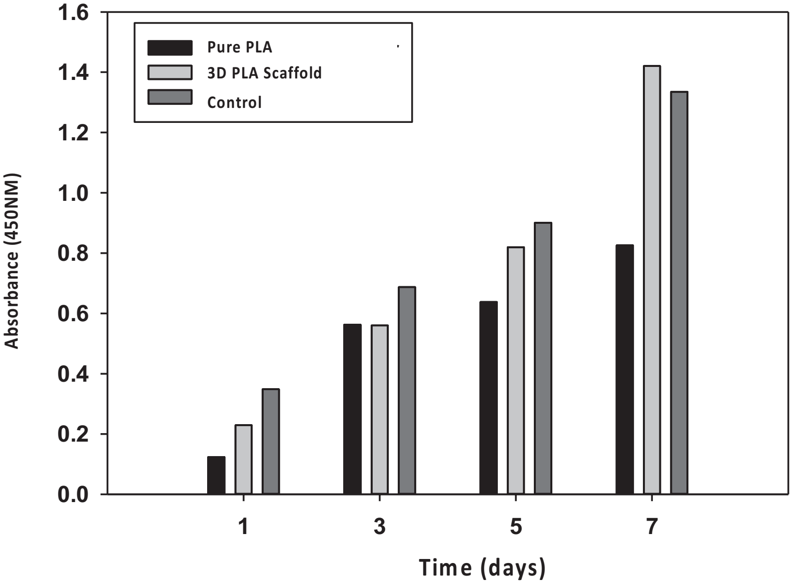

Fig. 11.10 Cell proliferation assay (1, 3, 5, and 7 days)

higher proliferation and maturation (Martins et al. 2018). As such, the use of 3D printing may be considered not only a tool to build a scaffold but an instrument to create a physical functionalization of the PLA.

5.3.3 Cell–Scaffold Interaction Analyzed by Confocal Microscopy

The analysis of the interaction of the cells with the PLA 3D scaffolds was performed with the CellTracker™ Green CMFDA kit (5-chloromethylfluorescein diacetate). This kit contains a fluorescent dye to evaluate the cellular interactions and localization. After cells incubation, the contrast medium is retained, which allows us to track the adhered cells that are interacting with the 3D PLA scaffold surface. Such analysis is possible since the dye has a free penetration through the cell membrane. For this test, 1 × 10^4 cells/mL were seeded on 3D PLA scaffolds and left for 24 h. Afterward, they were washed with PBS and incubated at 37 °C with SRF/Cell Tracker medium for 1 h, after which time the medium was removed and rewashed with PBS. It was left with complete medium Alpha-MEM for 2 h. Finally, they are washed with distilled water and fixed with 4% PFA. Samples were observed under confocal laser microscopy, with wavelengths of 492 and 517 nm (LASAF, Leica, Germany).

3D PLA scaffold showed the presence of osteoblastic cells adhered to the surface with pseudopodia prolongations. This supports that both the design and the printing method favors cell adhesion, confirming also the previous cell adhesion test. As reported before, this behavior is related to the small and large pores, which enhances cell behaviors such as a growth pattern following the scaffold topography (Kennedy et al. 2016, Faroque et al. 2014, Murpgy et al. 2010). As seen in Fig. 11.11, the confocal images obtained after 24 h showed an increased interaction of the cells over the scaffold (b) when compared with pure cell clusters over non-printed PLA (a).

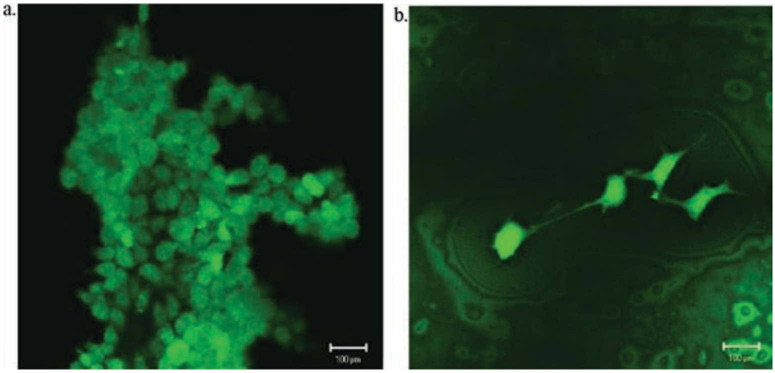

Fig. 11.11 Confocal microscopy analysis. (**a**) Clusters of osteoblasts over pure PLA. (**b**) Osteoblasts over 3D PLA Scaffold

6 Conclusion

Bone tissue regeneration is a complex task to achieve. This process must consider the host response and the biomaterial to be applied as well. This biomaterial will be designed and build under a "mimicking philosophy," trying to recreate the lost bone tissue. In this sense, 3D printing gives the opportunity to recreate the defect, and to enhance different topographical aspects to enhance the biological response, especially when a biocompatible polymer like PLA is selected as the main material. Our characterization demonstrated that the obtained 3D PLA scaffold offers promising advantages to be considered as a core structure for tissue engineering. This scaffold is reproducible, homogeneous, stable, and can present important microscopic details to obtain the positive biological response observed by cells.

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Chapter 12

Nanoparticles as Artificial Chaperons Suppressing Protein Aggregation: Remedy in Neurodegenerative Diseases

Sarita Tripathi, Samridhi Pathak, and Avinash Kale

Contents

Abbreviations

AD	Alzheimer's disease
AED	Antiepileptic drugs AED
ALS	Amyotrophic lateral sclerosis
API	Active pharmaceutical ingredients
Aβ	Amyloid-β

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BBB	Blood–brain barrier
BPD	Benzoporphyrin derivative
EFPP	EGCG–Fe (III)/PVP nanoparticles
ESM	Ethosuximide
HD	Huntington's disease
MRD	Microscopic residual disease (MRD)
MRI	Magnetic resonance imaging
NiPAM:BAM	N-isopropylacrylamide: N-tert-butylacrylamide nanoparticles
NIR	Near infrared laser
PAMAM	polyamidoamine
PDAC	Pancreatic ductal adenocarcinoma
PET	Positron-emission tomography
PNBs	Plasmonic nanobubbles
pPhD NP	Trojan horse nanoparticles
PPI	polypropylenimine
SLNs	Solid lipid NPs (SLNs)
SPECT	Single-photon emission computed tomography
TGA	Thioglycolic acid
TTR gene	Transthyretin gene

1 Introduction

The proper three-dimensional conformation of a protein sis central to various cellular processes such as the organization of cell structure, maintenance of cellular homeostasis, cell division, and cell signaling (Lambert 2019). However, during stress conditions, proteins fail to fold correctly de novo or remain incorrectly folded leading to the formation of protein aggregates that accumulates in cells and internal environment of the body (Alam et al. 2017; Chiti and Dobson 2006). Protein misfolding and aggregation are associated with a group of diseases, known as amyloidosis, which encompasses more than 20 different diseases (Alam et al. 2017; Chiti and Dobson 2006). These amyloids formed as a result of continuous protein aggregation and unregulated protein folding results into four subtypes of the amyloidosis (Chiti and Dobson 2006). These four subtypes are named AL amyloidosis, ATTR amyloidosis—ATTRm or ATTRwt amyloidosis, AA amyloidosis, and dialysis-related beta2-microglobulin amyloidosis (ABM2) (Tanaka et al. 2010; Dember 2006; Ueda et al. 2019; Gertz et al. 2015; Izumiya et al. 2018). AL amyloidosis affects the plasma cell in the bone marrow resulting in multiple myeloma while AA amyloidosis is associated with chronic inflammatory diseases such as rheumatic diseases, familial Mediterranean fever, chronic inflammatory bowel disease, tuberculosis or empyema, and so on. ATTR is the most common type of hereditary amyloidosis caused due to mutation in the transthyretin (TTR) gene (Tanaka et al. 2010; Dember 2006; Ueda et al. 2019; Gertz et al. 2015; Izumiya et al. 2018). Systemic amyloidosis caused due to prolonged experience of dialysis to remove impurities in the blood by mechanical filtration is commonly known as Dialysis-related beta2-microglobulin amyloidosis (Tanaka et al. 2010; Dember 2006; Ueda et al. 2019; Gertz et al. 2015; Izumiya et al. 2018). It is also known as ABM2 (amyloid associated with the beta-2m protein), due to the aggregation of beta2-microglobulin, which is generally cleared in the normally functioning kidney (Tanaka et al. 2010; Dember 2006; Ueda et al. 2019; Gertz et al. 2015; Izumiya et al. 2018).

Protein misfolding, aggregation, and accumulation are the major underlying cause of neurodegenerative diseases such as Alzheimer's disease (aggregation of beta-amyloid), Huntington's disease (accumulation of huntingtin protein), and Parkinson's disease (aggregation of alpha-synuclein protein), and so on (Umemura et al. 2018). These conditions of "proteinopathies" have profound consequences in humans like provoking cell membrane oxidation, interference with ion homeostasis, the mitochondrion functioning, and inter- and intracellular signaling, thus inducing apoptosis (Umemura et al. 2018). The abnormal and progressive accumulation of insoluble β-sheet enriched protein aggregates propagates with age increasing the severity of disease leading to the death of the patients (Umemura et al. 2018).

At present times, no proper definitive pre-diagnostic tool or curative treatment exists for such diseases. Hence, symptomatic management is of paramount importance to promote quality of life. Additionally, with the aging population, it becomes very difficult to manage such diseased conditions as they are more prone to the complexity of these proteinopathies. The current area of research involves understanding the mechanism of amyloidogenesis, inhibiting protein aggregation under intra-/extracellular space, augmenting the clearance of protein aggregates, and lowering of toxicity arising due to soluble oligomers. Effective interventions are urgently needed to deal with neurodegenerative disorders worldwide.

Advancement in the arenas of nanotechnology has led to the development of a completely new era in medicine, particularly as a promising diagnostic and prognostic tool (Maddela et al. 2021). Nanomedicines provide potential solutions to many of our current challenges in treating cancer, cardiovascular, and neurodegenerative diseases, as well as other pathogenic illnesses. It has come a long way in providing new strategies for prophylactic, diagnostic, and therapeutic applications.

Nanoparticles have shown to significantly affect the protein aggregation (Shammas et al. 2011; John et al. 2018). They act as artificial chaperons in inhibiting protein aggregation (Shammas et al. 2011). As nanoparticles have small size and large surface area, they tend to have enhanced bioavailability (John et al. 2018). NPs block these oligomeric species that are neurotoxic in nature, and this will be of great concern to the biological perspective in the field of nanobiotechnology. NPs have also been reported to cross the blood–brain barrier (BBB), making it to be an intriguing candidate to understand its effect on protein aggregation, subsequently resulting in neurodegenerative disorders, such as amyloid-beta peptide aggregation driven Alzheimer's disease (John et al. 2018).

This chapter provides a facile overview of nanomedicine-mediated targeting of protein aggregates in order to overcome neurodegenerative disorders via suppression of mode of aggregation and protein denaturation. This piece of information as represented in Fig. 12.1, truly highlights a notable aspect of nanotechnology with tremendous implications in biology and medicine.

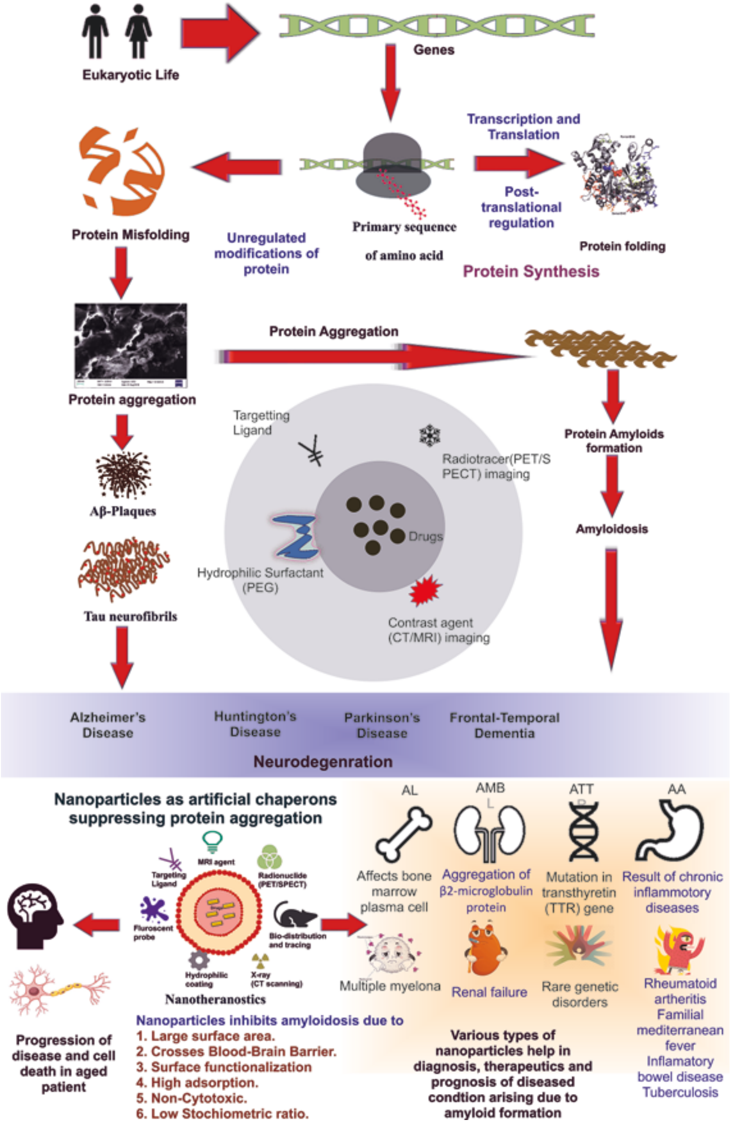

Fig. 12.1 Overview of the role of nanoparticles acting as chaperones in suppressing protein aggregation

2 Mode of Action of Nanoparticles in Inhibition of Protein Aggregation

A growing number of evidences have shown that nanomaterials can influence protein aggregation to a great extent. However, their impact on Aβ aggregation kinetics remains quite controversial. NPs can either promote or retard amyloid fibrillation depending on their particle size and surface functionality. The NP features such as surface chemistry, diameter, and electric charge modulate the Aβ aggregation to a varying extent. Diameter of NPs has been shown to alter the extent of inhibition, whereas electric charge influences the aggregate morphology (Sukhanova et al. 2019).

Similar to protein-based natural chaperons, nanoparticle-based artificial chaperones also interact with misfolded protein/oligomer/protofibril. This kind of chaperone activity of the NPs is because of the presence of multiple adsorption sites on their surface, which in turn interferes with the protein aggregation process. The high surface area of NPs is modified with numerous functional groups that enable NPs to interact with the aggregating protein of target via multivalent binding (Zaman et al. 2014). Binding of nanoparticles to protein is governed by non-covalent interactions like hydrophobic and hydrogen bonding. There are two possible modes of action of nanoparticles interfering amyloid-β aggregation (John et al. 2018). Firstly, these particles may sequester monomeric form and reduce the local protein concentration required for aggregation (John et al. 2018). This would eventually shift the monomer–oligomer equilibrium away from fibrillation toward off-pathway targets. Second, nanoparticles may bind to oligomers as well as depleting the sub- and near-critical nuclei. Such interactions would also hinder with the elongation process by blocking the binding sites for further addition of monomers on aggregates (Zaman et al. 2014).

As shown in Fig. 12.2, nanoparticles are known to perturb monomer-critical nuclei equilibrium by binding efficiently to active Aβ monomers, oligomers, critical nuclei, and protofibrils on their surfaces via weak interactions thereby reducing the local concentration of Aβ protein critical for the fibrillation process. This delays nucleation and/or elongation time of Aβ aggregation and their associated cytotoxicity (John et al. 2018). NPs are also capable of sequestering free circulating toxic Aβ oligomeric species through the "sink effect" further alleviating AD pathogenesis (Brambilla et al. 2012).

3 Advantages of Nanoparticles over Other Chemical Entities as Protein Aggregation Inhibitors

Nanoparticles have garnered special interest in combating neurodegenerative disorders because of their intriguing properties like small size, large surface/mass ratio, easy penetrance across the blood–brain barrier (BBB), unique structural superiority,

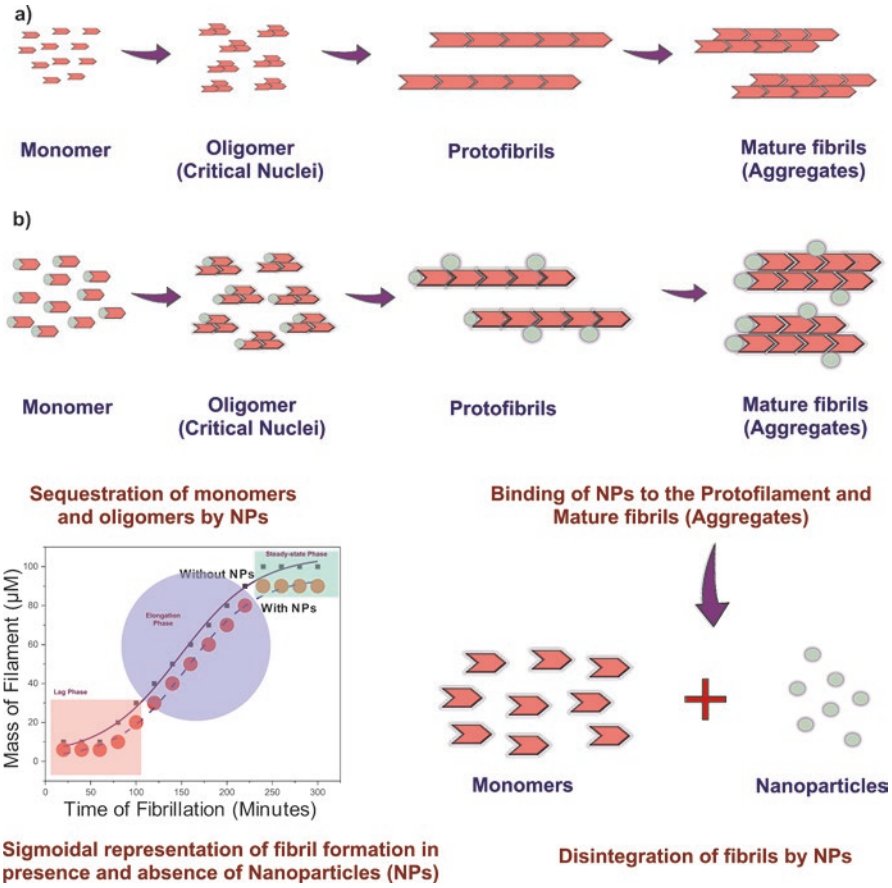

Fig. 12.2 Dynamics of fibril formation during the process of amyloidosis. (**a**) Steps involved in fibril formation in absence of nanoparticle. (**b**) Steps involved in fibril disintegration upon nanoparticle binding

and ease of surface functionalization and modification. Most of the nanoparticles are noncytotoxic in nature and are known to have high adsorption capacity/capability (Phelan 2018). They are easy to synthesize and have great in vivo stability. Unlike other drugs, nanoparticle inhibitors exhibit promising inhibitory properties at a remarkably low stoichiometric ratio. Several studies provide deeper mechanistic insights of NP-based inhibitors that are carefully and rationally designed to effectively manage neurodegenerative diseases and other proteinopathies (Sukhanova et al. 2019). Nanoparticles also act as nanoprobes. They exhibit optical properties that are suitable for the detection and imaging of aggregates or plaques. This also enables us to determine the dosage levels and monitor the prognosis of treatment toward a disease (Phelan 2018).

Nanoparticles represent a powerful tool to transport drugs across biological barriers. It may also increase the half-life of conjugated drugs and enhance their uptake in brains. Additionally, NPs are known to last longer in our circulatory system (Lockman et al. 2003). They even cross blood–brain barrier (BBB) without compromising its integrity and permeability (Lockman et al. 2003; Zhang et al. 2017). Although the exact mechanism remains unclear, it is suggested they may be transported via endocytosis or transcytosis or even by passive diffusion (Zhang et al. 2017). One of the leading roles that these NPs are playing in biomedical research is for their ability to act as nanotheranostics (Xue et al. 2018). This integrated approach of the diagnostic and therapeutic function of NPs has shown exciting potentials toward precision nanomedicine. It has also been reported that Trojan horse nanoparticles (pPhD NP) are used for the delivery of ultrasmall, fully active pharmaceutical ingredients (API), which is used for both dual-modal imaging and trimodal therapeutic functions. pPhD NPs enable tumor penetration and cell internalization. pPhD NPs are known to help during the visualization of biodistribution of the APIs by near-infrared fluorescence imaging, tumor accumulation, and its therapeutic effect by magnetic resonance imaging (MRI) (Xue et al. 2018).

4 Amyloid-β Aggregates in Alzheimer's Disease

Alzheimer's disease (AD) is a progressive neurodegenerative disorder affecting the older population. It is clinically characterized by loss of memory and other cognitive abilities, which exacerbates with age and eventually leading to death. The key hallmark in AD pathogenesis is the self-assembly of amyloid-β peptides into β-sheet enriched fibrillar aggregates that gets deposited extracellularly as plaques in AD patient's brains. AD is also associated with the accumulation of neurofibrillary tangles formed by hyperphosphorylated tau protein in the brain (Kumar et al 2015). Amyloid-β (Aβ) monomers exist in two isoforms $A\beta_{40}$ and $A\beta_{42}$ differing in only two amino-acid residues at C-terminal (Kumar et al 2015). Although $A\beta_{40}$ is predominantly present, $A\beta_{42}$ peptides have shown to have higher aggregation propensity and neurotoxicity. Since Aβ aggregation is the central process leading to AD pathologies, the discovery of agents that block or interrupt or redirect the oligomerization and/or fibrillation process could prove as an effective treatment of amyloidosis (Kumar et al 2015).

Recent therapeutics for AD are merely beneficial as they delay and/or alleviate the onset of symptoms to a moderate extent improving the quality of life. But none of them can arrest the disease progression or reverse the pathologies. With the increasing cases of AD worldwide, new approaches to develop viable pharmacotherapeutics for AD have now become more challenging in modern medicines (Kumar et al 2015).

4.1 Nanoparticle-Based Inhibition of Amyloid-β Aggregates

To date, considerable efforts and progress have been made in developing various kinds of Aβ aggregation inhibitors like nanoparticles (Wang et al. 2013a), small molecules (Wang et al. 2013a; Nie et al. 2011; Scott et al. 2011; Wang et al. 2013b), peptides and peptide mimetics (Wang et al. 2013a; Aileen Funke and Willbold 2012), protein microspheres (Wang et al. 2013a; b; Richman et al. 2011), metal polymers, and antibodies (Wang et al. 2013a, Watt et al. 2014). These agents display low efficacy due to their ability to interact with peptide monomers in 1:1 ratio (Sun et al. 2012) Other major issues governing the limited therapeutic use of these inhibitors are its inability to permeate the blood–brain barrier (Poduslo et al. 1994), decreased in vivo stability, and complex synthesis process (Lockman et al. 2003).

NPs are also known to enhance the rate of protein fibrillation by surface-assisted nucleation (Zaman et al. 2014; Linse et al. 2007). Molecular dynamics simulation revealed how nanoparticles can catalyze the self-assembly of peptides into fibrils via condensation-ordering mechanism (Auer et al. 2009). For instance, anionic gold NPs (Zhang et al. 2009), cerium oxide particles (Zaman et al. 2014; Linse et al. 2007), quantum dots (Linse et al. 2007), TiO_2 NPs (Mohammadi and Nikkhah 2017), carbon nanotubes (Linse et al. 2007), and peptide-functionalized ϒ- Fe_2O_3 nanoparticles (Skaat et al. 2011).

In contrast, NPs identified as inhibitors Aβ fibrillation include fullerenes (Xie et al. 2014), carbon nanotubes (Li et al. 2011), N-acetyl-L-cysteine capped quantum dots (Sukhanova et al. 2019; Xiaoab et al. 2009), gold nanoparticles (Ma et al. 2013; Gao et al. 2017), and polymeric nanoparticles (Zaman et al. 2014). Seong Il Yoo et al. reported inorganic CdTe nanoparticles stabilized by thioglycolic acid (TGA) are capable of inhibiting the fibrillation process. These NPs associates with oligomers/100–300 monomers at once via van der Waals interactions rather than individual monomers. Such powerful van der Waal forces driven by high electron density on CdTe inorganic nanoparticles are unlikely to form with organic nanoparticles explaining their opposing effect on amyloid aggregation kinetics. Other interactions like hydrophobic forces and hydrogen bonding cannot be strong due to the hydrophilic nature of TGA coating and its difficulties in competing with strong H-bonds stabilizing the oligomers. The inhibition mechanism resembled functionalities of certain proteins and short-peptide inhibitors responsible for perturbation of amyloid aggregation in humans (Yoo II et al. 2011). At a particular ratio of peptide and particle concentration, amino-modified polystyrene NPs accelerated the fibrillation process in solution at low particle surface area and retarded the same at high particle surface area (Cabaleiro-Lago et al. 2010). Apart from inhibition, there had been some reports that report the dissolution of existing amyloid fibrils using NP-based systems. Under near infrared (NIR) laser irradiation, peptide-modified AuNPs (Kogan et al. 2006) and thioflavin-conjugated graphene oxide (Li et al. 2012) are capable to dissolve amyloid aggregates. Such NP-based photothermal therapy can be used to selectively target such macromolecular assemblies and remove them efficiently (Li et al. 2012). It is also considered to be safe and efficacious than traditional chemotherapy.

The NP features such as surface chemistry, diameter, and electric charge modulate the Aβ aggregation to a varying extent. Diameter of NPs has been shown to alter the extent of inhibition whereas electrical charge influences the aggregate morphology (Moore et al. 2017).

4.2 Gold Nanoparticles

Gold nanoparticles (AuNPs) can act as nano-chaperones to inhibit and modulate Aβ40 fibrillization with therapeutic potential in AD. Gold nanoparticles have received special interest due to their ease of synthesis and super biocompatibility. Smaller size AuNPs significantly delayed or completely inhibited the Aβ aggregation whereas larger AuNPs accelerated the aggregation (Zhang et al. 2009; Moore et al. 2017). However, AuNPs have self-tendency to aggregate into large clusters which accumulate in the liver and spleen posing health problems. Hence, this factor needs to be taken into consideration while developing AuNP-based nanodrugs.

A study by Yi-Hung Liao et al. demonstrated that anionic AuNPs of 30 nm diameter inhibited the fibrillization of amyloid-β40. Aβ40 monomers incubated with AuNPs were redirected to form fragmented short fibrils and spherical oligomers with reduced neurotoxicity. Exposure of preformed fibrils to AuNPs resulted in ragged Aβ species and amorphous aggregates. To their surprise, NPs preferentially associated with mature fibrils structure and not amorphous aggregates. In addition, they found that only carboxyl-modified AuNPs prevented fibrillation and not amine-conjugated AuNPs. It has been reported that negative surface potential is critical for the interaction between Aβ40 and AuNPs (Liao et al. 2012). Irradiation of weak microwave fields (0.1 W) to Aβ42 peptides-AuNPs complex results in irreversible inhibition of conjugated inhibition of Aβ amyloidogenesis (Araya et al. 2008).

Smaller size NPs are more effective in abrogating Aβ aggregation. For example, PAA coated gold nanospheres of both 8 nm and 18 nm reduced the equilibrium plateau by ˃90% at a stoichiometric ratio of 1:2,000,000 and were found to be the most potent inhibitors of Aβ aggregation (Moore et al. 2017). Several studies report that anionic AuNPs exhibit super inhibitory capabilities over cationic AuNPs. For example, anionic citrate and PAA (polyacrylic acid) coated NPs are more efficient in prohibiting aggregation of amyloid-β protein than cationic CTAB (cetyltriemethylammonium bromide) and PAH (polyallylamine hydrochloride) modified NPs. NPs with the same electric charge but different surface chemistry also display variation in inhibitory properties. Like PAA-coated NPs are more potent in inhibiting Aβ aggregation than citrate-coated NPs (Moore et al. 2017).

High surface curvature in the case of smaller NPs provides a platform for sequestration of $A\beta_{40}$ monomers. To support experimental observations, the authors described a theoretical model of NP induced changes in local solution conditions. Curved and charged NPs alter the local environmental conditions such as pH, ionic strength, or charge density in the vicinity of $A\beta_{40}$ monomers thereby affecting the aggregation kinetics. Greater magnitude of surface charge induces pronounced changes in molecular organizations within the local milieu. Cationic NPs attract chloride and hydroxyl ions increasing the local pH and induce negative charge density whereas anionic NPs draw tris and hydronium ions decreasing the local pH and induce negative charge density. Different counterions reorganize to balance out the NPs surface charge. This disturbs the chemical equilibrium of such ionic species that ultimately manifests into asymmetry between local and bulk solution conditions. There occurs a dynamic exchange of protein between these environments impeding the fibrillation of amyloids or their destruction. This indeed imparts a greater inhibitory effect extending several nanometres beyond the surface of nanoparticles (Moore et al. 2017). Furthermore, NPs coated polymeric PAA produces steric hindrance that preferentially localizes protons instead of ions altering the local pH drastically. Hence, PAA-coated NPs are more effective than monomeric citrate coated NPs against Aβ aggregates (Moore et al. 2017). Hongchen Liu et al. have shown that an optimum negative charge density is required to achieve the most effective inhibition of Aβ fibrillogenesis. They synthesized four polymeric NPs (NP0, NP5, NP10, and NP20) with an equal number of hydrophobic groups but with increasing negative charge densities. Intriguingly, all their experimental results were congruent with NP10 showing the strongest Aβ inhibitory potential in a dose-dependent manner. NP10 also showed severe changes in aggregates morphology and protected cells from $A\beta_{42}$-induced toxicity in SH-SY5Y cells. In a high ionic strength environment (200 mM NaCl), the electrostatic interactions between NPs and $A\beta_{42}$ were greatly reduced and subsequently lowered the NP10 inhibitory effect. This implicated that electrostatic interactions play a crucial role in halting $A\beta_{42}$ aggregation (Liu et al. 2016).

The inhibitory property of NPs is further enhanced by implanting efficient anti-amyloid molecules such as peptides, polymers, epigallocatechin-3-gallate (EGCG), and curcumin onto the NPs surface. Such surface functionalization helps in improving the specificity and binding affinity between anti-amyloidogenic inhibitors and Aβ species. Curcumin-functionalized gold nanoparticles have shown promising results in inhibiting the amyloid fibrillation and disintegration of preformed fibrils on its own. Disintegrated fibrils also have low cellular toxicity. Au–curcumin complex is more efficient in retarding Aβ aggregation than curcumin or Au–NPs individually. The enhanced performance can be attributed to water solubility and multiple curcumin moieties on the Au surface giving rise to multivalent interactions with Aβ oligomer/fibrils. Curcumin is known to have anti-amylogenic properties. However, its therapeutic application is limited due to its hydrophobic nature and insolubility in water. Preparation of water-soluble curcumin-based conjugates can overcome this problem (Palmal et al. 2014).

4.3 Polymeric Nanoparticles

Polymeric nanostructures emerge as a promising candidate for its anti-amyloidogenic abilities due to their super-biocompatibility and low toxicity. Most importantly, the presence of rich functional groups allows them to regulate the adsorption of various amyloid species inhibiting their fibrillation.

Copolymeric N-isopropylacrylamide: N-tert-butylacrylamide (NiPAM:BAM) nanoparticles, having a nominal size of 40 nm were found to inhibit the fibrillation process of amyloid-β protein. The particles increase the time of nucleation in the amyloid-β aggregation process and reduce half-time for fibrillation ($t_{1/2}$) with minimal effect on the elongation step. This extension of the lag phase was clearly dependent on both the amount and surface characteristics of nanoparticles. With a decrease in the ratio of two monomers, NiPAM and BAM, lag phase time was seen to increase significantly. At a ratio of 100:0 NiPAM:BAM, there was a tenfold increase in lag time as compared to the 50:50 ratio of NiPAM:BAM (Cabaleiro-Lago et al. 2008).

Polymeric NPs were also used as a scaffold for anchoring different peptides onto their surface and evaluated for suppressing Aβ aggregation (Song et al. 2014; Skaat et al. 2012). FDA approved PLGA (D, ʟ-lactic acid-co-glycolic acid) nanoparticles are widely used as a potent drug delivery system for sustained release of encapsulated pharmaceuticals with increased life span. PLGA-NPs have also shown to induce conformational changes in Aβ protein by converting them into unstructured off-pathway aggregates alleviating the associated cytotoxicity (Xiong et al. 2015). In vivo studies using Aβ-overexpressing (5XFAD) as a mouse model, administration of DBP-loaded PLGA nanoparticles via a systemic route alleviated AD-associated pathologies like reduction in Aβ accumulation, neurodegeneration, neuroinflammation, and cognitive impairment in transgenic mice (Jeon et al. 2019).

Sairava et al. observed that fluorinated NPs interfered with fibrillation by inducing α-helix rich structures in $A\beta_{42}$ peptides. This drastically reduces the Aβ oligomers mediated toxicity in neuroblastoma cells (Saraiva et al. 2010a). Sulfated and sulfonated polystyrene nanoparticles were extensively evaluated for their anti-oligomeric property using $A\beta_{42}$ as a model system. Such highly acidic groups possibly interact with basic residues (Lys16 and Lys28) located within the regions that are critical for oligomerization. Subsequently, induce unordered structural transitions in $A\beta_{42}$ disrupting or retarding the fibrillation process and reducing cytotoxicity (Saraiva et al. 2010b).

4.4 Anti-Amyloidogenic Molecules Functionalized Nanoparticles

Although a number of anti-amyloidogenic small molecules have been investigated for their Aβ aggregation inhibition capabilities, these molecules are less efficacious owing to poor chemical stability (Craig and Bhatt 1997), substandard solubility

(Hong et al. 2002), low bioavailability (Walle et al. 2004; Engel et al. 2012), poor permeability to biological membranes (Abbott et al. 2006), and requirement of high doses to achieve the desired effect in vivo (Arakawa et al. 2006). Nanoscale preparations of several anti-amyloidogenic molecules improve their biocompatibility intra- and/or extracellularly as well as multivalent binding capacity. This significantly increases their aggregation inhibition potency up to 10^5-fold in magnitude as compared to their respective molecular form.

Zexiu Liu et al. developed a dual-inhibitor system EFPP (EGCG–Fe (III)/PVP) nanoparticles with enhanced Aβ inhibitory potential. The effect is governed synergistically with modulation of the primary nucleation phase with weak hydrophobicity by PVP and elongation phase with antioxidant properties of EGCG. In addition to this, EFPP NPs are readily synthesized, highly stable in body fluids, and is rapidly eliminated from the body (Liu et al. 2019).

4.5 Peptide-Functionalized Nanoparticles

Peptide inhibitor-based nanoparticles (PINPs) have advantageous of non-immunogenicity, penetrance across BBB, effective removal of Aβ plaques from the brain, protection from AD pathologies, and high theranostics ability (CT/MRI or PET/SPECT). Such studies pave ways for the design and synthesis of NP-based multifunctional inhibitors (Gregori et al. 2017).

Most of the peptide inhibitors are derived from the sequence of an amyloid-β protein. Mostly, the sequences from central hydrophobic region Aβ16–20 (KLVFF) (Tjernberg et al. 1996) and C-terminal end Aβ39–42 (VVIA) Aβ39–42(Gessel et al. 2012) are particularly used. These peptide fragments interact with the β-sheet region of Aβ, due to sequence similarities, via hydrophobic interaction, and hydrogen bonding. However, a strong tendency to self-aggregate and the resulting toxicity hinders the use of such peptide-based inhibitors. Additionally, these inhibitors are more susceptible to proteolytic degradation. A novel poly(amino-acid) nanoparticle containing dipeptides Poly (N-acryloyl-L-phenylalanyl-L-phenylalanine methyl ester) (polyA-FF-ME) severely affected the kinetics of $A\beta_{40}$ fibrillation. This retardation was observed probably due to hydrophobic interactions between FF residues and corresponding residues within $A\beta_{40}$ fibrils. However, the $A\beta_{40}$ aggregation promoting effect was observed when the FF residues pairs were replaced by L-alanine pairs. No mechanistic inference was provided for this opposing effect (Skaat et al. 2012). In 2015, Neng Xiong et al. designed a novel heptapeptide KLVFFRK (LK7) and conjugated onto the surface of PLGA (poly lactic-co-glycolic acid) NPs to obtain a nanosized inhibitor, LK7@PGLA-NPs. LK7 functionalized nanoparticle showed remarkably strong anti-amyloidogenic ability as compared to free LK7 and alleviated cytotoxicity at a concentration as low as 20 μg/mL. NP conjugation also leads to improved peptide stability by restricting the conformation flexibility. The incorporation of two basic amino acids further strengthened the association of peptide and Aβ (electrostatic interactions between basic residues RK in LK7 and acidic residues ED in Aβ), which in turn lowers the concentration of Aβ and thereby aids in preventing their aggregation (Xiong et al. 2015).

In recent years, nanoscale liposomes, multifunctionalized with different ligands have also gained much attention as carriers of therapeutic agents to special regions in the body. It was found that the potency of peptide RI-OR2-TAT (retro-inverso Ac-rGffvlkGrrrrqrrkkrGy-NH2) in as $A\beta_{42}$ aggregation inhibitor was dramatically increased when linked to nanoliposomes (NL) composed of sphingomyelin and cholesterol. There was a 50% reduction in in vitro oligomerization of Aβ peptides at a remarkably low molar ratio of 1:2000 of peptide inhibitor nanoparticles to Aβ. The probable explanation for this enhanced activity would be trapping of Aβ monomers/oligomers by basic amino acid residues on several inhibitory peptides (as many as 1600 peptides) on each NL surface. This would lead to the simultaneous interaction of multiple peptides with Aβ species. Moreover, the captured Aβ peptides might also undergo the "sink effect" by their insertion into the lipid membranes (Gregori et al. 2017). Another novel study showed that even the conformations and orientations of conjugated peptides also play an important role in governing the inhibitory capacities. Here, AuNPs surface was fabricated with different Aβ derived peptide fragments (CVVIA, CLPFFD, VVIACLPFFD, etc.) in different manners to control Aβ aggregation and related toxicity. All peptide of AuNPs inhibited $A\beta_{42}$ aggregation and reduced Aβ-induced toxicity to different extents at a strikingly low molar ratio of around 0.0016–0.026 of peptides to $A\beta_{42}$. Among them, VCD10@AuNP was the most potent $A\beta_{42}$ inhibitor while CVA5@AuNP and CLD6@AuNP exhibited moderate inhibitory capability. VCD10 (VVIACLPFFD) peptides were conjugated to AuNPs in a tilted and branched fashion to incorporate more peptides. The negatively charged Asp and hydrophobic Val were exposed to NP/solution interface to promote inhibition. The conjugation pattern made VCD10 expose its binding sequences of VVIA and LPFFD and make them accessible to interact with $A\beta_{42}$. This enhanced the interaction between VCD10@AuNPs and $A\beta_{42}$ species prevented Aβ from aggregating into large fibrils. VCD10@AuNP–Aβ complexes could also improve the cell viability from 48 to 82%, convert toxic $A\beta_{42}$ species into less toxic or nontoxic species. Densely packed CLD6 and CVA5 conjugated on AuNPs surface mainly adopted β-sheets and α-helix suggesting exposure of terminal residues of Asp in CLD6@AuNPs and Ala in CVA5@AuNP. Changes in peptide/liquid interfaces burying the peptide sequences critical for Aβ binding leads to weakened interactions between NP-coupled peptides resulting in lower inhibitory effects. CLD6@AuNP and CVA5@AuNP showed less inhibition of Aβ42 aggregation than VCD10@AuNPs (Xiong et al. 2017).

Many amino-acid based polymeric nanoparticles have garnered attention for their biomedical uses due to their potential biocompatibility, nontoxicity, and non-immunogenicity. A novel poly(amino-acid) nanoparticles containing dipeptides Poly (N-acryloyl-L-phenylalanyl-L-phenylalanine methyl ester) (polyA-FF-ME) severely affected the kinetics of $A\beta_{40}$ fibrillation. This retardation was observed probably due to hydrophobic interactions between FF residues and corresponding residues within $A\beta_{40}$ fibrils. However, the $A\beta_{40}$ aggregation promoting effect was observed when FF residues pairs were replaced by L-alanine pairs. No mechanistic inference was provided for this opposing effect (Skaat et al. 2012).

4.6 Nanoparticle-Based Metal-Chelation Therapy

Several studies suggest that oxidative stress in the cell may be a major contributing factor for the initiation and progression of neurodegeneration, leading to AD. Various transition metals are oxidative instigators and participate in redox reactions. Imbalances in metal ion regulation catalyze and stimulate the formation of free radicals. Normal metal ion distribution gets severely altered in different CNS diseases including AD (Markesbery 1996). These metal ions like iron, zinc, and copper have also been found at elevated concentrations within amyloid plaques in the brains of Alzheimer's patients (Barnham et al. 2004). They readily associate with amyloid-β peptides and induce nucleation and promote their aggregation. Discovery of agents targeting interactions between such metal ions and peptides might prove a therapeutic potential in AD patients. Although, the administration of metal chelators (trientine, D-penicillamine, and bathocuproine) (Cherny et al. 2000) has merits, they pose certain limitations mainly because they cannot cross the blood–brain barrier. Moreover, they might trap some essential metals required for the normal physiological functioning of different proteins. Metal chelation therapy along with appropriate drug delivery systems should be developed to prevent or reverse Aβ accumulation (Cherny et al. 2000).

Metal chelation therapy involves the use of high-affinity chelators that not only diminish/abolishes metal ions effect on Aβ but also completely solubilizes the metal-mediated aggregates of fibrils. Interestingly, the chelators–nanoparticles complex has the ability to penetrate BBB, chelate metals, and bring excess metals out of the brain. Nanoparticle delivery systems allow the slow and prolonged release of such chelators lowering the effective concentration at the site of accumulated metal ions and limit the removal of essential biomolecular metals. As an approach to fight against both metal-induced aggregation and neurotoxicity, Liu et al. had proposed a model for developing iron chelators with active functional groups for nanoparticle conjugation. This chelator–nanoparticle complex can be used for dealing with metal-associated neuro-oxidative damage by reducing the metal load in the brains of AD patients (Liu et al. 2010).

Zn^{+2} ions form a strong complex with Aβ monomers promoting the formation of insoluble non-fibrillar aggregates by hydrophobic contacts (Noy et al. 2008). Such aggregates are of higher toxicity to neuronal cells than those formed by self-assembly of Aβ alone. Iminodiacetic acid-conjugated nanoparticles (IDA-NP) play a role of bifunctional nano-modulator similar to other chelators like EDTA (Cherny et al. 2001) and 5-chloro-4-hydroxy-7-iodoquinoline (CQ) (Grossi et al. 2009; Li et al. 2013). The IDA groups on IDA-NPs IDA-NP sequestered Zn^{+2} completely (752 μmol/g) from amyloid species, significantly reducing Zn^{+2}-mediated aggregation. IDA-NP, due to its negatively charged hydrophobic surface, and was able to inhibit on-pathway Aβ fibrillogenesis (Liu et al. 2017). Even Cu (I) chelator D-penicillamine conjugated to nanoparticle via a disulfide or thioether bond has shown promising results in resolubilizing copper-Aβ aggregates in vitro (Cui et al. 2005). Se/Ru NPs are more efficient in prohibiting fibrillation of amyloid-β peptides than Ru NPs. They concluded that Ruthenium prominently enhances the binding capacity of Se/Ru nanoparticles (surface modified with L-Cys) to $A\beta_{40,}$ thereby blocking the metal-binding site of $A\beta_{40}$ peptides and suppressing the metal-induced aggregation of $A\beta_{40}$. Subsequent reductions in intracellular ROS generation and protection of PC12 cells against apoptosis were also observed (Yang et al. 2014).

Additionally, the lipophilic character of chelators that resulted in poor bioavailability and toxic side effects could be lessened by their conjugation of chelators to NPs (Liu et al. 2009).

4.7 Nanoparticles as Nanotheranostics in Proteinopathies

Nanotheranostics is an emerging field in the area of nanotechnology that combines "therapeutics" and "diagnostics" in order to simultaneously and sequentially diagnose and treat a particular diseased condition (Muthu et al. 2014). This technology can also monitor the prognosis of a disease during a treatment regime thereby providing for the real-time assessment of the condition. The advantage of combining these two aspects of therapeutics and diagnosis saves time and money. It is also beneficial as it has the tendency to bypass the undesirable effects of treatment strategies that are employed separately (Muthu et al. 2014). One of the major challenges faced by biomedical experts during the treatment of neurodegenerative disorder and multiple cancer is the development of a targeted drug delivery vehicle (Singh et al. 2020). Theranostics, with different functions as shown in Fig. 12.3, can provide a means of manipulation of certain properties of nanoparticles (NPs). This in turn provides for the association of any drug on to the surface of the NPs (Singh et al. 2020; Choudhury and Gupta 2019). These multifunctional nanoparticles as described in Fig. 12.4 provide a revolutionary treatment regime by stimulating the interactions between the targeted site and the NPs in order to promote physiological response and minimize the side effects of the drug. Techniques like magnetic resonance imaging (MRI), positron-emission tomography, single-photon emission computed tomography, and clinical nuclear imaging systems are capable of tracking such multifunctional NPs (Lee and Li 2011).

Although various mechanisms and targets have been identified/developed for the treatment of CNS-related proteinopathies, the success rate for the treatment involving these targets has been very negligible. This is usually attributed to the fact that most of the organic matter are unsuccessful in crossing the BBB, there is a nonselective distribution of drugs within the brain, opsonization of plasma protein in the circulatory system, and side effects due to the nontargeted release of drugs within a patient (Ramanathan et al. 2018). It is quite noteworthy that most of the NPs have higher cellular uptake as compared to the microparticles (Ramanathan et al. 2018).

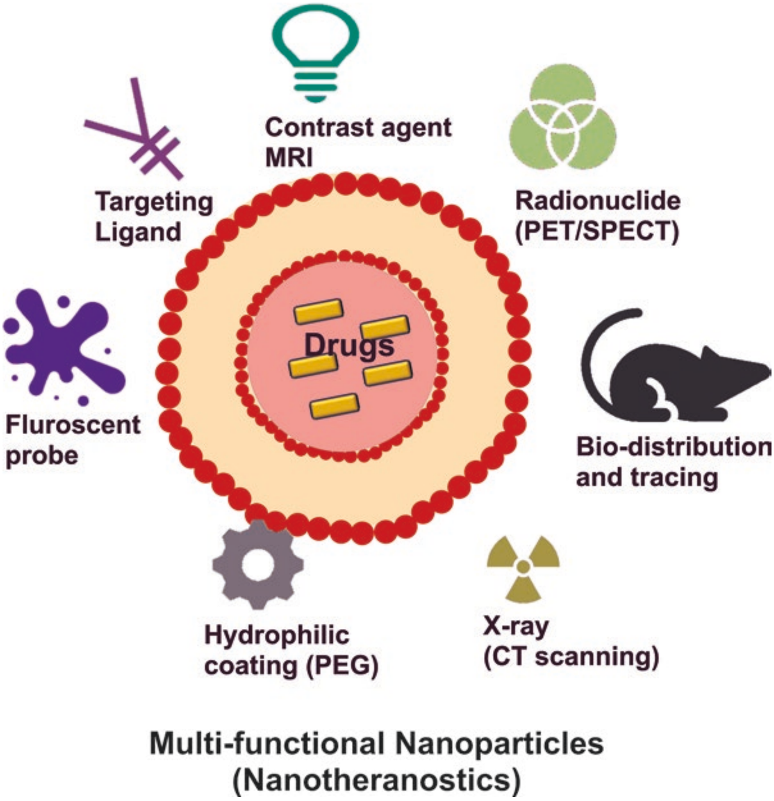

Fig. 12.3 A multifunctional nanoparticles representing differential features that make it useful for diagnostics, therapeutics, and prognosis

This is usually attributed to their small size and mobility, thereby allowing them to target a variety of cellular and intracellular processes. However, the optimum size of the nanoparticle is very much essential as a size smaller than 6 nm for the NPs may lead to their rapid elimination from the body during renal filtration (Muthu et al. 2014). The hydrophobic coating of the NPs makes them more prone to elimination from the system via opsonization; hence, hydrophilic coating of the NPs is of paramount importance (Muthu et al. 2014). Mostly, biodegradable copolymers like polyethylene oxide, polyethylene glycol (PEG), poloxamer, polysorbate 80 (Tween 80), and poloxamine, which are known to have hydrophilic properties, are widely used to overcome such problems (Muthu et al. 2014). Increment in the size distribution of any NPs beyond 100 nm leads to a reduction of their bio-distribution ability, which are subsequently captured by kupffer cells and eliminated by macrophages (Jeelani et al. 2014).

Another property that makes nanotheranostic unique from any random NPs is its property to fluoresce due to the presence of the quantum effect of the quantum dots. They also have a very high ability to absorb and transport a variety of substances such as small molecules, proteins, and probes due to their increased surface to volume ratio (Jeelani et al. 2014; Wu et al. 2019). The property of fluorescence is quite unique to quantum dots and is size-dependent, which allows them to absorb light and emit the spectra at a specific wavelength within the range of blue to red. Carrier-mediated transcytosis is the method utilized to transport most of the nutrients, amino acid, glucose, and purine bases. To facilitate this delivery mechanism, variety of NPs are designed in different shapes and sizes such as nanocubes, nanoplates, nanorods, nanospheres, nanotetrapods, nanoprisms, and nanobelts. However, large molecules like an antibody, lipoproteins are transported via receptor−/adsorptive-mediated endocytosis (Muthu et al. 2014; Wu et al. 2019).

There have been several routes of delivery for drugs using nanoparticles but few of them have been widely studied in mice model systems. These are oral route, inhalation or intra-tracheal installation, and intravenous (IV) route. However, the fate of such a delivery route still needs to be explored in human models for predicting and evaluating the fate of NPs during their delivery mechanism (Li et al. 2020).

Small nanovehicles prepared of chitosan polymeric core and designed via ionic gelation with tripolyphosphate (TPP) and polyamine-modified F (ab′) portion of IgG (anti-amyloid antibody) biosensor was used to target the cerebrovascular amyloid formed during cerebrovascular amyloid angiopathy (CAA) and AD (Ramanathan et al. 2018). This study carried out by Agyare et al. has shown promising results in mice models. In a variety of studies, radioisotopic tracing of the quantum dots is done to trace the intranasal administration of the nanoparticles. In one such study, ibotenic acid and β-amyloid were injected via intra-cerebroventricular for the assessment of its neuroprotective ability. It was found that this kind of nanoparticle increased the spatial learning and memory of AD models of the rats (Muthu et al. 2014; Ramanathan et al. 2018).

Such nanotherapeutics have also shown promising results in the treatment of epilepsy which is again a CNS disease characterized by paroxysmal neural discharge resulting in recurring and spontaneous epileptic seizures (Degrauwe et al. 2019). A study by Huang et.al. utilized a chip to release antiepileptic drugs AED ethosuximide (ESM). The chip was designed such that it had an electrically conductive flexible polyethylene terephthalate (PET) substrate, upon which drug-carrying core–shell magnetic NPs were deposited using the electrophoretic method. It was observed that the release of drugs upon the magnetic field application caused a reduction in spike wave discharge thereby suggesting a plausible role in decreasing the seizures in epileptic patients. A study by Bhatt et al. showed the role of solid lipid NPs (SLNs) encapsulating rosmarinic acid (RA) in effective treatment and management of HD by enhancing the drug delivery to the brain (Degrauwe et al. 2019).

The newer advent in the field of nanotheranostics is the development of smart systems commonly known as remotely triggered systems. These systems are designed in such a way that they release the drug to the target site when there is an externally triggered stimulus. The triggers that are commonly used are visible or near-infrared (NIR) light, X-rays, radiofrequency waves, ultrasound, and electric or magnetic fields (Lee and Li 2011). Remotely triggered nanotherapy has an advantage of controlling the duration of treatment that can be turned “on” or “off” in real time, thereby reducing the toxicity of the drug to the non-affected cells (Sneider et al. 2017). An example of such a theranostic is designing of remotely activated Thermodox, which is in its phase three clinical trials. It is a temperature sensitive nanovehicular system that releases the anticancer drug doxorubicin when there is a sudden increase in the temperature, which is usually activated by radiofrequency (RF) pulse or high-intensity-focused ultrasound (HIFU). It can also be traced inside the patient system upon the coupling of this nanovehicle with an imaging system (Sneider et al. 2017).

Another successful example of remotely controlled theranostics that has been FDA approved includes phototriggered multi-inhibitor nanoliposome (PMIL) (Wu et al. 2019). It is designed such that it can encapsulate photosensitive, noncytotoxic, hydrophobic drug benzoporphyrin derivative (BPD), and PLGA-PEG conjugated cabozantinib inside a lipid bilayer. This was used in the treatment of human pancreatic ductal adenocarcinoma (PDAC) (Wu et al. 2019). Exposure to near-infrared light triggers the release of BPD leading to tumor cell apoptosis and micro vesicular damage. It simultaneously releases PLGA-PEG conjugated cabozantinib thereby inhibiting antiapoptotic function of tumor cells, angiogenesis, and so on (Sneider et al. 2017).

Development of plasmonic nanobubbles (PNBs), which is a product of photothermal triggering has proved advantageous in real time in vivo detection of microscopic residual disease (MRD), which is the major cause of tumor resurgence and metastases after oncosurgery (Degrauwe et al. 2019). One such PNB that was designed, used clusters of gold nanoparticles (60 nm) conjugated to panitumumab and was readily taken up by receptor mediated endocytosis upon exposure to a short laser pulse, which leads to the formation of transient, photomechanical vapor nanobubbles. This was used for the activation of PNBs to detect MRD over cell destruction caused by gold nanoclusters (Degrauwe et al. 2019; Sneider et al. 2017).

As can be seen from the above example, a lot of studies have been done for both cancer detection and treatment by using multifunctional nanoparticles (Langbein et al. 2019). Similar studies can be designed in order to develop nanoparticles for sequestering and disintegration of protein aggregates that lead to the various neurodegenerative diseases (Choudhury and Gupta 2019; Langbein et al. 2019).

5 Superparamagnetic Iron Oxide Nanoparticles

Magnetic nanoparticles prove useful exclusively in brain-related disorders mainly because of their theranostic potential. They can simultaneously diagnose, treat, and monitor the disease progression. Being sensitive to brain cells, they can be used as a vehicle to deliver multimodal imaging agents and therapeutic drugs to specific areas of the brain (Cai et al. 2020). Ultrasmall superparamagnetic iron oxide (USPIOs) nanoparticles coupled to phenothiazine-based near-infrared (NIR) fluorescent dye as novel theragnostic agents exhibited enhanced fluorescence on binding to Aβ species as evidenced by in vivo NIR fluorescence and magnetic resonance imaging in the brain of double transgenic mice. They were able to successfully block aggregation of Aβ peptides and disaggregate any preformed Aβ plaques, at IC50 of 11.7–32.1 ng/mL, which is far superior to phenothiazine-based inhibitors (Cai et al. 2020). They could effectively protect the human neuroblastoma cells SH-SY5Y cells from apoptosis associated with amyloid deposits $A\beta_{42}$ by carefully regulating the expression of different pro- and antiapoptotic proteins (Cai et al. 2020).

6 Nanozymes

Taking into consideration the proteolytic and antioxidant activities of polyoxometalates (POMs) and cerium oxide nanoparticles (CeONPs), Yijia Guan et al. rationally designed a bifunctional nanozyme, Ceria/Polyoxometalates hybrid (CeONP@POMs) that could effectively dissolve Aβ aggregates and reduce intracellular reactive oxygen species (ROS). Additionally, this artificial nanozyme benefits the injured cells and promotes proliferation, regulates microglial activation, cross BBB, and protects neurons from Aβ-induced toxicity (Guan et al. 2016). Also, Aβ oligomers can mediate Ca^{+2}mediated degeneration by directly incorporating into cell membranes of the target neurons and form Ca^{+2} channels. This severely affects the cell's calcium homeostasis initiating the cascade of ROS generation. Polyvinylpyrrolidone-functionalized molybdenum disulfide MoS2 NPs exhibited multifunctionalities against amyloid-related pathogenesis. Qiusen Han et al. reported that MoS2 NPs inhibited Aβ aggregation, dissociation of Aβ fibrillar structure, scavenging the radical species, and maintaining Ca^{+2} homeostasis. This was the first report showing the potential of MoS_2 nanoparticles in blocking Aβ-formed calcium channel in neuronal cells and thereby reducing intracellular Ca^{+2} accumulation and subsequent damage to cells (Han et al. 2017).

7 α-Synuclein Aggregates in Parkinson's Disease

Parkinson's disease is a neurodegenerative disorder, also referred to as synucleinopathy, affects six million individuals globally. It is characterized by progressive loss or degeneration of dopaminergic neurons in the substantia nigra of the midbrain and subsequent development of intracytoplasmic Lewy bodies. A missense mutation in the α-synuclein gene gives rise to familial PD. Neuronal Lewy bodies and Lewy neurites in PD is majorly composed of α-synuclein (αSYN) along with different neurofilament proteins and other proteolytic proteins (like ubiquitin and heat shock proteins). Apart from motor and nonmotor symptoms, PD-affected individuals show bradykinesia, muscular rigidity, and tremors (Armstrong and Okun 2020; Miraglia et al. 2015). Like AD, only symptomatic treatments are available to date with no full-proof therapies providing neuroprotection (Garbayo et al. 2013).

In recent years, dendrimers have drawn special attention due to its capability to combat neurodegenerative disorders. Dendrimers are highly defined artificial macromolecules with nanometer scale. The most promising aspect of dendrimers is the ability to deliver drugs in a very controlled and specified manner. They possess a number of possibilities to interact with and respond to different biomolecules including proteins. Surface multifunctionality properties allow construction of surfaces carrying a multitude of charges or motifs to connect with biological targets and bring about desired physicochemical and/or biological effects (Abbasi et al. 2014; Svenson and Tomalia 2005). Over the last two decades, there are reports demonstrating the de novo inhibition of protein fibrillation as well as the dissolution of preformed infectious fibrils. Dendrimers act by preventing the formation of β-sheet structures to inhibit the fibrillation. To decompose the already formed fibrils, they disrupt existing β-sheets or their agglomerates (Heegaard and Boas 2007; Klajnert et al. 2006; Rekas et al. 2007).

In vitro studies by Rekas et al. showed that amino-terminated polyamidoamine (PAMAM) dendrimers of three different generations (G4, G5, andG6) could inhibit αSYN fibrillation as well as dissolve preexisting fibrils. These two effects were both concentrations and generation dependent. With an increase in dosage and generation, the inhibitory efficiency increased (Rekas et al. 2007).

Even phosphorus (Milowska et al. 2012), Viologen–Phosphorus (Milowska et al. 2013), and carbosilane (Milowska et al. 2015) dendrimers affect αSYN fibrillation in a similar manner. Carbosilane dendrimers are also known to partially protect mouse nerve cells (mHippoE-18) from rotenone induced damage by reducing intracellular ROS level and mitochondria mediated apoptosis. This might be due to the reduced effect of rotenone following its attachment to the surface of dendrimers and/or its encapsulation (Milowska et al. 2015). Laumann et al. found that at noncytotoxic concentrations, polypropylenimine (PPI) dendrimers either modified with urea (PPI-U) or N-methyl-thiourea (MTU) were able to partially clear αSYN aggregates from human melanoma cells in a generation- and concentration-dependent manner. However, PPI-MTU dendrimers were found to be potent than PPI-U because of their high cell penetrating ability (PPI-MTU being more hydrophobic than PPI-U). Moreover, for both PPIs, an increase in generation number further enhanced the fibril-solubilizing properties and cytotoxicity. This could be explained by the increased number of active groups on higher generation dendrimers that lead to better clearance ability as more and more groups interact with αSYN fibrils. Secondly, more active groups coupled with higher molecular volume could break open the cell membranes leading to cytotoxicity (Laumann et al. 2015).

Interestingly, curcumin has a strong affinity to αSYN in non-amyloid-β component region affecting the aggregation of αSYN by making it more diffusive (Ahmad and Lapidus 2012). Due to the poor solubility of curcumin, Taebnia et al. developed a nanoparticle-based drug carrier amine-functionalized mesoporous silica nanoparticles (AAS-MSNPs) with high loading efficiency. As compared to free drug, curcumin-loaded AAS-MSNPs were more stable and could interact more strongly with αSYN leading to significant inhibition of fibrillation and associated cytotoxicity. This study introduces AAS-MSNPs as a powerful means to formulate poorly aqua-soluble drugs for PD and other treatments (Ahmad and Lapidus 2012).

8 Huntingtin Protein in Huntington's Disease (HD)

Huntington's disease is a rare neurological disorder clinically characterized by motor, psychiatric disturbances, and cognitive decline. It is an autosomal dominant inherited disease caused by an expansion of CAG (36 repeats or more) trinucleotide polyglutamine (polyQ) repeats in Huntingtin (HTT) gene. This eventually results in fibrillation of polyglutamine repeats into toxic intracellular aggregates. The longer the CAG repeat, the earlier the onset of symptoms. However, a detailed molecular basis is yet to be elucidated. HD is influenced by epigenetics, oxidative stress, metabolic and nutritional factors. Efforts to target inhibition of huntingtin protein aggregation can prove beneficial in HD treatment (Nayak et al. 2011).

Small molecule osmolytes have the potential to act as chemical chaperones for either suppressing or repairing aggregation of proteins along the length of intra- and extracellular space (Arakawa et al. 2006). Recent discoveries demonstrated that the nano form of sugar-based osmolytes works as efficient chemical chaperones as compared to their molecular form (Pradhan et al. 2017). Mandal et al. synthesized trehalose conjugated Au nanoparticles (Au-trehalose) of 20–30 nm Au core and about 350 trehalose molecules per particle on the surface and evaluated their polyglutamine aggregation inhibition properties. Authors used HD150Q cells expressing a truncated N-terminal huntingtin containing 150 glutamine residues, fused to an enhanced green fluorescent protein as a model system for HD. It was observed that Au-trehalose enters into cells, inhibits mutant huntingtin aggregation (via multivalent interactions with the huntingtin protein), and reused the cells from HD mediated toxicity. The plasmonic nature of Au NPs permitted easy monitoring of Au-trehalose uptake and blocking of the aggregation process under light conditions (Debnath et al. 2016). Zwitterionic poly(trehalose) nanoparticles with an iron oxide core were found to be more efficient, 1000–10,000 times better than molecular trehalose, in inhibiting Polyglutamine-based (PolyQ) mutant Huntingtin protein aggregation both in vitro and in vivo. This enhanced performance of nanotrehalose over molecular trehalose can be attributed to several properties. The zwitterionic shell with numerous functional groups (cationic and anionic) allows NPs to make multiple contacts with cell membranes resulting in their maximum cellular uptake and minimum cytotoxicity. A large number of trehalose molecules (80–200) per nanoparticle offer multivalent interactions with huntingtin protein yielding effective inhibition of their agglomeration. Also, ease of transport across BBB enabled nanotrehalose to suppress polyglutamine inclusions in the brain of HD mice at micromolar concentrations (Debnath et al. 2017).

Another study by the same group demonstrated that nanoscale preparation of zwitterionic iron oxide functionalized with amino-acid-based osmoprotectants like glutamine and proline enhanced inhibitory efficiency (typically by 1000–10,000) as compared to molecular glutamine and proline (Pradhan et al. 2018). In 2019, the same group revealed that the nanoparticle form of quercetin, a potent anti-amyloidogenic, and antioxidant drug, displays polyglutamine aggregation inhibitory abilities at 1/50th lower dose than that of molecular quercetin. Nanoquercitin showed enhanced water-solubility, high chemical stability, increased bioavailability, and multivalent interactions. Moreover, the slow release of quercetin intracellularly also contributes to reduced toxicity, which is not the case with molecular form (Debnath et al. 2019).

Considering such results, future research should be directed in designing and developing such high-performance nanodrugs with biodegradable and biocompatible nanoparticle rather than iron oxide. Exploring such an option can prove to be an attractive tool for the prevention and treatment of PD.

9 Future Prospects of Nanoparticles in Prevention of Proteinopathies

Many essential treatment prospects of neurodegenerative diseases arising due to amyloid formation have been utilized using nanoparticles. They have played a role in targeted drug delivery, imaging of the site of amyloidosis, crossing of blood–brain barrier (BBB), and so on. There needs to be a paradigm shift in the research of nanotheranostics in order to understand the adverse effect of nanoparticles and their interaction physiology with that of cells and organs in an organism. Modern-day aspect of treatment of CNS-related proteinopathies requires a successful transfer of the effective drug in the affected neuronal cells. This BBB barrier is usually overcome by either active transfer or passive transfer of multifunctional nanoparticles, which have the drugs either encapsulated within them or coated on to their surfaces. However, this study has been very less understood and requires additional exploration at designing an efficient system that not only crosses the BBB but also makes the bioavailability of the drug to the affected site in an appropriate dosage. Also, care must be taken that the nanoparticles can be assimilated out of the system once the targeted delivery has been achieved. This will help in reducing the toxicity of the nanoparticle to the patient. This field of nanotechnology in medicine has a lot of significance in early diagnosis, on-time treatment, and real-time prognosis of CNS-related diseases such as AD, PD, HD, and epilepsy.

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Chapter 13
Metal–Organic Framework-Based Nanostructures for Biomedical Applications

Shivani R. Pandya and Sachin B. Undre

Contents

1 Introduction: Metal–Organic Framework-Based Nanostructures

The nanomaterials are the foundations of nanoscience and nanotechnology. Recently, nanomaterials have been assisting various fields of nano science as it acquires outstanding fundamental properties and structural features in between those of atoms and bulk materials. The self-assembly of nanomaterials which opened a new window of research through the controlled formation of nano-sized particles with distinctive chemical, biological, optical, magnetic, and electronic properties. Various metal nanomaterials of gold, silver, platinum, metallic oxides

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nanoparticle of titanium, silicon, zinc, iron, and semiconducting nanomaterials as zinc sulfate, and cadmium sulfate are used as carrier or marker depending on a purpose used for biomedical applications (Yaqoob et al. 2020; Maddela et al. 2021). Recently, in the development of nanotechnology, organometallic nanoparticles (OMNPs) with metal–organic frameworks have now emerged in order to enhance the structural potential when compared to nanoscale particles (Zhang et al. 2020). Metal–organic frameworks are usually amorphous nanomaterials also known as coordination polymers attached to metal nanoparticles that were first unearthed by Robson in 1989. Since this discovery, many researchers around the globe took interest in the engineering and evolution of MOFs for nano biomedical, drug delivery, catalysis, separation, magnetism, storage, luminance, biosensing, and many more applications. However, metal–organic framework-based nanostructures (MOFsN) are considered as the new cohort organometallic hybrids that might also be classified according to the dimensions and order of organic–inorganic material participating into the synthesis. As the development of nanotechnology progressed, many researchers studied the synthesis, characterization, functionalization, and biotoxicity of MOFsN. Due to this advancement, a structured understanding was developed about numerous MOFsN being promising platforms for biomedical applications. In 1989, the metal–organic-based structural frameworks, also known as porous materials, were first synthesized, and reported by B. F. Hoskins et al. (Hoskins and Robson 1989; Zhang et al. 2020). The MOFsN frameworks are organic–inorganic metal combined crystalline complex materials with a systematic arrangement of positively charged metal ions surrounded by linker such as organic molecules. The metal ions at the center that form a bond with functional groups of the organic linkers together produce a repeating, cage-like structure. As an emerging and favorable class of potential hybrid materials, it has drawn great consideration for various applications due to their unique features, high porosity, a wide range of void shapes, higher surface areas, and multifaceted structural frameworks. Numerous potential applications of MOFsN have been reported such as drug delivery systems, biosensing, biocatalysts, magnetic resonance imaging (MRI), optical molecular imaging, separation, magnetism, and energy (Yang and Yang 2020).The MOFsN possess not only porosity type materials but also shows a nanometer scale size with enhanced surface activities due to organic linkers, which leads to a great superiority in the field of biomedicine (Meng et al. 2020). The MOFsN frameworks were synthesized by using chromium metal at central with 1,3,5-benzene tricarboxylic acid or trimesic acid and 1,4-benzenedicarboxylic acid as organic linkers. The first time loading and releasing activities of MOFsN for the Ibuprofen drug encapsulation to enhance control drug release profiles were studied by Ferey et al. in 2006 (Horcajada et al. 2006). Several studies have been reported on surface modification of metal nanoparticles using multiple functional groups, for instance, biological molecules and fluorescent materials as organic linkers for the synthesis of MOFsN through the various synthetic methodologies. These innovative surface modifications show major advantages for the development of liquid separation, liquids purification, gas separation, electrochemical energy storage, chemical catalysis, sensors, and many biomedical applications. The research and development in the area of

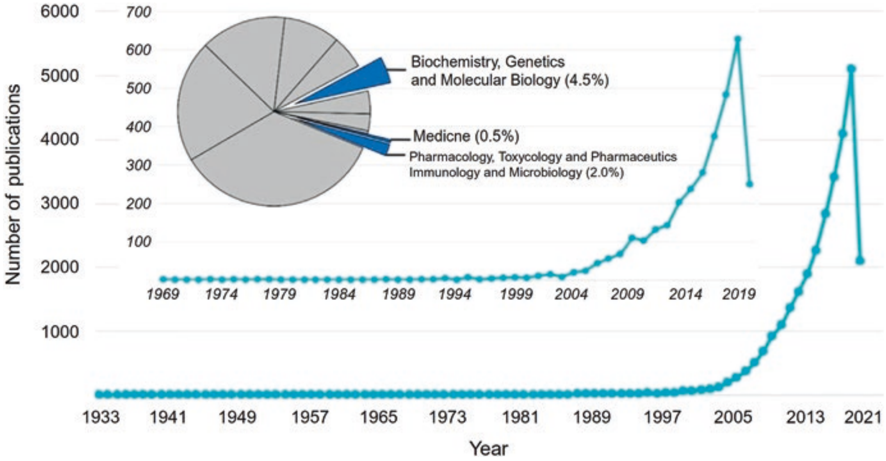

Fig. 13.1 Publication rate of work carried out on MOFs over time particularly in the biomedical applications (Barbosa et al. 2020) (Copyright 2020, Chapter 4, Metal-Organic Frameworks for Biomedical Applications, Page: 69–92, Elsevier publication)

MOFs as given in Fig. 13.1 with respect to publication in this area (Barbosa et al. 2020). Also, work done in the area of biomedical sciences is also highlighted.

1.1 Synthesis and Structural Properties of MOFsN

The synthesis of the MOFsN could be obtained through surface functionalization of metal with organic linkers such as simple organic molecules, biomolecules, dendrimers, polymers, amino acids, supramolecular, which eliminate several difficulties correspond to the stability, size, and structural properties. Jian Wang et al. reported and elaborated four categories of the surface modifications of metal NPs along with advantages and deficiencies molecular frameworks (Zhang et al. 2020). These categories are (a) covalent post-synthetically modification, (b) coordination modulation and coordinative post-synthetically modification, (c) noncovalent post-synthetically modification, and (d) modifications on the external surfaces of MOFs (Fig. 13.2).

1.1.1 Covalent Post-Synthetically Modification

The modification that deals with the metal are generally covalently conjugated with drugs or biomolecules organic linkers to the metal, which consist of the click chemistry and conjugation reacting mechanisms (Fig. 13.3).

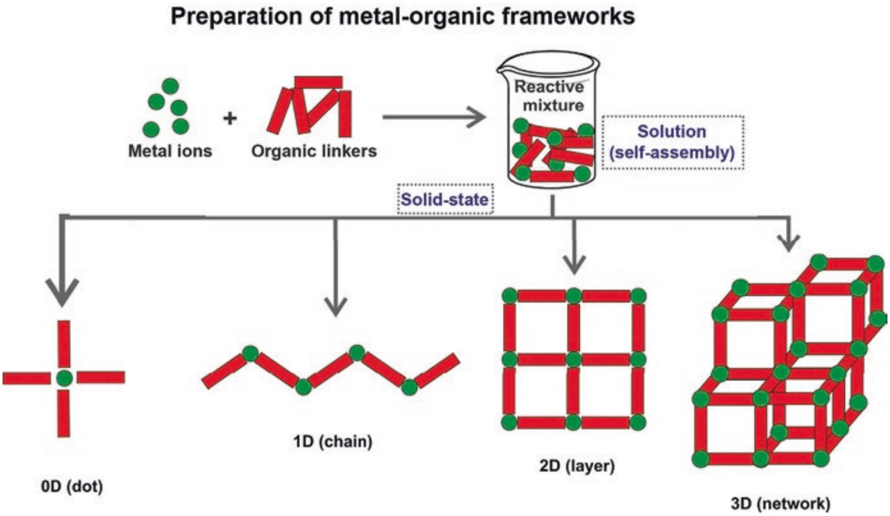

Fig. 13.2 Representation of the synthetic approach of MOFsN and their self-assembly in different dimensionalities. (Barbosa et al. 2020) (Copyright 2020, Chapter 4, Metal-Organic Frameworks for Biomedical Applications, Page: 69–92, Elsevier publication)

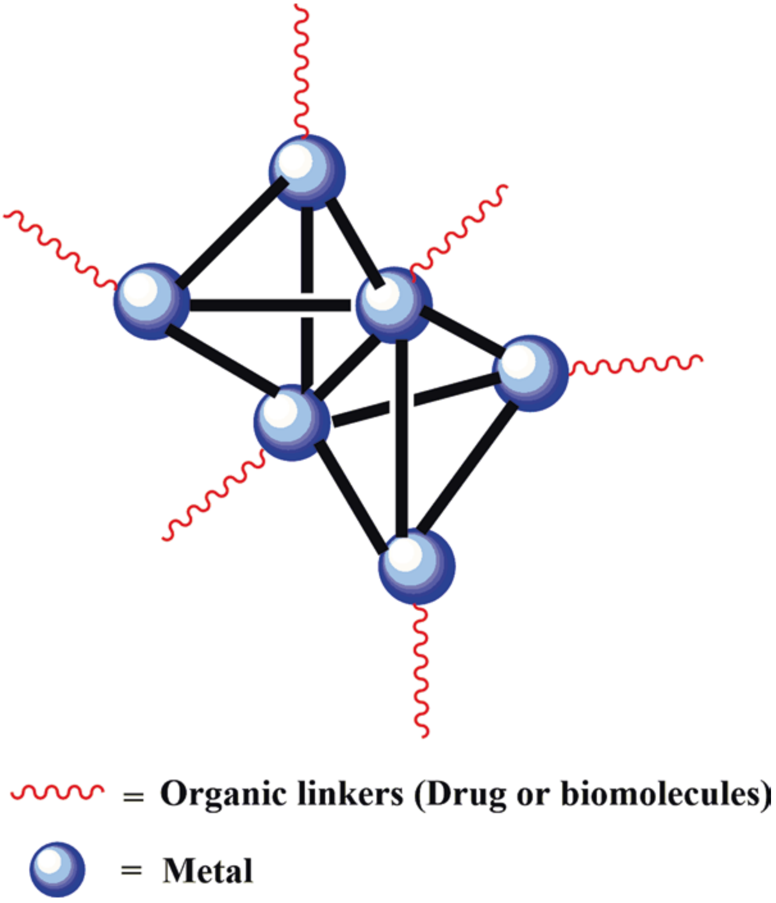

Fig. 13.3 The conjugation reacting model of the covalent post-synthetically modification

The drugs and biomolecules can covalently bind to the metal in MOFsN. In 1999, the first effective covalent post-synthetic modification of MNPs was carried out by Kiang et al. (Kiang et al. 1999). Furthermore, many researchers put their sincere efforts on covalent post-synthetic modification by using organic linkers like peptides, DNA, amine-modified cytosine, carboxylic acids, hydroxyls and thiols, green fluorescent protein, and biomacromolecules such as nucleic acid and protein and further studied for development of numerous applications in the field of biochemical and biomedical sciences (Begum et al. 2019; Kalaj and Cohen 2020; Ivancova et al. 2019; Guo et al. 2020). However, successful covalent conjugation of biomolecules is possible due to the presence of electrophiles in MOFsN with a strong binding ability (Nowroozi-Nejad et al. 2019).

The covalent conjugation plays a critical role for structural and functional control in MOFsN responsible for generating porosity and flexibility, which are afforded for designing materials specifically moderated toward future potential applications (Vardhan et al. 2019). Currently, covalent post-synthetically modified MOFsN show significant applications, and their physicochemical and biocompatible properties make them encouraging materials for drug storage, sustainable drug delivery systems, bio imaging, biosensing, magnetism, and gas adsorption (Chen and Wu 2018; Cui et al. 2018; Rojas et al. 2019).

1.1.2 Coordination Modulation and Coordinative Post-Synthetically Modification

The organic linkers such as drugs, biomolecules are coordinated to the metal for the synthesis of MOFsN through coordination chemistry, which includes ligand interchange. The coordination mechanisms are possible when the sidechain of the molecules has active functional moieties that bind to the metals for the genesis of networks with a higher degree of dimension (Cai et al. 2019a). The active terminals are the structural feature that facilitates amino acids (amino acids with carboxylic groups which provide a sequence of strong coordination approaches because of their huge negative charge density) and peptides to coordinate with central metal at definite angles and directions for the formation of MOFsN through coordinate post-synthetically modification (Rojas et al. 2017).

Generally, coordinative post-synthetically modification is significant to modify the surface functionality of MOFsN for developing biomedical applications, which can be possible during the synthetic methods (Segura et al. 2019). The major advantage of the coordination modulation synthetic method is the active surface modification of MOFsN, which is carried out during the synthetic process with biomolecules or simple organic molecules acting as interlocutors or modulators.

Many researchers have reported in situ coordination modulation process on surface modification by using DNA, biotin (Gkaniatsou et al. 2017), folic acid, porphyrin, phosphates, thiols, carboxylates, and imidazoles on the surfaces of MOFsN (Forgan 2019; Gkaniatsou et al. 2017; Abánades Lázaro et al. 2020; Kan et al. 2018; Park et al. 2016; Röder et al. 2017; Wang et al. 2018).

He Tin et al. have reported that the MOFsN microcapsules have a crystalline type material and rigid reticular structures that were prepared by using polymers or supramolecules through coordinative post-synthetically modification (He et al. 2018). They have expanded a competitive coordination modification in order to synthesize this MOFsN based microcapsules with new bowl-like structures. The formation of bowl-like structures of MOFsN is due to partial disintegration through the competitive reagents. In addition to this, flexibility is introduced into the rigid skeletons which is an innovative approach in designing MOF-based microcapsules with novel structures.

Hence, coordination mechanism is significant to produce extended active surfaces of MOFsN network structures, though green and scalable synthesis with very high chemical stability and better porosity. These types of MOFsN contain a high degree of dimensionality and fundamentally the most attractive structural features associated with their use as ligands also called surface ligand exchange (Cui et al. 2020).

1.1.3 Noncovalent Post-Synthetically Modification

The noncovalent post-synthetically modification consists of molecular interacting mechanisms such as electrostatic interaction, hydrogen bond interaction, Vander Walls forces, and dispersion forces. These molecular interactions between organic linkers and metals generate intermolecular forces (IMF) which are responsible for the binding of metal with molecules having active functional moieties.

However, MNPs are not stable and get agglomerated quickly they are stabilized using various stabilizing agents like PVA, PEG, citric acid, and so on (Zhao and Asuha 2010; Laurent et al. 2008). The MNPs of 1–100 nm size have been extensively studied, and their colloidal suspensions used as ferrofluids having many potential applications in electronics, material sciences, pharmaceutics, tissue engineering, biophysical, nanomagnetic thin films, nanomagnetic coating, magnetic biosensor, interacting activities inducing agent, biomedical, and biochemical sciences (Obaidat et al. 2019). Apart from having fundamental scientific interests of MOFsN, they can also assist in the development of novel applications in various electrical, industrial, and medical fields. Their exceptional and novel size dependent properties have developed remarkable research for designing new applications in nanotechnology and biomedical sciences (Jiang et al. 2019). Their synthesis and surface engineering are widely been studied due to their potential applications in magnetic fluids (Wu et al. 2016), catalysts (Cardoso et al. 2018), biotechnology, magnetic resonance imaging (Zhou et al. 2019), data storage (Noqta et al. 2019), DNA separation (Noqta et al. 2019), alternative current (AC) magnetic field-assisted cancer therapy (Shengzhe Zhao et al. 2020), and environmental remediation of heavy metals (Jawed et al. 2020; Thakare et al. 2021), drug delivery, and hyperthermia treatment (Gholami et al. 2020). Due to their versatile applications, the stability of dispersed MNPs plays a critical role with a milder tendency for self-aggregation via coulombic forces (Yew et al. 2020). However, the MNPs are not stable and get agglomerated quickly and can be stabilized by using surfactants such as SDS, CTAB, MTOAC, Tweens, cinnamic acid, oleic acid sorbitol, and zwitterions (Ansari et al. 2020). The MNPs are involved for suitable surface modifications by several coating agents for instance dimercaptosuccinic acid (Gutiérrez et al. 2019), dextran, starch, PEG, chitosan, proteins, amino acids, silica, and others (Nosrati et al. 2017). In 2011, Wiogo et al. have described a stabilization of MNPs in biological media by a fetal bovine serum to increase the surface area to modify the MNPs for in vivo biomedical uses (Wiogo et al. 2011).

The tribasic citric acid was used by (Cheraghipour et al. 2012) to stabilize the superparamagnetic nanoparticles which not only increases the dispersity of MNPs in water but the terminal carboxylic group can give more sites for surface modification (Cheraghipour et al. 2012). Thus, MNPs could play a critical role in molecular, bimolecular, and electronic interactions with various stabilizers for maintaining their stability to optimize their structural and geometric activities. The dispersion studies of surface engineered MNPs with polar protic solvents such as water, ethanol, and buffers (phosphate and tris) have been reported (Pandya and Singh 2015). The studies on nonaqueous dispersant medium with a series of organic acids and dendrimers with their increasing alkyl chain have been reported by S. R Pandya et al. (Pandya and Singh 2015). Furthermore, they studied their dispersion activities and optical behavior directly with aprotic polar, protic–aprotic, and dendritic–aprotic polar solvents as dispersant systems. The dispersion activities and optical behavior in a series of first-tier dendrimers for their perfect stabilized aggregation and this impact of aggregation have been monitored through their UV interactions. An impact of a series of FA, OA, and CA that produce H+ in 1:2:3 ratios could critically influence their size and aggregation patterns. However, the above-mentioned studies are simple in nature and even enhance the purity and stability effects of the nanoparticles. The molecules like nucleoli, peptides, cysteine, pyrene, PEG, glucose dehydrogenase, and methylene green have been used and linked to the surface of MOFsN through controlled supramolecular interactions and several strong interactions (Komiyama et al. 2017).

1.1.4 Modifications on the External Surfaces

These modifications are commonly known as the absorbent mechanism and consists of the conjugation of biomolecules to the silica coating on the MOFsN. The organic linkers can be reformed on the outer surface of MOFsN by using silica-coated surfaces as an active absorbent required to adhere to the additional drugs or biomolecules to the surface of MOFsN. Several researchers and their coworkers successfully attached the biomolecules such as oligopeptide, folic acid, on the surface of MOFsN with a silica coating for developing sustainable and targeted drug delivery systems (Siafaka et al. 2016; de Araújo 2017; Achilefu and Black 2018). The difficulties of silica coating methods are sometimes toxicity caused by excess use of silica and hence creates a challenge for the developing applications (Gubala et al. 2020). The MOFsN has exceptional structural properties and evolution in the field of nanotechnology, hence, there are lots of studies on synthetic processes and post synthesis surface modifications of MOFsN for biological applications.

2 Biomedical Applications of MOFsN

Currently, investigation of MOFsN has attracted much attention to develop biomedical applications (Sun et al. 2020) because MOFsN are shown to have a hollow structure with some extraordinarily larger surface areas inside the molecules (Zeng et al. 2015). The organic–inorganic metal-fused systems might be easily reformed due to the organic branched linkers with active functional groups and synthesized through the self-assembly mechanism of metal-attaching species, which leads to M_4 type (multipurpose, multitasking, multitracking, and multifaceted) properties. The MOFsN have well-defined porosity types of structures that makes them different from other nanoparticle structures with higher potential activities and M_4 properties required for various biochemical and biomedical applications. MOFNs have drawn attention due to their various potential uses in the field such as gas storage, bio separation, biocatalysis, photonics, biosensing, MRI, pharmaceutics, biocatalyst, and biomedicine (Horcajada et al. 2012). Figure 13.4 depicts various functional applications of MOFsN in the various field of sciences (Fig. 13.5).

2.1 Drug Delivery Systems

Developing a sustainable and targeted drug delivery system is essential and significant to reduce side effects with increasing therapeutic efficacy of drugs through metabolic actions. Well-defined structure, larger surface area, outreach porosity, multi fabricated pore size, and outstanding surface functionalization of MOFsN are considered as encouraging nanocarriers for efficient drug delivery systems (Sun et al. 2020). Hence, exceptional chemical and physical properties such as surface adsorption, covalent binding, encapsulation, and functional molecules as building blocks of MOFsN make them significant nanocarriers for targeted and intracellular drug delivery system.

Recently, MOFsN is evolving hybrid high porosity nanomaterials that are assembled from metal ions or clusters associated with organic linkers and they have ever-increasing attention due to the exceptional physical structures and wider potential applications (Cao et al. 2020). The MOFsN along with high absorptivity, porosity, controlled drug-release mechanism, large storage capability, and hydrophobic (nonpolar)–hydrophilic (polar) nature have shown potential use for sustained and targeted drug delivery mechanism by accommodating drug molecules through conjugation or encapsulation (Rasheed et al. 2020; Cunha et al. 2013). The structural features of MOFsN enabled high drug loadings efficiency with controlled release moderated by simulated physiological and chemical conditions for hydrophilic and hydrophobic drugs (Horcajada et al. 2010; Wang et al. 2020). Table 13.1 summarizes some reported applications of MOFsN in the drug delivery system.

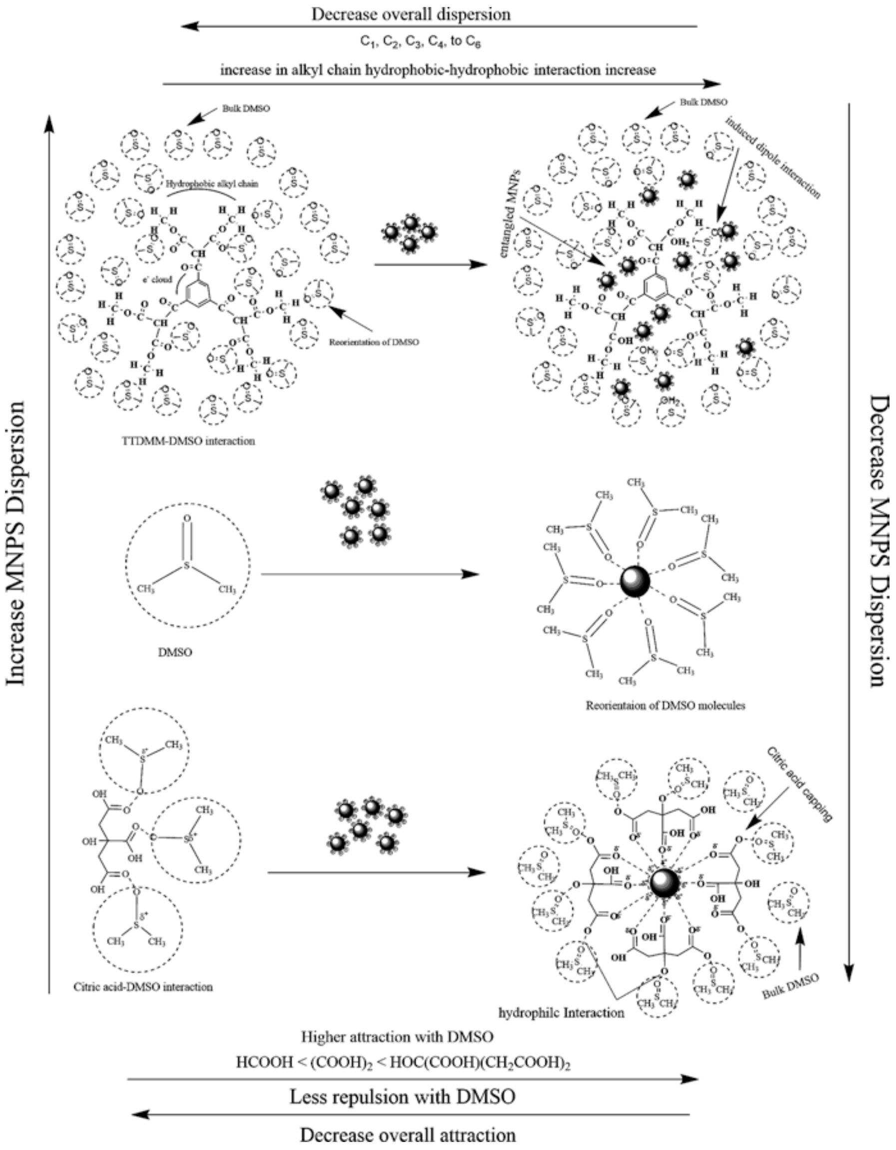

Fig. 13.4 The illustrations representing the surface coating of magnetic nanoparticle as the core for better stabilization (Pandya and Singh 2015)

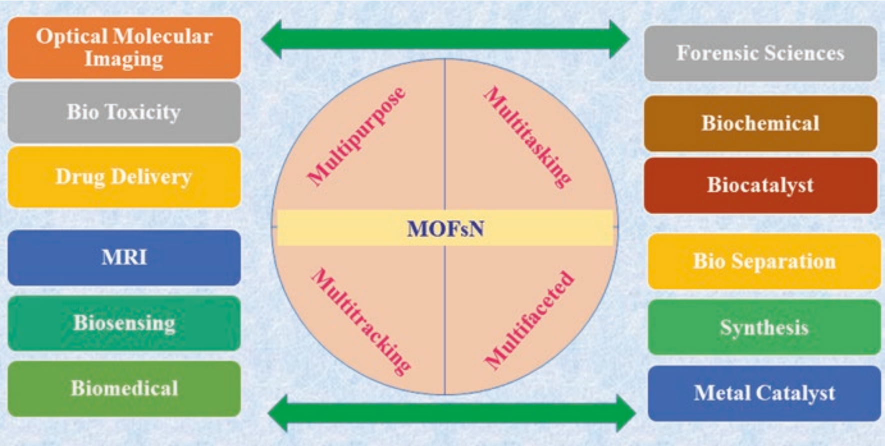

Fig. 13.5 The functional applications of MOFsN-based materials in various field of sciences

2.2 *Magnetic Resonance Imaging (MRI)*

MRI is an impressive diagnostic analytical tool for noninvasive (does not include a break in the skin) tomography of the inside arrangement and functions of living organisms as well as local properties of tissues that provides high longitudinal resolution images and deep tissue penetration without any involvement of radioactivity (Chen et al. 2020a; Brown et al. 2014). Basically, due to limited resolution, low imaging depth of penetration, poor spatial resolution, and low sensitivity in MRI, it becomes necessary to use contrast agents that play a vital role to improve MRI sensitivity through refining the contrast in areas with brighter or darker signals that are regularly administered in high doses (Boxerman et al. 2020). To overcome this problem, various studies have concentrated on developing multitasking imaging contrast agents or probes that incorporate several image improving activities into a particular system to achieve multitracking imaging functions in MRI (Shang et al. 2017). In this context, MOFsN has attracted great attention as promising MRI contrast agent attributable to its exceptional paramagnetic/superparamagnetic properties which can create large magnetic centers under the influence of an external applied magnetic field (Wong et al. 2020; Giliopoulos et al. 2020). Hence, such central shell hybrid MOFsN provides an ideal platform for targeted delivery of other imaging and beneficial agents to unhealthy tissues because they are effective at very lower concentrations and can also be engineered target specific through surface modification using essential molecules (Chowdhury 2017). Also, MOFsN with carboxylate as organic linkers shows a high capacity for drug loading or release and T_2-weighted (MRI sequence to quantify effectiveness) MRI properties with low toxicity (Li et al. 2015; Horcajada et al. 2010).

Meng et al. reported MOFsN having Fe^{3+} assembled octahedral structure by using a solvothermal reaction and graphene oxide (GO) as an organic linker,

Table 13.1 Some reported applications of MOFsN in drug delivery system

Metal/oxide	Organic Linker	Drug	References
Zn_4O	3,5-Dimethyl-4-carboxypyrazolato	5-Fluorouracil, caffeine, benzocaine, and para-amino benzoic acid	Noorian et al. (2020)
Zn (II)	Imidazole and polyacrylic acid	Doxorubicin	Cai et al. (2019b)
SiO_2	Poly(ethylene glycol) modified folic acid (PEGFA)	Doxorubicin	Xie et al. (2018)
Zr	Diaminostilbenedicarboxylate	Ibuprofen	Sarker et al. (2019)
Fe (III)	1,3,5-Benzene tricarboxylic acid	Caffeine	Cunha et al. (2013)
Fe/La	Benzene-1,3,5-tricarboxylic acid	Doxorubicin	Lin et al. (2019a)
Zr (IV)	1,4-Benzenedicarboxylate	Caffeine	Kandiah et al. (2010)
Fe (III)	Pyridine-3-carboxylic acid	Nicotinic acid	Miller et al. (2010)
Zr	Phosphonoacetate ligand	Cisplatin	Lin et al. (2019b)
Fe (III)/ Fe_3O_4	Carboxymethyl dextran, trimesic acid	Doxorubicin/daunorubicin	Cherkasov et al. (2020)
Zn	$(CH_3COO)_2$ and imidazolate-2-carboxyaldehyde (2-ICA)	Methylprednisolone	Xu et al. (2020)
Cu	Gelatin microsphere biopolymer	Methotrexate	Md et al. (2018)
Zr (IV)	Amino-triphenyl dicarboxylic acid	Doxorubicin	Chen et al. (2018)
Zn	Terephthalic acid	Oridonin	Chen et al. (2019)
Cu/Zn	1,2-Bis(4-pyridyl)ethylene/hydrogel	Antibacterial effects	Gwon et al. (2020)
Fe	Sodium dodecyl sulfate (SDS)	Insulin	Zhou et al. (2020)
Fe	O-carboxymethyl chitosan	Doxorubicin	Lin et al. (2020)
Zr	Triethylamine	Camptothecin	Chen et al. (2020b)
Mg	Tetrakis (p-benzoic acid) pyrene	Fluorouracil	Hu et al. (2020)
Fe	Trimesoyl1,3,5-trimethyl malonate ester (TTDMM) dendrimer	Silibinin and methotrexate	Pandya and Singh (2016)

offering a strong T_2-weighted contrast with low cytotoxicity (Meng et al. 2017). D. Zhang et al. reported innovative cell membrane-coated porphyrin MOFsN based O_2-evolving photodynamic therapy (PDT) for homologous cancer cell targeting along with MRI and fluorescence imaging (dual mode imaging) biomedical applications (Zhang et al. 2019). The MOFsN has a superparamagnetic nature accountable for the enhancement of contrast to distinguish death and live tissues with limitless penetration and admirable imaging aptitude in MRI which could serve as robust and innovative materials to develop biomedical applications (Peller et al. 2016).

Hence, MOFsN are transpiring hybrid materials made up of metal ions/clusters as a core attached to organic linkers and their ability to transport huge numbers of paramagnetic and superparamagnetic metal ions (Pei et al. 2014). These MOFsN are considered as superlative and potentially offer advantages as MRI contrast agents and enhanced attention due to the probability of three-dimensional (3D) images with high longitudinal resolution (Qin et al. 2017).

2.3 Biosensor

Recently, several research scientists have been working on new and novel applications of MOFsN to exploit them as electrode triggered materials that are required for evolving electrochemical activity with high selectivity and sensitivity to diagnose trace amounts of biologically active molecules. Physicochemical properties such as pore sizes, high surface areas, multitasking surface activities with active sites of MOFsN are responsible for their use as an ideal biosensor agent for electrochemical reactions (Wu et al. 2015; Carrasco 2018). The reported typical data of the MOFsN used as a biosensor for various biomedical sensing is given in Table 13.2 (Zhou et al. 2018).

Generally, post-modified methods were used for the synthesis of MOFsN-based electrode biosensors with the linking of $-NH_2$ or –SH functional groups and many others (Yang and Yang 2020). Some have rarely been reported MOFsN with significant electrochemical activity as electro biosensors without post-modification synthetic methods (Liu et al. 2017b). However, some of most electrochemical active MOFsN restrict over application in the field of electrochemistry detection due to poor water stability, which is related to electrochemical reactions generally carried out in a water environment (Fang, Zong, and Mao 2018; Taylor, Dawson, and Shimizu 2013). The MOFsN-based biosensors categorized in groups such as raw MOFsN, grafting approach, and bulk MOFsN according to their complexity and concerning the preparation methods for biosensor development (Carrasco 2018). The MOFsN having controlled size, shape, and morphology along with unique conductive properties and their preparation includes inorganic metal and organic linkers that have significantly enhanced the performance for biosensor development (Yang et al. 2018).

Table 13.2 The reported data of MOFsN based biosensors (Copyright 2018, Nanoscaled Metal-Organic Frameworks for Biosensing, Imaging, and Cancer Therapy, Advanced Healthcare Materials 7 (10): 1800022 (1–21))

MOFsN	Analyte	Recognition method	Recognition limits	References
H(2)dtoaCu	ds-DNA	FBS	1.3×10^{-9} m	Chen et al. (2013)
Zn(II)-MOFs	HIV ds-DNA	FBS	10×10^{-12} m	Zhao et al. (2016)
PCN-222@SA	DNA	ES	0.29 fM	Ling et al. (2015)
Dy-MOFs	Ebola virus RNA sequences	FBS	160×10^{-12} m	Qin et al. (2016)
MIL-101	Thrombin; oxytetracycline	FBS	15×10^{-12} m; 4.2×10^{-9}	He et al. (2017)
Cu-3(BTC)(2)@ SiO_2/BDC-PANI	Atrazine	CIS	0.01×10^{-9} m	Chen et al. (2017)
Hemin-MOFs/ PtNPs	FGFR3 mutation gene	ES	0.033 fM	Bhardwaj et al. (2015)
Fe-MIL-88B-NH_2	Alpha-fetoprotein	CMA	3 pg mL^{-1}	Zhou et al. (2016)
Au/hemin@ MOFs	Thrombin	EAS	0.068×10^{-12} m	He et al. (2017)
Fe3O4/g-C3N4/ HKUST-1	Ochratoxin A	FAS	2.57 ng mL^{-1}	Hu et al. (2017)
AuNPs/Ce-MOFs	Lipopolysaccharide	EAS	3.3 fg mL^{-1}	Shen et al. (2016)
Pt@ UiO-66-NH2	Telomerase activity	ES	$2.0 \times 10^{(-11)}$ IU	Ling et al. (2016)
516-MOF	Vomitoxin; salbutamol	EBS	0.70 pg mL^{-1}; 0.40 pg mL^{-1}	Liu et al. (2017a)
Mn-BDC@ MWCNT	Ascorbic/uric acid, dopamine	ES	0.01; 0.002; 0.005×10^{-6} m	M.-Q. Wang et al. (2016)
Ag@Au nanoprism MOFs	Glucose	PBS	0.038×10^{-3} m	Huang et al. (2017)
MIL-100(Cr)-B	H_2O_2	ES	0.1×10^{-6} m	Dai et al. (2017)
pFeMOF/OMC	H_2O_2	ES	0.45×10^{-6} m	Liu et al. (2017b)
R-UiO	Intracellular oxygen	RLS	–	Xu et al. (2016)

FBS Fluorescence biosensor, *FAS* Fluorescent aptasensor, *ES* Electrochemical sensor, *EAS* Electrochemical aptasensor, *EBS* Electrochemical biosensor, *CIS* Conductometric immunosensor, *CMA* Chemiluminescence metalloimmunoassay, *PBS* Paper-based biosensor, *RLS* Ratiometric luminescent sensor

3 Conclusion

The MOFsN are an interesting class of organic–inorganic metal combined porous crystalline nanomaterials with a systematic arrangement of positively charged metal ions surrounded by multifunctional organic molecules or ligands and have attracted increasing attention in current years in fundamental scientific interest and potential attractive several applications. The MOFsN consider as M_4 (multipurpose, multitasking, multitracking, and multifaceted) types materials with innovative and improved structural activities which play an extremely important role in increasing the biomedical and biochemical applications. Besides this, MOFsN as nanosized materials with variable physical, chemical, and biological properties that are more efficient as compared to bulk materials. The modern innovative and possible applications required a better potential metal–organic nanostructure-based formulations with extraordinary structural activities perceived as a tool and riders for biomedical applications such as drug delivery, MRI, biosensors, biocatalyst, bio separation, and many more associated with a decrease of environment and human health risks features. According to the intensified investigations on MOFsN exhibit important advantages and outstanding materials with minimized toxicity, which shows impacts at all stages of the development and evaluation of biomedical applications, which will increase their use in research areas. More active surface functionality of MOFsN could be designed and synthesized in order to meet the increasing biomedical requirements. MOFsN are excellent contrast agents that provide a new platform for the detection and diagnostics therapy in MRI. The synthesis and characterization of MOFsN for biocatalysts and bio-separation, biosensor, purification, drug delivery, medicine, energy-harnessing, and energy-storage fields show high growth and significant increase during the last decade. The scope and focus of this chapter are to study the strategies of MOFsN fabrication and its use for the expansion of biomedical applications.

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Chapter 14
Biological Conjugates: Potential Role in Biomedical and Pharmaceutical Applications

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1 Introduction

Biological conjugates are a combination of any synthetic polymer covalently attached to the counter biological part like proteins or peptide. These biological conjugates play a crucial role in the biomedical field like tissue engineering, wound healing, and designing of novel drug delivery systems. As these biomolecules are from diverse known biological origins it is easy to engineer it and link with synthetic polymer for the formulating drug and to undertake its study like its adsorption, reactivity, and its use in targeted drug delivery system (Duncan 2003; Hoffman 2000; Hoffman and Stayton 2004). Bioconjugates was designed to achieve better stability, solubility, and compatibility compared to the native proteins (Caliceti and Veronese 2003; Vandermeulen and Klok 2004). The realization of its importance came to practice after recognizing its role in different areas of applications like agriculture, food, environmental, medical, and pharmaceuticals. For example, secondary metabolites of plants like guar gum in pharmaceuticals, microbial biosurfactants—rhamnolipids, surfactin, glycoproteins, and so on, for its use in environmental applications, agricultural applications, medical applications, and many other. Especially, with the advancement in the pharmaceutical sector, it became very evident that any drug can be used rarely alone. It is always that a combination of two or more polymers (known as excipients) are used for offering various pharmaceutical functions with respect to the stability and bioavailability. Moreover, for use of any active ingredient in suspended, oral, or masked form, the combination of excipients is a prerequisite (Jans et al. 2017). Even the dosage form is another crucial factor in the pharma sector. For deciding and optimizing the dosage forms, different parameters need to be considered namely. physiochemical characteristics of the drugs, additives used in a formulation, and its associated biological factors. The mixed excipients in the formulation must be nonreactive with each other and compatible with each other with no compromise in formulation stability and reactivity (Ahuja and Scypinski 2001).

The word excipients mean either acquire or to collect. The excipients were also considered as the medium for medicaments as supportive nonreactive ingredients and also as an ingredient for achieving better consistency in the pharmaceutically active medicament. As per the Indian pharmacopeia 1996, the excipients were described as novel substances used as pharmaceutical aids and maintaining the consistency of the formulation. The common examples would be the honey, talc, paraffin (liquid), and so on (Sakamoto et al. 2013). Mostly all the dosage formulation have active ingredients offering the surety of drug release, drug stability, and availability linked with the synthesized drug. These excipients depending on the nature of formulations can be simple like diluents or coloring additives or can be complex like antioxidants or preservatives (Ahuja and Scypinski 2001).

The majority of the information of excipients can be extracted from the official books like pharmacopeias, which are published with the sole intention to help formulators for choosing the best excipients and to understand its cross reactivity. However, the pharmaceutical formulations are challenging as finding new drug molecules. For example, to formulate any pharmaceutical formulation starting from the selection of solubilizers, binders, fillers, emulsifier, oils, adjuvants, stabilizers, thickeners, coatings, sorbents, preservatives, coloring agents, buffering agents, viscosity imparting agents, chelating agents, surface-active agents, and humectants are needed to be chosen accurately (Aulton 2002; Saha et al. 2018; Kalasz and Antal 2006). However, some formulations require powdered substances to be solubilized later within the stomach and some are required to be liquid and get absorbed during early digestion. In most of cases, solubility plays a crucial role in drug absorption in the body, within a stipulated time frame. Hence, release and absorption phenomena can be monitored and studied according to the potential and compatibility of solubility enhancers added within the formulations. For, in vivo administration polymers are chosen as with respect to its adaptability and stability in different physicochemical parameters like pH, temperature, and so on. Hence, there is always demand for new formulation with better suitability in pharmaceutical industries even though old drug candidates have better effectiveness in the body.

Additionally, the bonds and monomers actually decide the surface and bulk properties of the chosen polymer for the formulation. Depending on the actual site of reactivity, the chosen polymer is considered better as a drug carrier system and also for target specific drug delivery (Sarkar and Alexandridis 2015; Prasad et al. 2017). Surface enhancement also plays a key role in the compatibility and stability of pharmaceutical formulations. Surface reducing substances are useful for bringing two interfacial layers to a potential where favorable solubility can be achieved. It is also beneficial to have solubility for partially or completely insoluble substances like active pharmaceutical ingredients. For example, sodium lauryl sulfate, lecithin, span-20, tween-60, tritonX-100, and carboxy methylcellulose are the chemicals that are routinely used as an excipient in different pharmaceutical formulations (Fig. 14.1). Such excipients possess detergent-like properties having polar and nonpolar groups within the same structure to perform suitable chemical reactions to enhance binding, solubility, and stability.

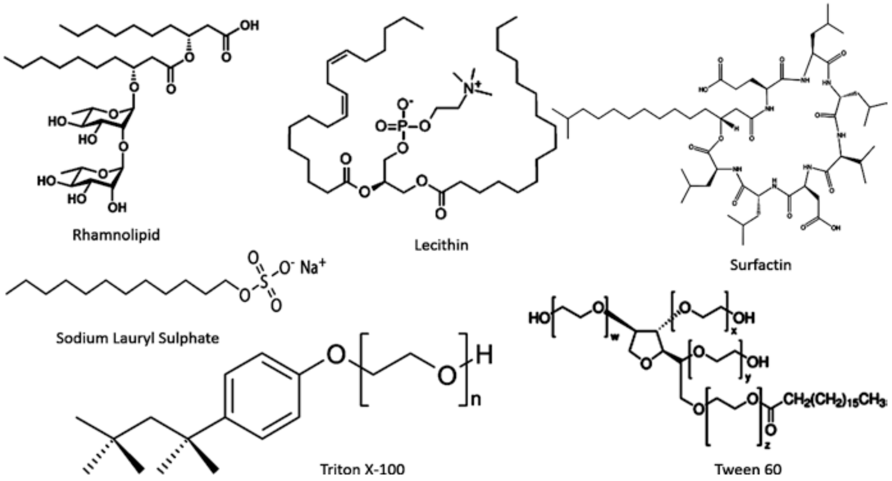


Fig. 14.1 Excipients used in the pharmaceuticals

2 Usage of Biological Conjugates from Natural Sources

In today's world, natural products are preferred over synthetic products. Where the source of nature has been traditional in the new pharmaceutical. More interest increased toward natural production and their use. Various biodegradable polymers are produced by microorganisms, which are essentially renewable. Mostly natural compounds are made up of carbohydrates or proteins, hence they are freely available, cheap, biocompatible, and nontoxic. These characteristics promote the inclusive use and need for natural products in pharmaceutical industries and food industries. (Vroman and Tighzert 2009; Sabalingam and Jayasuriya 2019).

Numerous pharmaceutical excipients are derived from animals (gelatine, stearic acid, beeswax, etc.), microorganisms (xanthan gum, pullulan), marine organisms (e.g., agar, carrageenan, alginate, fucoidan), plants (cellulose, sugars, starch, alginates), and mineral (calcium phosphate, silicone dioxide, paraffin) (Pifferi and Restani 2003).

3 Pharmaceutical Excipients of Microorganism's Origin

Microorganisms are so small microscopic organisms that are widespread in nature and are valuable for life. But some are also harmful. They are found in all three domains of life: Archaea, Bacteria, and Eukarya. Archaea, cyanobacteria, and Bacteria are prokaryotic organisms, all unicellular and multicellular organisms like fungi, algae, protozoa, plant, and animals are eukaryotic organisms included in Eukarya (Alamgir 2018).

Microorganisms are producing some extracellular carbohydrate polymers known as Exopolysaccharides (EPS). Different exopolysaccharides, which are found in bacteria and fungi, show a great diversity of structural combinations and unique properties (Moscovici 2015).

Microbial production displays various advantages over algae-derived products, like reproducible production to circumvent environmental influences and gain a high quality of the final product. Microbial EPS has many potential applications like easily obtained, biocompatible, nontoxic, renewable resources in medical use and pharmaceutical industries.

Only a few polysaccharides obtained from microorganisms, which are used as an excipient in pharmaceutical industries. Some excipients such as cellulose, dextran, xanthan gum, gellan gum, hyaluronic acid, are derived from bacteria while, many other excipient chitosan and cellulose, alginate, carrageenan, fucoidan, pullulan, are derived from different algae and fungi.

4 Cellulose

Cellulose is a renewable, biodegradable, and most abundant polymer in nature. It is composed of a linear chain of many β-(1–4) linked D-glucose units, and linear chain of β-(1–4)-D-anhydroglucopranosyl units. Cellulose is produced by many microbes including *Phaeophyata, Rhodophyta, Acetobacter, Rhizobium, Salmonella, and Sarcina,* and so on, are reported for the production of cellulose (Dahman 2009; Shoda and Sugano 2005).

Additionally, microbial cellulose shows desirable mechanical properties like high tensile length, elasticity, high strength, and fibrous structure. Cellulose is mostly used in tablet coating agent as it is sterilized without any modification of its properties. With the advancement in the field of pharmaceutical science and nanotechnology, nanocellulose from the microbial origin is now becoming a promising applicant in a controlled drug delivery system (Hu et al. 2009; Wan et al. 2009; Mohite and Patil 2013).

5 Nanocellulose

Nanocellulose is the sequestered product of cellulose with nanoscaled (1–100 nm) of the main structural material. The formation of nanocellulose initiates with microfibril presents in cellulose fibers. These fibers are composed of elementary fibrils forming the main structural part. In these elementary fibrils, cellulose is arranged in both crystalline and amorphous forms. Furthermore, microfibrils in cellulose are composed of cellulose nanocrystals (CNC) linked with cellulose nanofibers (CNF) (Li et al. 2013; Robles 2014). Microfibrils possess core properties like high crystallinity, elasticity, high water holding, and polymerization property (Lee et al. 2014). The raw material for the formation of nanocellulose includes wood, agricultural waste (viz. wheat straw, rice straw), algae, and so on. Nanocellulose is reported in three major forms (1) CNC (cellulose nanocrystals (2) CNF (cellulose nanofibrils), and (3) BC (bacterial cellulose) (Dufresne 2012; Klemm et al. 2011).

6 Importance of Nanocellulose

Nanocellulose possesses various characteristics from traditional materials like crystallinity, special morphology, geometrical dimension, high specific surface area, barrier properties, bioavailability, free toxicity, and so on. Due to this uniqueness, using nanocellulose different products with applications in paper industries like composite reinforcement, pharmaceutical applications like novel drug delivery systems and tissue engineering are used currently (Österberg and Cranston 2014). With respect to the properties of nanocellulose, it is divided for application into three different parts, that is, physical, chemical, and biological. Nowadays, most of the applications are focused on biological aspects in context to biomedical applications.

7 Application of Nanocellulose

7.1 Diagnostics

Carbon nano fibers (CNFs) are used as gold nanocomposites in biological template aqueous suspensions. The developed diagnostics showed excellent biocompatibility, structural design with superior conductivity. The CNFs entraps horseradish peroxidase (HRP) with an allowance of HRP biosensors allowing detection of hydrogen peroxidase with the detection limit of 1 μM (Zhang et al. 2013). The thin films of CNFs are also used for the immobilization of antibodies using the adsorption process. These molecules activated with TEMPO are also used for capturing the biomolecules like anti-IgG (Zhang et al. 2013; Orelma et al. 2012). The other major application of CNFs is in copolymer grafting. Furthermore, this peptide possesses a specific affinity to human IgG, conjugated to the grafted polymer with high selectivity. For better biocompatibility, proteins like collagen, elastin, hyaluronan, and human epidermal growth factor (H-EGF) were immobilized on the bacterial cellulose (BC) (Andrade et al. 2010; Fu et al. 2013).

7.2 Tissue Repair

Nanocellulose membrane serves as a barrier against infection, fluid loss, and increases the painkilling effect and increases the bioavailability of drugs. Nanocellulose also absorbs the fluids during most inflammatory stages, sacking it late in a controlled and trouble-free manner (Pereira et al. 2013). To add more, the nanocellulose has many applications in wound dressing due to its properties like biocompatibility, better water absorption capacity, and flexible surface chemistry (Dugan et al. 2013) (Fig. 14.2). Bacterial cellulose also provides better moisture-controlled environment near wound surfaces and also can easily be removed after the healing with almost no sticking effect. The published reports on BC indicate high tissue regeneration with high cell formation and proliferation resulting in a higher recovery rate compared to that of the normal wound healed by the skin repair or healing cream (Czaja et al. 2007). Further advancement shows that composite membranes composed of BC, gelation, and alginate showcased better growth of 3T3 type cells indicating the potential composited for skin/tissue regeneration (Nwe et al. 2010).

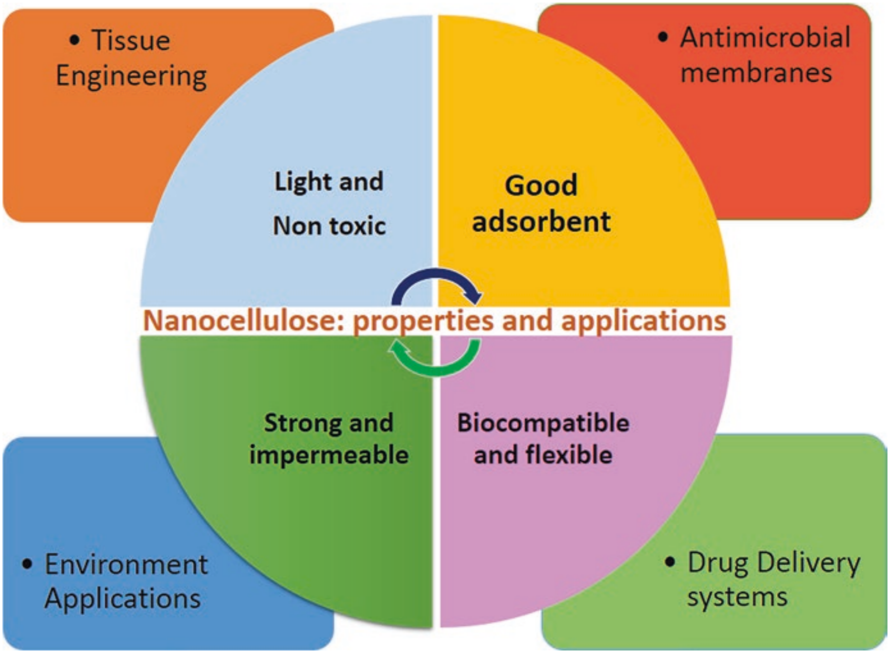


Fig. 14.2 Properties and application of nanocellulose

8 Drug Delivery

The presence of the hydroxyl group in nanocellulose provides many sites for surface modification. Surface modification of nanocellulose leads to the release of nonionized or hydrophobic drugs that normally binds to nanocellulose. For example, poly caprolactone chains might be conjugated onto CNC for drug delivery (Kalia et al. 2014). Few reports suggest that methylcellulose form a polymer network by cross-linking phenomena for controlled drug released (Kalia et al. 2014). In one of the published reports, itraconazole was stabilized by the nanocellulose matrix increasing its dissolution rate and in vivo performance (Kolakovic 2013). Better stability in CNFs was reported using spray-dried technique for the formation of fast dissolution tablets (Kolakovic et al. 2014). Furthermore, the biggest advantage of using nanocellulose is a rare combination of absorbing exudates and wound healing capacity (Trovatti et al. 2012).

9 Aerogels and Hydrogels

A unique formulation of nanogel comprising of bacterial cellulose and surfactant was produced by polymerization. This nanogel displays thermal responsive behavior which can be correlated with lessen hydrogen bonding with temperature (Wu et al. 2013).

Aerogels are light molecular weight gels with a high load of actively active compounds (Garcia-Gonzalez and Smirnova 2011). They are generally prepared using the hydrogels or wet gels with suitable drying technology helping the gels characteristic to remain intact. The weblike structure with high porosity, surface reactivity, and high nanocellulose content make the prepared aerogels an excellent candidate for removal of recalcitrant compounds like dyes, materials having thermal insulation capacity, and so on. (Chen et al. 2014).

Hydrogels are cross-linked polymer gels having strong ionic and physical interactions to absorb and hold water. Due to its transitions ability, the sol–gels with properties of temperature, pH adaptability, and high ionic strengths, they are extensively used in biomedical fields for novel drug delivery system (Elisseeff 2008; Jagur-Grodzinksi 2010). Newly developed hydrogels include the injectable hydrogels, supramolecular hydrogels, and double membrane hydrogels are becoming a novel potential for drug delivery based on nanocellulose. One of the best examples studied is of doxorubicin hydrochloride: a model drug designed for the drug release study. In this study, it was found that the drug was able to release over extended 7 days and the study revealed that the drug release behavior follows the Fickian diffusion process and the combination of pluronic acid/CD Dox hydrogels/CNCs were found to have significant membrane transport mechanism. One step ahead, the bacterial nanocelluose was also tried for its potential application in a controlled drug delivery system using serum albumin as a model drug (Muller et al. 2013).

Biodegradable hydrogels composed of CNCs as fillers were used potential drug carriers for nanoparticle loading in nontoxic, injectable, and biodegradable hydrogels (Yang et al. 2013).

10 Transdermal Drug Delivery System

Bacterial cellulose is currently significantly used in the development of a transdermal drug delivery system with special applications in wound healing (Huang et al. 2013; Moritz et al. 2014). For the controlled transdermal formulation of berberine, 3D network of bacterial cellulose was used and characterized. Using this formulation, the drug release time was increased significantly in comparison with the commercially available composition. The characteristics like pH dependence, sustained release by diffusion process with active wound healing mechanism was observed with this formulation. The system also shows high biocompatibility and physiochemical strength suitable for an efficient trans drug delivery system.

11 Hyaluronan/Hyaluronic Acid (HA)

Hyaluronic acid is an anionic linear polysaccharide consisting of D-glucuronic acid and N-acetyl-D-glucosamine. It was defined in 1934. Firstly, it is found from animal tissue, especially from rooster combs, and now it is produced by bacterial recombination. It plays a significant role in living microorganisms and the human body as a form of sodium hyaluronate (Chong et al. 2005; Kogan et al. 2007; Necas et al. 2008). Primary, this product was accepted for use in topical issues and cosmetic applications. Later, bacterial hyaluronan has been permitted for eye surgery by FDA-USA in 2011 and medical device certification in 1995 (Kim et al. 2014). Sodium hyaluronate is used for sustained-release preparation of recombinant human growth hormone based on its safety and efficacy confirmed by clinical studies in 2014.

HA is the most important constituent of the extracellular matrix and provides mechanical and structural support in synovial fluid in the eyes and connective tissues (Yadav et al. 2008). HA is also playing an important function in cell signaling, regulating immune response, and also in migration of cells (Almond 2007; Zeng et al. 1998). Some hyaladherins play a crucial role in the degradation pathways of HA.

The pervasive distribution of hyaluronic acid namely hydrophilicity, biocompatibility, and biodegradability makes hyaluronic acid best for biomedical needs. These properties have led to an increase in the use of HA in the drug delivery system. The composition of HA and its characteristics have led to an increase in its residential time used mainly for the topical cream formulation (Barbault-Foucher et al. 2002; Yerushalmi et al. 1994). The hydrophilic nature of HA was used to lessen the nonspecific interactions in the bloodstream. It was also reported that the unilamellar structure of HA is also useful for liposome mediated drug delivery systems (Peer et al. 2003).

11.1 HA-Based Bioconjugates

For better stability and availability of HA on the nucleic acid vector, many groups use the covalent bonding side of HA as a building block for the self-assembly of nanoparticles. There are several reports suggesting the role of HA in bonding with nanoparticles, for example, the HA was conjugated with the PLL using sodium cyanoborohydride for self-assembly of nanoparticles (Takei et al. 2004). The copolymer obtained was able to easily make a complex with the PLL. The HA is also one of the best receptors possessing the receptor-specific targeting properties as demonstrated in the suitable carrier for nanoparticles after injection in animal models. Usually, HA can be easily activated with the highly reactive O-acylisourea, which can easily react in basic amine groups for the known for the nonviral polymeric nucleic acid carrier having biocompatible target-specific advantage. The bioconjugates formed by using HA were found to form a complex with siRNA with electrostatic interaction using the amine groups. The experiments suggest the less molar percentage resulted that the inability of conjugates to form complexes with siRNA having less positive charges (Jiang et al. 2008). Furthermore, to complement the in vivo experiments performed by the Jiang group also finds good results with the xenograft experiments. Chemical conjugates of HA will affect the receptor specificity and also its uptake of the drug delivery system. Less molecular percentage results in the inability to form the conjugates with siRNA. Furthermore, the optimized nanoparticles were tried for in vivo experiments in tumor therapy to treat liver cirrhosis with anti-transforming growth factor (Park et al. 2011; 2010). Furthermore, to increase the biodistribution of HA, nanoparticles were intravenously injected in mice having induced tumors and observations were noted at different time intervals (Choi et al. 2010).

It was evident that hydrophobic small molecules drugs with hydrophobic core can be used in context to the drug delivery system. But it was found that in the context of the nucleic acid delivery system the hydrophilic system might cause the problem. However, few reports are published showing evidence that the hydrophobic nature of the molecule is used for drug delivery avoiding the possible effects of CTAB (Maksimenko et al. 2005). For further betterment, optimization was done as the nucleic acid carrier, the low molecular weight will be cross-linked with cystaminebisacrylamide (CBA). In other cases, a study in caveolae-dependence size of particles play an important role rather than HA can be used as a ligand for an intracellular compartment. It has been reported particle size influence the uptake with a size of 200–500 nm can be preferably endocytosed (Rejman et al. 2004).

11.2 HA-Nanoformulated Drugs

HA was used in tissue engineering and drug delivery system due to its immune system neutrality, biocompatibility, and biodegradability (Freed et al. 1994; Ganau et al. 2012). These characteristics allow the formulation made by HA with higher capacity of drug tolerance, fewer side effects, less risk of cytotoxicity, and genotoxicity compared to other nanomaterials (Greish et al. 2012).

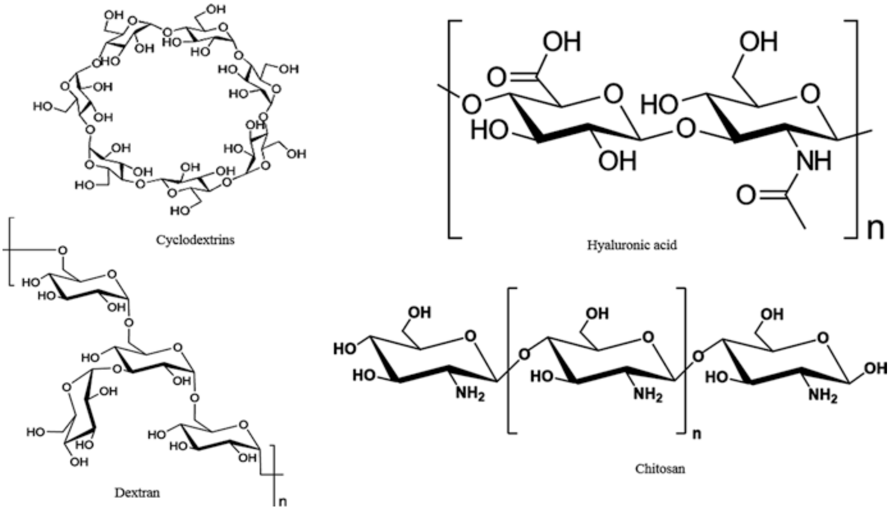
HA plays important roles in cell adhesion, growth and migration, wound healing, and necro-oncogenesis (Knudson and Knudson 1993; Rooney et al. 1995). HA increases better primary brain tumors compared to present central nervous system development (Delpech et al. 1993). For glioma patients, the formulation in a combination of HA and anticancer agents. The combination saw the overexpression of CD44 in glioma cells representing the role of HA nanoparticles for the primary brain tumors. Experiments with cell lines demonstrated that even low expression of HA receptors shows better efficacy in drug carriers in glioma subsets. HA ceramide-based nanoprobes show better tumor target in in vivo and in vitro conditions (Cho et al. 2012). To add more, HA nanoparticles show a better response to glioma cells with respect to the exogenous and endogenous application of HA nanoparticles. HA oligomers suppress the malignant capacity of glioma cells and can be used as the inhibitory lethal agent increasing the apoptosis and downregulating the key cell survival mechanisms (Gilg et al. 2008).

For the production of HA nanoshells, technical issues regarding its drug formulation and encapsulation came, especially for the low molecular weight HA. However, this limitation was overcome with choosing drugs with an anionic domain of HA forming nanoagregates, even with high molecular weight HA. The best example is of cisplatin mixed with HA. In this case, HA nanoparticles were made by spontaneous aggregation because of strong ion complex, formed between cisplatin and HA with a particle size of around 100–200 nm (Jeong et al. 2008). The experimental data clearly indicate the significant increase in capacity around 67–81% with continuous sustain drug release for several days and also in uptake in cell lines (Jeong et al. 2008). The pharmacokinetics and pharmacodynamics test supports the data for validation and further usage in different drug delivery systems. Even the formulated HA nanoagregates were found to target the tumor neurospheres (TNFs) for resting/inhibiting the glioma cells. HA nanoparticles were proved to be an efficient carrier for antineoplastic drugs and further can be used as an option for novel therapeutic approaches for glioma cell inhibition.

12 Cyclodextrins

Cyclodextrins have received relevant importance in the excipients used to formulate the medicines. The ability of various types of cyclodextrins viz. α, β, and γ CDs to bind with various excipients have received considerable attention for designing a novel drug delivery system (Loftsson and Duchene 2007). The combination of outside hydrophobic surface and inner hydrophilic surface helps to host the molecules with a low polarity that can be inserted in the cavity. The presence of bonds like hydrophobic, electrostatic, and hydrogen bonding leads to thermodynamically favorable conditions as a carrier for different drugs (Liu and Guo 2002). From the reaction kinetics point, the presence of weak interactions between the CDs and other excipients help the molecules to achieve rapid equilibria between the molecules freely moving in the solution. The equilibrium is so sensitive that it can lead to the change in ionization potential of combined excipient with respect to its solubility and affinity leading to either formation of the complex or total rupture of the formulation (Thompson 1997; Perlovich et al. 2003).

The advantage of using CDs in the drug delivery system is the presence of hidden labile groups or bonds within the CDs structure contributing stability in oral and solid-state formulations (Fig. 14.3). Furthermore, add on the CDs possesses the remarkable chaperone effect which can be used to overcome major challenges in the production of biopharmaceuticals with solubility and permeability balance issues (Lipinski 2000; Davis and Brewster 2004). The property of CDs to extract the lipophilic component from biomembranes has led CDs to act as permeation promoters. Due to this property, it was reported that the complex of CDs and drugs can reduce or minimize the side effects of the gastrointestinal, dermal, or other sensitive human tissues sensitive to drug contact (Amdidouche et al. 1994). All these characteristics of CDs will lead to facilitate the drug administration almost through any route and also to switch from classes II and IV to the ideal class I as per the biopharmaceutical classification system (Loftsson et al. 2004). The derivatives of CDs with improved side chains and less reactivity are in continuous search for achieving better solubility and better biocompatibility.


Cyclodextrins

Hyaluronic acid

Dextran

Chitosan

Fig. 14.3 Microbial origin polysaccharides used as pharmaceutical excipients

With better structural details and utilization of CDs in novel designing of the drug delivery system is envisioned. Researchers are trying to designed CDs in oral formulation for better controlled release and also site-specific delivery systems (Ikeda et al. 2000). Better formulation of CDs helps for colon targeting prodrugs and plasmids for gene therapy (Ortiz Mellet et al. 2011; Kulkarni et al. 2012). With the amphiphilic and aggregate forming nature of CDs, the formulated nanospheres can easily be loaded with a high proportion of the hydrophobic drug-forming complexes and other interacting complex drug molecules (Quaglia et al. 2009; Yameogo et al. 2012). Moreover, the CDs networks can be designed to fit most of the biomedical and pharmaceutical demands, leading to open paths to provide novel drug delivery systems having better and advanced performance.

13 Cyclodextrins Nanostructure

The use of CDs for better drug delivery is possible by the transformation of CDs in the monomers that can copolymerize with acrylic/vinyl monomers. Techniques like free radicals and controlled/“living” polymerization are used to achieve considerable development and versatile combination of monomers (Lopez-Madruga 2002). The first step is to synthesize acrylic/vinyl derivatives in a combination of CDs exhibiting similar reactivity in comparison to the monomer components of hydrogels. The diverse varieties/combinations are possible due to the presence of the hydroxyl group in each CD with the challenge lying in the synthesis of monofunctional monomers (Alvarez-Lorenzo et al. 2011). By improving CDs with specific applications, a list of commercially available CDs monomers is very limited, which has restricted its application in biomedical and pharmaceutical fields (Janus et al. 2003). However, few reactions were successful for the synthesis of CD derivatives with one or more double reactive bonds. The best example is the combination of large molecules like vancomycin, cefazolin with the molecular imprinted networks of acryloyl α CD and acryloyl β CD to form a complex that can interact with many CD units. The prepared complex formulation was able to polymerize and able to change the site specificity of the molecule depending on the preferences of reactive sites (Kettel et al. 2011). Once the site specificity is set, the resultant developed imprinted particles were able to load twice the drugs compared to normal CD networks in the absence of large molecules. Another example is of the formation of enhanced network formation using the amphiphilic molecules, by a combination of phenylalanine with bisacryloyl β-CD monomers having electrostatic interactions. These networks were able to distinguish the enantiomers of phenylalanine (Piletsky et al. 2005). Derivatives of monotosyl derivatives of β-CDs group are used for the functionalization of the natural polymer as performance improvement polymers as drug carriers (Luzardo-Alvarez et al. 2012). The other technique used for nanogel preparation for the drug delivery system is the precipitation polymerization technique. Using this technique, the nanogels with the size of (106–115 nm) are used as cores for coating the shell layers of compounds. The final nanogels after phase transition show a significant decrease in the particle size (around 65–90 nm). The reduction in size leads to increasing the prolonged release of the drugs (Liu et al. 2009). The other published reports suggest that grafting of β-CDs leads to slight changes in the critical soluble temperature but significantly increases the loading of ibuprofen and further delays the drug release at 25 and 37°C. Furthermore, the interpenetrating polymer networks displayed the pulse release subjected to the different temperatures behaving like a smart drug delivery system.

Another notable experiment was with respect to the creation of biodegradable CD networks which involves the coploymerization of poly (D, L-lactic acid) with beta cyclodextrin. The composition of the beta cyclodextrins and the number of reactive groups determines the size of nanospheres in the reactive gels (60–260 nm) (Lu et al. 2008).

13.1 Cyclodextrins and Medical Devices

Apart from the server as drug carriers, CDs can also play an important role as an insertable medical device for the prevention of certain pathological conditions. Medical devices can now be inserted/implanted in the boy with functioning crucial role in the therapeutic and diagnostic role for management of ill patients (Alvarez-Lorenzo et al. 2010). Incorporation of the drugs with the maintenance of mode of action of the medical device shows promising efficiency in curing wounds, in tissue regeneration, and adverse events prophylaxis like restenosis and infection. To add further advantages of medical devices is that it offers a better platform for the targeted drug delivery system with minimizing and immune-specific response, graft rejection, and biofilm formation (Arruebo et al. 2010).

There are two approaches followed for preparation of drug dispersing/eluting medical devices: (a) those which can hold the bulk of drug material constituting the medical device during its fabrication or later on the step of presoaking (b) those that integrate the drugs in the outer layers with help of coatings procedures like covalent binding. CDs could be useful in the retention of drugs both inside and also on the surface of the medical device.

Very few reports are showing the combination or usage of the CDs in the medical devices, however, it was reported that CDs can reduce protein adsorption with increasing the blood compatibility (Zhao and Courtney 2009). Furthermore, CDs can be easily coupled with the textile materials for better color and fragrance retention. The combination also shows the unique combination of antimicrobial and insect repellent characteristics (Hebeish et al. 2008). The hanging of CDs was explored for formulating the drug-eluting contact lenses without changing the properties like viscoelasticity and mechanical characteristics (Rosa dos Santos et al. 2009). In one of the reported experiments, the glycidyl methacrylate was copolymerized with components for creating the network binding points for the β-CDs. The formed networks hang a few (2–3 ether bonds) using hydroxyl groups. The pendant β-CDs show a significant ability to load diclofenac (1300%) and also showed no drug leakage during storage in conservation liquids. Furthermore, diclofenac release was also found to be continued for more than 15 days in the lacrimal fluid. The flexibility of this technique was also adapted for hanging of other derivatives of β-CDs. It was shown in derivatives that pendant γ-CDs hinder/inhibit the adsorption of the lysozyme and at the same time, α-CDs decrease the deposition of lysozyme but increase the absorption of albumin in comparison to the β-CDs diminishing the protein sorption on comparison to the control. Furthermore, γ-CDs show twofold affinity for the miconazole drug with an increase in drug-loading capacity up to 170 mg/g. These formulations of miconazole and CDs showed complete inhibition pathogenic yeast *Candida albicans* biofilm formation in in vitro conditions (Schofield et al. 2006).

14 Dextran

Dextran is a complex polymer of anhydro-glucose, composed of α-D-(1–6) linkages with side branches via α-1,2,α-1-3, or α-1,4 linkage (Fig. 14.3). It was discovered in the 19th century and considered as the first example of exopolysaccharide from a microorganism. Dextran is found from sucrose by species of bacteria (e.g., *Leuconostoc* and *Streptococcus*). It is also used as an oral tablet excipient, which has been marketed in Japan (Nwodo et al. 2012; Esawy et al. 2012). With clinical importance, low molecular weight dextran has therapeutic importance as a plasma volume expander and as an excipient in artificial tears (Van Sr and Hennink 2007; Mehvar 2000). The unique combination of the easy bioavailability, compatibility, and chemical synthesis makes dextran an ideal candidate as a drug delivery biopolymer (Heinze et al. 2006).

15 Dextran-Based Nanoformulations

Different varieties of dextran based nanoparticles formulation were described in the reports with the specific aim of enhancing the nucleic acid delivery. There are also different approaches reported for using dextran in polymer matrix-based formulations for example, the reports by Stefaan designed carriers for delivery of SiRNA (Raemdonck et al. 2008; Raemdonck et al. 2009a, b). Hydrogels prepared form the cationic dextrans were formulated using the inverse emulsion photo polymerization using mineral oil medium for better availability and adsorption. To impart the cationic charges in the hydrogels, the cationic methacrylate monomers were coploymerized. The resultant formulation showed excellent biodegradability under defined physiological conditions irrespective of the carbonate ester linking to the dextran backbone (Raemdonck et al. 2009a, b). In comparison to the commercially available lyophilized dex-nanogels, the formulate dextran nanogels were able to siRNA more with a maximal loading capacity of 50 pmpl of siRNA. From the results of confocal microscopy, it was evident that the reporter gene was knockdown but the endocytosed dextran nanogels were found to be accumulated in the acidified organelles likely endolysosomes. Furthermore, the reports also indicated that the dextran nanogels having antitumor necrosis factor (anti-TNFα) siRNA mediates gene silencing with minimum toxic effects, activating macrophages without any assistance from endosomolytic tools. Furthermore, in the same report, it was clearly indicated the si-DEX-NGs was much better than other nanoformulations based on polymeric carriers like chitosan, polyamidoamine dendrimers (Jensen et al. 2012). Also looking to the immune conditions, none of the nanogel formulations causes lysis of erythrocyte; on the contrary, the positive nanogels show the platelet aggregate formation. Flow cytometry data confirm the interactions of nanogels with the platelets and leukocytes and again showing a high level of cellular binding (Naeye et al. 2011).

There are few reports indicating the significance of the efficiency of the dextran-based nanoformulations to overcome the chemotherapeutic failures. The prime example is the use of dextran nanoformulation in the multidrug resistance for osteosarcoma. The siRNA-based nanogel was targeted toward the ATP-binding cassette of transporter B1 gene. Dextran particles were combined with stearyl moieties and were coated with polyethylene glycol. The results indicated that the formulated nanogels lead to the downregulation of MDR1 genes and reversed the MDR phenotype and resensitize the cell lines showing the cytotoxic effects of doxorubicin (Bachelder et al. 2010; Broaders et al. 2009). Furthermore, dextran-based nanoformulation was used in developing gene therapy. The investigated reports by Jean Frechet group show the efficiency of the formulation constituted of the acetal-modified dextran. They have designed the protein and vaccine adjuvant delivery systems to antigen-presenting cells (APCs) (Bachelder et al. 2010; Broaders et al. 2009). The hydrophobic acetal groups have modified the nanogels soluble in the organic solvents making it feasible for the production of micro and nanoparticles for encapsulation of proteins via standard emulsification methods (Bachelder et al. 2010). The optimization for efficient gene delivery was done in both phagocytic and non-phagocytic cells by incorporation of the small amount of a degradable cationic polymer in acetal-modified dextran (Cohen et al. 2010).

15.1 Nucleic Acid Nanoparticles Coated by Dextran

To improve the in vivo performance, different polysaccharides coating of nanoparticles was considered as an important alternative to PEG-mediated formulations (Lemarchand et al. 2004). Surface coating using different polysaccharides was successfully demonstrated in the use of different drug delivery systems. The use of different types of dextrans viz.: native dextran, charged dextran, and modifications based on its charges, hydrophobicity, and hydrophilic nature was tested for coating polymeric as well as lipid vesicles. The aggregation property of dextran can modulate the protein adsorption with much more colloidal stability and biocompatibility (Chauvierre et al. 2010; Mizrahy and Peer 2012). Recently, the Delgado group has reported the formulation design of the solid lipid nanoparticle (SLNs) modified by the combination of dextran and protamine for efficient gene delivery (Delgado et al. 2012; Delgadob et al. 2012). In the gene delivery system, a vector carrying the formulation of dextran–protamine–DNA complex was absorbed on the SLN surface by the electrostatic process. The prepared nanoparticles showed the high transgene expression with in vivo expression studied in rats and by intravenous injection in mice (Delgado et al. 2012). The gene delivery was successful because of the combination/addition of dextran and protamine in the formulation. The presence of dextran in the formulation increases the biocompatibility and also influences the cellular uptake mechanism for improvement of transfection efficiency (Delgado et al. 2012; Delgadob et al. 2012).

16 Chitosan

Chitosan is a biodegradable, biocompatible compound and commonly used as a pharmaceutical excipient. It is deacetylated chitin, which is a natural product extracted from marine sources and many fungi. Chitosan is a natural linear polysaccharide made up of β-(1–4) linked D-glucosamine and N-acetyl-D-glucosamine (Roberts 1992).

Chitosan has unique properties like nontoxic, biodegradable which indicates its potential applications as pharmaceutical excipient such as drug carries, wound healing agent, and in drug delivery system (Hussain 2011).

The specific characteristics like its mucoadhesiveness and membrane permeability make it an ideal candidate for usage in the novel drug delivery system and tissue engineering (Riva et al. 2011; Dash et al. 2011). Moreover, the advantage of deacetylation of D-chitosan exposing the D-glucosamine at pKa approx. at 6.5 and solubilizing in acidic condition makes chitosan favorable candidate in mucosal drug delivery system (Rudzinski and Aminabhavi 2010). The efforts are still going on identifying the chemical route of the quaternization of D-glucosamine moieties for making chitosan a better bioavailable polymer in drug delivery systems (Thanou et al. 2002).

16.1 Chitosan-Based Nanoformulations

Therapeutic nucleic acids were coated in the chitosan hydrogel nanoparticles by cross-linking the chitosan polymeric chains via covalent or weak interaction forming the nanogels matrices for drug delivery systems. Chitosan nanogels can be formed by mixing the alkaline TPP phase ratio with an acidic solution. The important point in the formation of nanogel is the chitosan: TPP ratio for stable solidified NPs (Janes et al. 2001). The chitosan nanogels are made either using pure chitosan or blended with other hydrophilic compounds. The ionic gelation of the chitosan is used to stabilize chitosan complex made with different polymers or bioactive compounds. The resulting structure is a more biocompatible and versatile nanostructure (Janes et al. 2001). Furthermore, it has been demonstrated that the more crosslinked polymer matrix is preferable for better gene expression and extended release of the pDNA (Csaba et al. 2009; Lee et al. 2007). For an efficient gene delivery system, the transfer efficiency is mainly dependent on the molecular weight of the chitosan, the combination of low molecular weight of chitosan/TPP showed better in vitro gene transfer. In addition, the low molecular weight chitosan/TPP particles exhibit significant transgene expression comparable to the low molecular weight chitosan polyplexes in absence of TPP (Csaba et al. 2009). This study served as a basis for leading to optimization studies for chitosan usage in the siRNA drug delivery system. With the advancement in technologies, the Gaspar group designed the supercoiled (sc) pDNA in chitosan nanoparticles using the inotropic gelation technique (Gaspar et al. 2011). It is an established fact that the sc-DNA outperforms in transfection efficiency in its relaxed circular form (oc) and the linearized forms (Remaut et al. 2006). These experiments have assured that optimization of chitosan with pDNA topology will bring better results in gene transfer applications.

16.2 Nanoparticles Coating

Apart from the functions in nanoparticle formulation, nucleic acid complexation, chitosan also plays important roles as a coating material for the surface modification in different nanoparticles. For instance, many groups reported adaptation in the biodegradable and biocompatible formulation of nanoparticles with chitosan (Chung et al. 2010). Because of its cationic nature, the chitosan can easily bind with the negative charge PLGA leading to positive zeta potential. Other than PLGA, the types of solid hydrophobic nanoparticles used for the template coating is PIHCA poly isohexylcyanoacrylate. The PIHCA with chitosan shell was used to complex siRNA for targeting the Ras homologous A protein which can promote cell proliferation and metastasis. The intravenous injections of these combinations inhibited breast cancer proliferation without any signs of in vitro toxicity in comparison to the untreated anesthetized animals. The comparison was done with respect to bodyweight progression, vital organs histological assessment, and quantification as biochemical markers with renal and pancreatic function (Pille et al. 2006). Furthermore, glycol chitosan showed a remarkable humoral and cellular immune response when compared to the immunization with naked pDNA (Khatri et al. 2008).

17 Herbal Excipients

Excipients are the components or substances which are intentionally added to the formulation of a dosage form. They are different uses like as disintegrants, glidants, adhesives, binders, diluents, sweeteners, and so on. Chemicals are generally used as chemical excipients but they are also extracted from plants and animals. The excipients which are extracted from plants are known as herbal excipients which are used as a chemical excipients. Herbal excipients are biocompatible, cheap, easily available, nontoxic, low cost, availability, soothing action, and nonirritant nature.

Herbal excipients are cheap, easily available, and nontoxic. Depending on the requirement, formulations can be developed and modified. They have a great advantage to overcome synthetic analogs. They can be used as diluents, disintegrate, colorant, binder, lubricant, and many more, in various types of formulations. They are biocompatible and capable of giving additional nutrition to the developed dosage form. There are so many plants that are there from which components are extracted. From the lower group to higher angiosperms, plants contain compounds that can be used as excipients.

18 Natural Gums

Gums and mucilages are present in high quantities in plants, animals, seaweeds, fungi, and other microbial sources, where they perform several structural and metabolic functions; plant sources provide the largest amounts.

Two types of gums are based on the charge they carry (Venkata 1992).

1. Nonionic seed gums: guar gum, locust bean gum, tamarind gum, xanthan, amylose, arabinans, cellulose, and galactomannans.
2. Anionic gums: arabic gum, karaya gum, tragacanth gum, gellan, agar, algin, carrageenans, and pectic acid.

Based on the source and availability, that is, from where the gum is extracted, there are four different types of gums:

A. Marine origin/algal (Seaweed) gums: agar, carrageenans, alginic acid, laminarin.
B. Plant origin: (1) shrubs/tree exudates—gum arabica, gum ghatti, gum karaya, gum tragacanth, khaya and albizia gums; (2) seed gums—guar gum, locust bean gum, starch, amylose, cellulose; (3) extracts—pectin, larch gum; (4) tuber and roots—potato starch.
C. Animal origin: chitin and chitosan, chondroitin sulfate, hyaluronic acid.
D. Microbial origin (bacterial and fungal): pullulan, xanthan, krestin, dextran, curdian, emulsan, schizophyllan, Baker's yeast glycan, lentinan, zanflo, scleroglucan.

Gums produced from plants are translucent and amorphous substances. Usually pathological products, gums are produced when the plants are growing under unfavorable conditions or when injured. Gums are plant hydrocolloids and may be anionic or nonionic polysaccharides. The applications of the various herbal gums in biomedical applications are listed in Table 14.1. On hydrolysis, gums yield sugar and salts of uronic acid (Gokhale et al. 2008).

Table 14.1 Herbal excipients and its biomedical applications

Common name	Botanical name	Family name	Biomedical applications	Drug delivery system	Drugs
Guar gum	*Cyamompsis tetraganolobus*	Leguminosae	Natural reducing agent, lowers the serum cholesterol level	Colon-targeted drug delivery, cross-linked microspheres	Albendazole, metronidazole, methotrexate
Gum Tragacanth	*Astragalus gummifer*	Leguminosae	Stabilizing, and binding agent for synthesis of metal nanoparticles. Increase the level of high-density lipoprotein	Hydrogel beads, cross-linked microspheres	Tragacanth
Kyara gum	*Khaya grandifolia*	Meliaceae	Controlled releasing agent, hydrogel nanocomposites (HNC) for environmental applications	Mucoadhesive and buccoadhesive	Nicotine
Xanthan gum	*Xanthomonas lempestris*	*Xanthomonas campestris*	Drug carrier, excipient for sustained release formulations, reducing and capping agent of nontoxic nanoparticles	Pellets. Controlled drug delivery system	Diclofenac sodium, theophylline
Acacia gum	*Acacia arabica*	Leguminosae	Suspending and emulsifying agent, sustained release carrier, reduction of systolic blood pressure	Osmotic drug delivery	Water-insoluble naproxen
Tamarind gum	*Tamarindus indica*	Fabaceae	Polymer to prepare sustained release formulations, mucoadhesive antioxidant, and cadioprotective agent	Mucoadhesive drug delivery. Sustained releases	Diclofenac sodium, verapamil HCL

18.1 Natural Gums and Nanoparticles

18.1.1 Guar Gum and Nanoformulations

Guar gum is used as a therapeutic in colon cancer because of drug retardant delivery systems. Guar gums are seen as the natural excipient for the production of highly stable nanoparticles. The Zheng group reported the three-dimensional cross-linked guar gum networks for the formulation of the Ag nanocomposites. From the results of the experiments, it was interpreted that guar gum can be an efficient carrier for the production of metallic nanocomposites, low-temperature catalysts (Zhenga et al. 2015). Furthermore, synthesized derivatives of guar gum can be further used for the formulation of nanoparticles with better drug-loading capacity. Methods like nanoprecipitation and sonication can be used for the formulation of guar gum nanoparticles and their derivatives. Reports indicate that guar gum nanoparticles can be used in the medical device like biosensors, improving the nutrient quality of food supplements, and pharmaceutical field (Gupta and Verma 2014; Soumya et al. 2010). Dodigouphas reported the guar gum nanoparticles formulation by the method of ionic gelation method and successfully demonstrated its application (Dodi et al. 2016). Method acid hydrolysis was used to design the water-dispersible nanoparticles without the use of any surfactant or stabilizing agent and even in the formulation of cross-linked biopolymer films. The nanoparticles formed using the cationic guar gum can be further preserved for a long time using cryopreservants (Abdullah et al. 2015). In case of the cardiovascular diseases having high cholesterol levels, nanoparticles formed by guar gum can be included along with the dietary supplements to lower the serum cholesterol level. Indeed, the guar gum nanoparticles showed significant effects on the hypocholesterolemic rats. Guar gum reduced more effectively low-density lipoprotein cholesterol level but simultaneously also contributes in the synthesis of compensation of concurrent treatment with cholestyramine (Samarghandian et al. 2011).

18.1.2 Nanoformulations from Gum Tragacanth (GT) and Kyara Gum (KG)

Gum tragacanth has characteristics like the nontoxicity, high bioavailability, high microbial resistance, and longer shelf life. The GT shows hydrogel properties and can be used in different medical applications using nanosilver for antimicrobial activity. The combination of the gum tragacanth and curcumin shows a significant increase in the surface hydrophilicity of the nanofibers (Ranjbar-Mohammadi and Bahrami 2016). GT is used in the synthesis of the metal nanoparticles or in in situ production of antimicrobial fabric and wound dressing (Ghayempour and Montazer 2017). Darroudi group reported the synthesis of the nanoparticles composed of a combination of zinc oxide and gum tragacanth (GT). The formulated nanoparticles were significant in activity and can be easily compared with the nanoparticles synthesized using harmful polymers or surfactants (Darroudi et al. 2013). GT gum was also used as a polymeric wall for the formulation of nanocapsules using the microemulsion method (Ghayempour et al. 2015). The addition of the GT in the hyperlipidemic diet of GT showed a significant decrease in cholesterol.

Kyara gum is hydrophilic natural gum with swelling properties. It can be used as a controlled releasing agent for drug delivery. Gum karaya was combined with polyvinyl alcohol with the nanofiber membrane formulation using electrospinning technology. In other reports, the formulated hydrogel nanocomposite possessing gum karaya was grafted with the polyacrylic acid acrylamide. The formulated hydrogel shows promising results as efficient adsorbent and for the removal of recalcitrant compounds like different dyes present in the industrial wastewater. Synthesized derivatives of gum karaya (HCN) were grafted with polyacrylic acid. These derivatives were biodegradable and have found application in the removal of cationic dyes in the different industrial effluents (Padil and Černík 2015; Mittal et al. 2016).

18.1.3 Xanthan Gum Nanoformulations

Xanthan gum is used in pharmaceuticals as a drug carrier due to its nonreactive and biocompatibility nature. Xanthan gum shows good compatibility with salts, pH, temperature, and viscosity of the solutions. Most researchers believe that xanthan gum can be useful for designing a sustained drug delivery system. Xanthan gum can be used as an important polymer as a coating agent in nanoparticles formulation and such nanoparticles have nontoxic nature and biodegradable efficiency. The unique combination of xanthan gum and locust bean gum leads to nanoformulation which can be thermally reversible and also can be used for tissue engineering and novel drug delivery system. The addition of polymers like silicon dioxide with a combination of xanthan and locust bean gum leads to the formation of the hydrogel with a significant change in rheological properties including the high viscosity and elasticity (Kennedy et al. 2015). As per the published reports, these hydrogels possess excellent characteristics like size control (61–108 nm), spherical morphology, bioavailability, and enhanced stability. The metastable complex formed between xanthan gum and lysine nanoparticles showed significant stability and distribution of steric hindrance (Xu et al. 2015).

18.1.4 Gum Acacia

Gum acacia is acidic polysaccharides composed of constituent sugars like galactose, arabinose, rhamnose, and glucuronic acid. For oral and pharmaceutical applications gum acacia is mixed with the tamarind gum as an emulsifying agent. Gum Arabic is also used as the microencapsulating agent for coating the enzyme endoglucanase. Due to the microencapsulation, stability and sustained release of enzymes were significantly increased (Bajpai et al. 2016). The method reported by Bajpai et al. showed that the zinc oxide nanoparticles with gum acacia and polyacrylate show better gelling characteristics. This hydrogel network was prepared using a hydrothermal approach (Bajpai et al. 2016). Using a chemical reduction approach, the silver nanoparticles gum acacia nanoparticles show high stability, small size, and biocompatibility. The reaction temperature, time, and concentration of the silver nitrate plays important role in maintaining the size of the silver nanoparticles. The size of the nanoparticles significantly decreased in size to about 35–40 nm. The nanoparticles of gum acacia show promising dispersion results in aqueous solution resulting in better stability, biocompatibility, bioavailability, and sustained drug delivery system. The gum nanoparticles form films with preferred polar properties and reducing the surface energy which leads to the tensile strength of drugs. These formulated gums show a decrease in systolic blood pressure with an increase of intestinal and renal excretion of Mg^{2+} and Ca^{2+} ions increasing the urinary hormone excretion. Using these nanoparticles also leads to a decrease of the Na+ ions excretion, phosphate, and urea excretion reducing the risk of cardiovascular arrest (Patel and Goyal 2015).

18.1.5 Tamarind Gum Nanoparticles

Tamarind gum and its synthesized derivatives are used for the preparation of nanoparticles. The mucoadhesive, biocompatibility, and bioavailability properties made the tamarind gum better option as a drug carrier in the oral suspension of irinotecan the anticancer drug. These nanoparticles were formulated using the ion gelation method with calcium chloride as cross-linking agent. The in vitro profile of this drug shows significant controlled release of drug with 60% of drug release in 12 h of the span. The formulation was also noted for its low toxicity and easy bioavailability (Saikia et al. 2013). Using the ion gelation method, the ciprofloxacin nanoparticles were synthesized with magnesium as a cross-linker. The formulated nanoparticles showed the maximum zone of inhibition against the micrococcus species. The in vitro studies of this formulation reveal that the ciprofloxacin-loaded nanoparticles possess extremely low cytotoxicity and better slow drug release rate (Dilbaghi et al. 2014). The derivatized tamarind gum (aminated TG) showed better self-assembled nanoparticles size around 60 nm with a low concentration in aqueous medium characterizing strong hydrogel network properties. The tamarind gum amino complex showed good antimicrobial activity in comparison to the chitosan and cyclodextrins (Simi and Abraham 2010).

19 Challenges

Despite many applications of nanotechnology in pharmaceutical industries, there are also few challenges associated with the drug designed in nano sized and with its therapeutic application system. The major factors facing challenges in the formulation are stability, drug delivery (sustenance and release efficiency), and its degradation mechanism (Prasad et al. 2019). The problem of self-aggregation at low drug concentrations affects severely its stability and entrapment variability (Barenholz 2012; Tiyaboonchai 2003). The typical example to cite this problem is of doxorubicin. Whenever the ionic strength rises or increases the nanoformulation of doxorubicin tends to self-aggregate affecting the efficiency, solubility, and stability of the formulation in biological solution (Liu et al. 2008). Along with self-aggregation, swelling phenomena of the drug nanoformulation is becoming a prime concern for designing a novel nano-based drug delivery system. The swelling lids to the gradual increase in the size affecting its shape and also formulation bioavailability (Liu et al. 2008). However, the solution to this problem can be by adjusting the pH of the biological solution in which the nanoformulation is suspended. The other modification can also be done by using the capping agent with pH sensitiveness for increasing the efficiency of the nanoformulation. Also, the mechanism of degradation seems to be uncontrolled. The problem arises when different derivatives of the polymers are used for increasing the efficiency and bioavailability of the nanoformulations.

Apart from the parameters involved in drug designing, the other concern which has raised concern is applications and its usage in the cell-targeted drug delivery system. The targeted drug delivery system was found to have severe implications as exposure of the body parts like skin, ingestion and cellular uptake, and so on. The particles that are smaller in size (<200 nm) will be entering the directly to the cells and the larger size particles will be phagocytosed by macrophages. The mechanism indicates that the fate of nanoparticle effectiveness will be decided by the biomarkers or the specific receptors it targets/carries along with it (Nikalje 2015). Additionally, the adverse effects underlying due to toxicity are yet to be completely evaluated and revealed. The impact of the size of particles and the diversity of the particles used to design the system is also yet to be resolved (Choudhury et al. 2017; Gorain et al. 2016).

The pharmacodynamics and kinetics of these nanosized particles are totally different compared to the coarse particles used in the drug delivery system. After the nanoparticle formulation application, the drug can translocate in the respiratory tract via endocytosis and usually gets deposited in the respiratory tract even sometimes bypassing the blood–brain barrier. In one of the reports, publishers have reported that nanoparticles can kill the human lung cells in the lab through Akt-mToR signaling pathway causing autophagic cell death (Liu et al. 2011).

20 Commercial Nanoformulations

There are only a few successful nanotechnology-based marketed formulations available (Prasad et al. 2019). Among the few important is the Abraxane, the anticancer nanoformulation supposed to be the first generation of nanodrugs, which is formally approved by the Food and Drug Approval authority. The other successful example is DNA nanostructures paranon nanolab products. The DNA structure was specifically designed for the treatment of human glioma tumors. The nanoformulation is safe in the preclinical trials and also shows significant results in the rise in the survival rate in murine models having the human glioma tumors. Furthermore, to add on is artificial blood vessels having the coating of heparin on collagen tubes. This formulation was used in gene therapy for curing cystic fibrosis and even in the early stages of cancer (Wicki et al. 2015).

21 Conclusion

The applications of biomolecule and polymer conjugation in the pharmaceutical industry are rapidly gaining attention worldwide. The ability to control the size, uniformity, shape, compatibility and bioavailability makes these conjugates special for targeting fatal diseases. The bioconjugate-based drug delivery system will offer uniqueness in terms of more drug-carrying capacity with more stability in in vivo and in vitro conditions. Many synthesizing methods, parameters, and dosage forms were optimized for making the system more proficient and effective. The prime advantage of the bioconjugates is its stability and biocompatibility with different types of targeted as well as sustain drug delivery systems. Although much of the work about the formulation and delivery part is researched and developed but still much more work will bring the system in a fairly economically viable and sustainable condition in the near future.

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Chapter 15
Biosurfactants Based Nano Micelles for Extraction of Biomolecules

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1 Introduction

Surfactants have unique molecular structures consisting of both hydrophilic head group and hydrophobic tail in one molecule. Surfactant molecules in water tend to gather at the surface area and have the ability to considerably decrease the surface tension of water. In the medium of oil–water, surfactant molecules arrange themselves at the interface with their hydrophilic parts in water and hydrophobic parts in oil, significantly reducing the interfacial tension. Many surfactants are able to form micelles (nano-sized) in the aqueous phase or reverse micelles in the organic phase through a self-assembly process when their concentrations in solution reach a certain value, which is called critical micelle concentration (CMC). Figure 15.1 shows the micellization of surfactant molecules in aqueous medium and organic medium. The surface or interfacial tension reduction and micellization properties of surfactants are exploited to greatly enhance the solubility of various molecules in aqueous or organic solvents. This is utilized in micellar extraction and reverse micelle

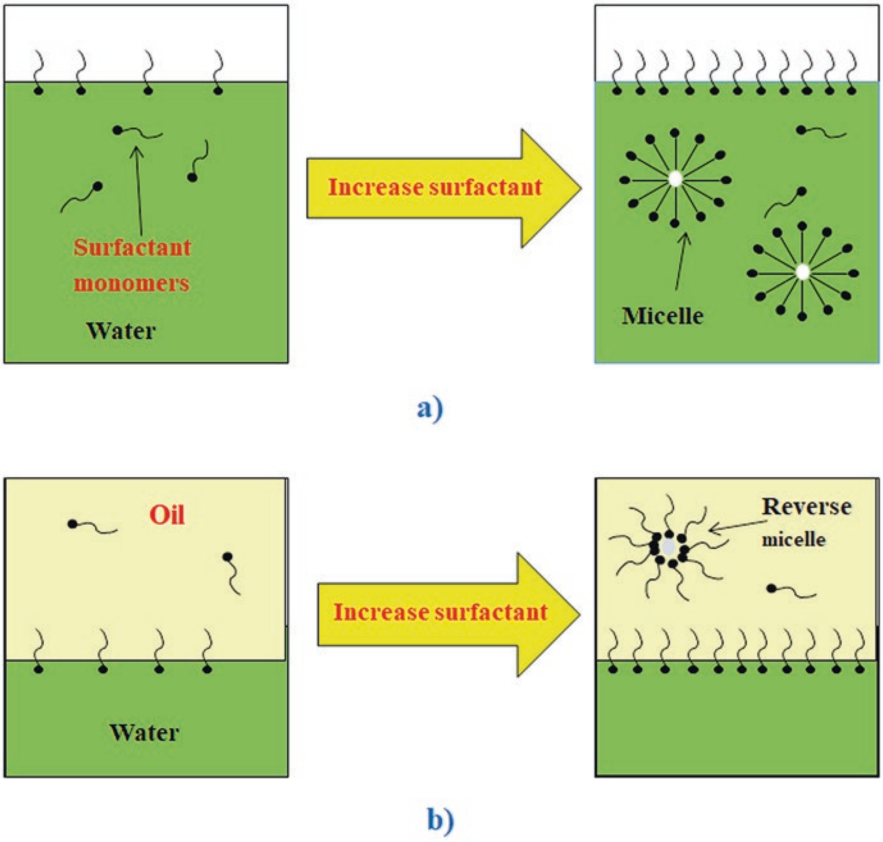

Fig. 15.1 Formation of (**a**) micelles and (**b**) reverse micelles

extraction to extract various biomolecules such as proteins, enzymes, and antibiotics. The main benefits of micelle-based extraction having low solvent intake, utilization of safe solvents, easy to operate, fast extraction process, high selectivity, and high extraction efficiency.

Many chemical surfactants such as sodium dodecyl sulfate (SDS), sodium bis(2-ethylhexyl) sulfosuccinate (AOT), cetyltrimethylammonium bromide (CTAB), triton, and Tween surfactants had been utilized in micellar and reverse micelle extraction (Bukman et al. 2017; Chen et al. 2017b; Jayachandran et al. 2019; Mohd-Setapar et al. 2009; Norazimah Mohamad-Aziz et al. 2013). Nevertheless, the negative impacts of chemical surfactants on the environment cannot be ignored. Careless release of chemical surfactants into the environment can cause contamination due to their toxicity and potential degradation products. With increasing awareness of the public on environmental issues and consumer demands on natural products, many manufacturers have turned to use materials from natural sources as alternatives to chemical materials. Biosurfactants are a good substitute to replace chemical surfactants owing to their environmental friendliness, good biodegradability, and low toxicity. Besides that, biosurfactants possess excellent surfactant properties and are stable at extreme temperatures and pH. Many biosurfactants have been discovered since the last few decades. These biosurfactants have many applications in different fields like pharmaceutical, cosmetics, food, detergent, environment bioremediation, and enhanced oil recovery. Many researches were carried out to examine the potential of biosurfactants for extraction purpose. The total amount of biosurfactants sold are estimated to reach 461,000 tons by the year 2020 (Jiang et al. 2020) while the global biosurfactant market is estimated to reach 5.52 billion USD by the year 2022 (Wang et al. 2020). The trend indicates that more chemical surfactants will be replaced by biosurfactants in near future.

The application of nano-sized micelles for extraction of biomolecules and biosurfactants as alternatives to micelle extraction based on chemical surfactants are the main subjects of this chapter and will be discussed through the contents. Section 2 briefly introduces the micellization process. Sections 3 and 4 provide the basic mechanisms of micelle-based extraction as well as the important factors affecting the extraction process. Several commonly studied biosurfactants for extraction purposes have been discussed in this chapter.

2 Micellization of Surfactant Molecules

Surfactant molecules occur as monomers in a solution at low concentration. Surfactant monomers gather to form aggregates through the self-assembly process when the concentration of surfactants reaches to CMC. Weak non-covalent bonds like electrostatic and hydrophobic interactions, Van der Waals forces, H-bonding, and weak covalent bonds like coordination bonds are the main driving forces for the self-assembly process (Kislik 2012). Packing factor “g” can be calculated through the morphology of surfactant aggregates which is shown in Eq. (1).

$$g = V_{\mathrm{hc}} / \left(a_0 l_{\mathrm{c}}\right) \tag{15.1}$$

where V_{hc} represents the hydrophobic chain volume in aggregate, a_0 denotes the head group of mean cross-sectional area in the aggregate, and l_{c} represents the extended hydrophobic chain length. Based on Eq. (1), the surfactant's length of hydrocarbon chain and head group dimension dictates the morphology of surfactant aggregates formed. Generally, surfactant aggregates will be in the form of spherical micelles if its packing factor is smaller than 1/3, cylindrical micelles if g is between 1/3 and 1/2, or vesicles if g is between 1/2 and 1. If g is greater than 1, the aggregates formed will be reverse micelles. Nevertheless, surfactant aggregates in practice may have a different morphology than one predicted using Eq. (1). Surrounding conditions like pH, ionic strength, and temperature can affect the micellization process.

Micellization of a surfactant system affects interfacial properties and solubilization behavior. In order to explore the potential application of surfactant, it is significant to comprehend the micellization behavior. Various techniques like small angle neutron scattering, dynamic light scattering (DLS), transmission electron microscopy (TEM), fluorescence quenching, and so on, are commonly used to investigate the micellization process. Simulation techniques like dissipative particle dynamics (DPD) methods and molecular dynamics (MD) are also applied to study the micellization process. Models can be developed based on free energy change during micelle formation to predict the properties of micelles (Lebecque et al. 2017). These experimental and simulation techniques are useful to examine the special effects of surfactant structure, physicochemical properties, surrounding conditions, and concentration on the micellization behavior of surfactant systems. In mixed surfactant systems, the balance between molecular interactions including hydrophobic interactions and electrostatic interactions also affects the micellization behavior.

Micellization of surfactants is very useful for solubilization of normally insoluble substances. Under appropriate conditions, surfactant micelles are able to selectively attract, encapsulate, and separate target substances from one medium into another liquid medium. These separation techniques (micellar and reverse micelle extraction) can be utilized for the extraction of various biomolecules including proteins, enzymes, and antibiotics.

3 Micellar Extraction

In aqueous solution, surfactant molecules can form micelles where the head is hydrophilic groups pointed toward bulk aqueous phase and tails are hydrophobically contained inside micelles forming a hydrophobic core, as shown in Fig. 15.1. The main driving force for micelle formation is hydrophobic interaction. The micelles are very useful for extracting hydrophobic biomolecules and separating them from the bulk aqueous phase. Conventional extraction methods for biomolecules have several issues including high consumption of volatile organic solvents, usage of toxic and hazardous solvents, utilization of high temperature, long extraction time, high energy consumption, and risk of remaining solvent in final products (Amiri-Rigi et al. 2016). The micellar extraction technique is a substitute method to eliminate organic solvents from the process while offering several advantages such as large oil–water interface area, low interfacial tension, high solubilization capacity, optical transparency, and high stability. In addition, micellar extraction using biosurfactants has minimal impact on the environment.

General procedures of micellar extraction involve adding surfactants into an aqueous solution containing target solutes and then adjust the extraction conditions such as temperature or ionic strength to obtain two distinct phases in the solution. Centrifugation can be incorporated to hasten the phase separation process. Formation of a cloudy phase often occurs during micellar extraction. This clouding phenomenon is a characteristic of nonionic or neutral surfactant systems indicating that a stable micellar phase is forming and separating from the bulk aqueous phase. The temperature at which clouding starts to occur is known as cloud point temperature (CPT). The micellar extraction involving clouding portent is recognized as cloud point extraction. During the extraction process, target solutes in the aqueous phase are encapsulated in micelles or adsorbed on micelles. Then the micelles gather and form the micellar phase. After cloud point extraction, the solution usually separates into two distinct phases: a bulk aqueous phase with low concentrations of surfactants and target solutes, and a concentrated micellar phase with a high concentration of target solutes. The micellar phase can be separated easily for further processing. Therefore, cloud point extraction is an effective way to significantly reduce the processing volume.

Products obtained from micellar extraction are free of toxic organic solvents because water is usually the only solvent during the extraction. By utilizing safe biosurfactants, the extraction products can be used directly in various consumer products. Micellar extraction had been studied for solubilization, extraction, and pre-concentration of many biomolecules (More and Arya 2019; Racheva et al. 2018; Tan et al. 2017). There are several important factors that need to be considered in order to achieve high extraction efficiency. The factors are surfactant type, surfactant concentration, temperature, ionic strength, and solution pH.

Many surfactants have been used for micellar extraction including biosurfactants like rhamnolipids, saponins, and bile salts (Amiri-Rigi et al. 2016; Peng et al. 2017, 2016). Surfactants can be differentiated into four categories depending on charge: nonionic, cationic, anionic, and zwitterionic. Micellar extraction mostly utilizes nonionic surfactants because they exhibit clouding behavior. Dehydration of polyoxyethylene (POE) chains on the surfactants causes the clouding process. Thus, the length of POE chains directly affects the clouding behavior. Generally, surfactants with longer POE chains have a higher capacity for dehydration and higher CPT. Ionic surfactants are rarely used in micellar extraction due to their strong electrostatic repulsions among micelles that hinder the clouding process. Several approaches had been tested to induce clouding in ionic surfactant systems such as the addition of high concentration of salt to shield the electrostatic repulsions (Amin 2016), mixing both anionic and cationic surfactants to reduce the net surface charge of micelles (Kumar and Shyamala 2019), and addition of counterions to neutralize the surface charge of micelles (Kukusamude et al. 2016).

Small amount of ionic surfactants is sometimes used together with nonionic surfactants to form a mixed micellar system. The ionic surfactants introduce electrostatic interactions to the micellar system and help to enhance extraction efficiency (Torres et al. 2018). However, CPT of the mixed micellar system will be higher than the corresponding nonionic surfactant system due to the presence of electrostatic repulsions among the mixed micelles. Different micellar systems will have a different affinity toward various biomolecules. Therefore, the most suitable surfactant system should be identified to ensure high extraction efficiency.

Concentration of surfactant affects the micelle formation and their morphology. Concentration above CMC must be used to ensure the formation of stable micelles. However, too high concentration of surfactant will lead to higher CPT, formation of unstable micelles, and a large volume of micellar phase that affects subsequent processing (More and Arya 2019; Tan et al. 2017). The amount of surfactant used in micellar extraction is usually just enough to form the micellar phase to solubilize desired solutes. This is to save costs and avoid the negative impacts of high surfactant concentration.

Extraction temperature directly affects the dehydration of POE chains on surfactant molecules. When the temperature is increased, hydrogen bonds at surfactant tails gradually decreased (Soto-Ángeles et al. 2018). This reduces interactions between surfactant and water molecules causing hydrophobicity of the surfactant molecules to increase. This favors the formation of a stable micellar phase. However, high extraction temperature is reported to have negative impacts on micellar extraction. At a high temperature, the micellar phase has a smaller volume and is more viscous (Tan et al. 2017). This will hinder the separation process and subsequent processing. Some biomolecules may also solubilize back into bulk aqueous phase at a higher temperature because their hydrophilicity is increased. In addition, most biomolecules are sensitive to temperature and will denature above a certain temperature. This also leads to lower extraction efficiency at a high temperature. Therefore, micellar extraction is usually conducted at a temperature near CPT or ambient temperature, where complete phase separation can be achieved, save operation costs, and ensure high extraction efficiency.

Presence of electrolytes in a solution can enhance the dehydration of POE chains. Thus, the addition of salts can be used to promote micellar extraction by reducing CPT of the surfactant system. Presence of salts may also increase the formation of the micelles and increase the size of the micelles hydrophobic cores (Samal et al. 2017; Soto-Ángeles et al. 2018). This will increase the number of molecules which may be solubilized into the micellar medium. Furthermore, salts in an aqueous phase can exert a salting-out effect on biomolecules and favors their solubilization into the micellar phase. Nevertheless, the addition of salts at high concentrations will have negative impacts on micellar extraction. More impurities may be extracted and this will lower the purity of desired biomolecules in the extraction product (Murugesan and Iyyaswami 2017). Presence of salts in a micellar phase can reduce the attractive interactions between micelles and solutes, leading to lower extraction yield (Malpiedi et al. 2015). Therefore, the type and amount of salts to be used in micellar extraction must be chosen carefully to ensure high extraction efficiency. In some cases, the addition of salts may not be needed at all.

Solution pH usually does not have significant effects on nonionic surfactants. On the other hand, amphoteric biomolecules can be in a polar form or neutral form based on the solution pH. Since micellar extraction mostly utilizes nonionic micelles, the biomolecules should be maintained in their neutral form by adjusting to appropriate pH to favor their solubilization into the micellar phase. Besides that, biomolecules are sensitive to surrounding pH and these are easily denatured above the stable pH ranges. Thus, the pH for micellar extraction of biomolecules must be chosen carefully to promote their solubilization into the micellar phase without causing degradation of the biomolecules.

Micellar extraction had been carried out for extraction, pre-concentration, and separation of various biomolecules such as proteins, enzymes, phenolic compounds, and drugs. Micellar extraction can be easily combined with other separation techniques to enhance the recovery of biomolecules. Adsorption using various sorbents such as resin (Ribeiro et al. 2015), nanoparticles (Gao et al. 2015), and the natural sorbent (Cao et al. 2017) can be used to separate desired biomolecules from impurities to improve the recovery. Adsorption also can be used to simplify the separation of the micellar phase by skipping centrifugation, filtering, and cooling steps (Pirdadeh-Beiranvand et al. 2017). Micellar extraction is often combined with solid-phase extraction incorporating ultrasound, microwave, enzyme digestion, and other technologies to extract biomolecules from plants or organic samples (Murugesan and Iyyaswami 2017; Ng et al. 2018; Peng et al. 2017). The combined techniques can be one step or multistep extraction and separation methods that offer many advantages over conventional solid-phase extraction methods including higher yields, higher efficiency, shorter extraction time, and environmentally friendly.

Many studies had reported that the micellar extraction process is effective and efficient for the extraction of biomolecules. Nevertheless, most micellar extraction experiments are performed in a laboratory involving small volume batch extraction. Several researchers have designed in situ continuous countercurrent cloud point extraction system to extract various biomolecules (Racheva et al. 2018; Ritter et al. 2017). Important factors affecting the continuous micellar extraction such as the feed to ratio of solvent, flow rate, agitation speed, and capacity of column are studied by them. Several other researchers designed automated flow system based on cloud point extraction for pre-concentration of complex samples (Cherkashina et al. 2018; Davletbaeva et al. 2016). These automated systems are greener, faster, more sensitive, simpler, and cheaper than conventional methods.

Micellar extraction is a good alternative for the extraction of biomolecules. It is particularly effective at extracting hydrophobic biomolecules due to strong hydrophobic interactions. By replacing chemical surfactants with biosurfactants, the extraction process can be made greener and more environmentally friendly. Several parameters such as the concentration of surfactants, ionic strength, temperature, and solution pH can influence the extraction process. They have much potential for automation and large-scale continuous operation. Nevertheless, there are some lacks in current micellar extraction studies. Notably, there are very few kinetic studies on micellar extraction. Good understanding of mass transfer and kinetics during the extraction is very important to design a good extraction process. Another need is to perform more studies on a large-scale and continuous micellar extraction to ensure that it is suitable for industrial applications.

4 Reverse Micelle Extraction

When surfactants are dispersed in oil–water solutions, they tend to gather at the boundary area and are responsible to reduce the interfacial tension. They also form aggregates known as reverse micelles in the oil phase due to the self-assembly phenomenon. This allows solutes in an aqueous phase to be solubilized easily into the oil phase through encapsulation by the reverse micelles. The surfactant molecules in a reverse micelle arrange themselves with their hydrophilic head groups developing an aqueous core and their hydrophobic tails pointed outward to bulk organic phase as shown in Fig. 15.1. This particular formation allows them to solubilize water and various hydrophilic molecules. Thus, reverse micelle extraction has gained much attention from researchers to study its potential for the extraction of biomolecules. Many reverse micellar systems including those based on biosurfactants have been reported as an efficient method for extraction of proteins, enzymes, antibiotics, plants active compounds, and other biomolecules. Reverse micelle extraction flow chart is depicted in Fig. 15.2.

The extraction process based on reverse micelle has many advantages compared to the conventional liquid–liquid extraction method. Since this micelles extraction greatly enhances the solubilization of biomolecules, more organic solvents including those which normally unable to extract biomolecules can now be considered. This is considered as a safe organic solvent which is generally used for the extraction process. Reverse micelle extraction also mitigates the formation of stable emulsion problems which is frequently faced in conventional liquid–liquid extraction that hinders the separation process. Another main advantage of using reverse micelles is that structures and activities of biomolecules can often be preserved. Encapsulation of biomolecules inside reverse micelle cores helps to avoid their direct contact with the bulk organic phase and reduce their degradation. Besides that, reverse micelle extraction is highly selective, easy to operate, conducted under mild conditions (room temperature and atmospheric pressure), and fast process. It also has the potential for a large-scale and continuous operation.

Extraction process based on reverse micelle is a two-step procedure consisting of backward and forward extraction. Generally, reverse micelles are prepared by mixing surfactants in solvents (organic phase). Then forward extraction is performed by mixing the reverse micelle solution and feed aqueous segment for a certain amount of time. Target molecules transfer from an aqueous part into a reverse micellar segment during forward extraction mainly due to electrostatic interactions and

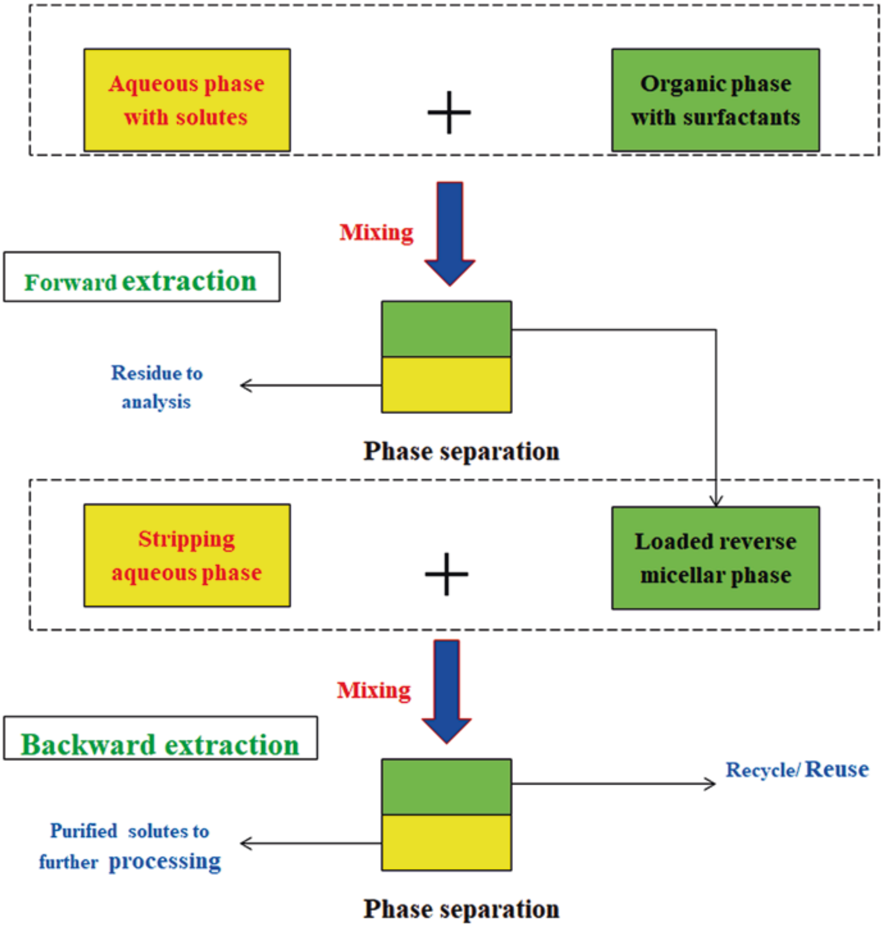

Fig. 15.2 Flow chart of the reverse micelle extraction process

hydrophobic interactions. The solution is left to separate into two immiscible phases after forward extraction. Centrifugation can be used to accelerate the phase separation process if needed. After complete phase separation, the reverse micellar phase is collected and mixed with another fresh aqueous phase to perform backward extraction. Generally, this extraction process is considered a difficult process as compared to forward extraction thus it usually takes a longer time. The reverse micelles are destabilized under appropriate extraction conditions so that target molecules in the reverse micelles can be unconfined into the aqueous part. Hence, after the mixing process, the solution is again left for phase separation. The aqueous phase containing the desired molecules is sent for further processing while the reverse micellar phase can be collected and reused. There are several important factors that need to be investigated when studying reverse micelle extraction. These factors are the type of surfactant, surfactant concentration, solution pH, ionic strength, feed concentration, and oil–water phase volume ratio.

As opposed to micellar extraction which mainly uses nonionic surfactants to extract neutral molecules, reverse micelle extraction is mostly conducted using ionic surfactants to extract oppositely charged molecules. The key driving power for the forward extraction process is due to the strong electrostatic contacts between solute charged particles and surfactant head groups. As expected, anionic surfactants like AOT are used to extract positively charged molecules while cationic surfactants like CTAB are used to extract negatively charged molecules. Nonionic surfactants are sometimes used for the extraction of molecules with neutral surface charge. In those cases, the solubilization process is mainly driven by hydrophobic interactions between nonionic reverse micelles and the solutes. Although hydrophobic interactions are weaker than electrostatic interactions, nonionic reverse micelles offer milder solubilization conditions that can be very helpful for protecting sensitive biomolecules from degradation during the extraction process. Zwitterionic surfactants are another type of surfactant that is rarely used in reverse micelle extraction. Their molecular structures consist of two closely located head groups with opposite charges separated by a short intercharge spacer. They are generally considered as neutral surfactants because the opposite charges on their head groups cancel each other out. However, they may show weak surface charges depending on the surrounding pH. Their micellization properties are in between nonionic and ionic surfactants.

Generally, zwitterionic and nonionic surfactants are sometimes added to ionic surfactants to form mixed reverse micelles. The neutral surfactants shield the head groups of ionic surfactants and reduce the electrostatic interactions. The synergistic effects will lead to considerably lower total CMC and enhance the solubilization of solutes into the reverse micellar phase. Several studies show that adding a low fraction of neutral surfactants significantly enhanced the extraction efficiencies of different proteins (Hemavathi et al. 2010; Mohamad-Aziz et al. 2019a). Nevertheless, a higher portion of neutral surfactants in a mixed reverse micellar system may cause precipitation and incomplete phase separation. Since the electrostatic interactions between ionic surfactants and solutes are also shielded by the neutral surfactants, the mixed reverse micelles can provide better protection for sensitive biomolecules compared to pure ionic reverse micelles.

In general, many surfactants and their combinations can be used for reverse micelle extraction. Over the past few decades, several biosurfactants such as rhamnolipids and sophorolipids had been tested for reverse micelle extraction of biomolecules (Chuo et al. 2019; Peng et al. 2014). Although electrostatic interactions are the main driving forces, other factors including hydrophobicity of surfactants, steric hindrance, and alkyl chain length also need to be considered in order to choose the most suitable reverse micellar system (Chen et al. 2017a; Garcia-Fonseca et al. 2016). The reverse micellar system should be able to achieve complete phase separation easily. Understanding the interactions between reverse micelles and biomolecules is crucial for the optimization of the extraction process.

When surfactant concentration continues to increase above its CMC, more reverse micelles will be formed rather than a substantial increase of reverse micelle size. This phenomenon can be explained based on Eq. (2):

$$\begin{aligned}&\text{Reverse micelle concentration}\\&\quad=\text{Surfactant concentration/Aggregation number}\end{aligned}\tag{15.2}$$

Aggregation number represents the molecules of the surfactant used to form one reverse micelle. The aggregation number of a reverse micellar system is mostly constant at surfactant concentrations near its CMC. Therefore, increasing the concentration of surfactants may directly enhance the reverse micelles amount as long as the concentration is not too high above its CMC. This permits the higher solutes to be extracted into the organic medium due to increased solubilization capacity. However, when the amount of reverse micelle becomes very high, they will collide with each other more easily and frequently. This will lead to deformation and destabilization of reverse micelles which will reduce the solubilization capacity (Peng et al. 2012). Micellar clustering also occurs at high surfactant concentrations and diminishes the total interfacial zone existing for extraction (Gaikaiwari et al. 2012b). Furthermore, there may be a size increase of reverse micelles when high surfactant concentration is used (Juang et al. 2012). This will cause the larger impurities to be extracted together during forward extraction (Gaikaiwari et al. 2012a). In general, surfactant concentration is an important parameter to be optimized so that maximum extraction yield can be achieved and surfactant usage can be reduced.

Due to the dominance of electrostatic interfaces in most of the extraction processes of reverse micelle, pH solution becomes a crucial factor for optimization purpose. Surface charges of amphoteric biomolecules always depend on their isoelectric point (pI) and surrounding pH. The biomolecules will possess a net positive surface charge if nearby pH is lesser than the value of their pI, total negative charge of the surface if the surrounding pH is higher than the value of their pI, and neutral surface charge if the surrounding pH is within their pI range. In addition, biomolecules are very sensitive to pH change which can denature effortlessly at a stable pH range. Besides affecting surface charges of solutes, solution pH also determines the ionic or nonionic forms of some biosurfactants based on their pKa value.

During forward extraction, the solution pH is adjusted so that the surfactant and target solute have opposite surface charges. It can increase the electrostatic attraction among them and promote solubilization of the solutes into the reverse micellar stage. For example, bovine serum albumin (BSA) with pI 4.7, forward extraction is conducted at solution pH 4 so that BSA molecules possess net positive surface charge and can be attracted easily to anionic AOT reverse micelles (Pawar et al. 2017). In a mixture of biomolecules with substantially different pI values, solution pH can be adjusted so that forward extraction only favors certain biomolecules. This is useful for separating desired biomolecules from impurities. As opposed to forward extraction, the solution pH in backward extraction is usually adjusted so that the surfactant and target solute have the same surface charges. As a result, the solutes will be expelled from reverse micelles into aqueous stripping phase due to robust electrostatic repulsions between surfactant and solute molecules. Nevertheless, very strong electrostatic interactions may cause unfavorable situations during reverse micelle extraction such as structural change of proteins, precipitation, and micellar clustering (Hemavathi et al. 2010; Peng et al. 2012). Thus, solution pH must be controlled carefully to maximize extraction efficiency without causing denaturation of biomolecules.

In some cases, the basis of adjusting pH according to pI may not be applicable due to the dominance of other interactions. Peng et al. (2016) reported that cellulase pI is lower than the pH of forward extraction when using mixed anionic rhamnolipids and nonionic Tween surfactants for the extraction. It is explained that the solubilization of cellulase into the reverse micelles are mostly affected by hydrophobic interactions instead of electrostatic interactions. The effects of pH are also less significant if neutral reverse micellar systems are used because electrostatic relations are not the main driving powers. In those cases, pH solution is usually attuned so that biomolecules have a neutral surface charge to promote their solubilization into nonionic reverse micelles.

Some surfactant solutions require a certain minimum amount of salts to form stable reverse micelles. NaCl and KCl are among the commonly added salts during reverse micelle extraction. The electrolytes in solution will be attracted to oppositely charged surfactant head groups and reduce electrostatic forces exerted by the head groups. Weaker electrostatic repulsions between the head groups allow surfactants to be packed more closely in reverse micelles. As a result, smaller and more stable reverse micelles are formed. Besides that, salts reduce the electrostatic attractions between solutes and reverse micelles, thus affecting the solubilization of solutes. The effects of salts are exploited in both backward and forward extraction to improve the final extraction yield.

Less amount of salt is usually mixed during forward extraction to promote the formation of functional and stable reverse micelles. Salt concentration can also be adjusted to control the size of the reverse micelles, thus larger impurities will not be extracted together. The type of salt added can affect solubilization differently. During forward extraction, kosmotropic salts such as NaCl are usually added for their salting out effects. Kosmotropic salts are able to reduce hydrophilicity of solutes and increase their hydrophobic interactions. Therefore, kosmotropic salts can enhance solubilization of solutes from an aqueous part into an organic part. Nevertheless, more salt concentration will affect forward extraction negatively. It may weaken electrostatic interactions between solutes and reverse micelles too much and reduce forward extraction yield. The reverse micelles may also become too small to encapsulate the solutes and hinder the solubilization process.

The concentration of salt added during backward extraction is usually higher than the one added during preceding forward extraction. The purpose is to greatly reduce electrostatic interactions between reveres micelles and solutes so that the solutes can be released into aqueous stripping phase. Size reduction of reverse micelles also helps to squeeze out the solutes and enhance their transfer into an aqueous phase. Salts of Chaotropic (KBr and KCl) are commonly chosen for their salting in effects. They weaken the hydrophobic interactions and destabilize reverse micelles, thus leading to improved solute recovery. However, a high concentration of salt may affect the development of electrostatic attraction around reverse micelles and hinders the release of encapsulated solutes (Peng et al. 2012). Besides that, sensitive biomolecules undergo conformational alteration when small molecules being squeezed out from the reverse micelles (Gaikaiwari et al. 2012a). It is important to understand the interactions between salts and biomolecules in order to choose the most suitable salt to be added during reverse micelle extraction. For example, Na, Ca, and Zn cations were found to have inhibitory effects on yeast laccase while K, Mg, and phosphate cations show activating or stabilizing effects (Mazı et al. 2012). High concentration of salts often causes denaturation of biomolecules and thus must be avoided.

Volume ratio between organic and aqueous segments is another factor that should be considered. For solutes that are insoluble in an organic phase, their solubilization depends on encapsulation by reverse micelles. The reverse micellar phase has its capacity to solubilize the solutes. Extraction capacity could be constant when a fixed amount of micelles segment is available during the reverse micelles process. During forward extraction, aqueous phase volume increases while maintaining a fixed organic part, the volume will significantly reduce the extraction efficiency (Juang et al. 2012). This is due to limited solubilization capacity provided by the reverse micellar phase to solubilize the increased amount of solutes in the feed aqueous phase. In addition, the solution becomes turbid when the aqueous phase volume is much larger than the organic phase (Hemavathi et al. 2010). This may indicate the formation of other microemulsion systems. As expected, increasing the organic part value while maintaining aqueous part of volume fixed will improve forward extraction efficiency owing to an improved number of available reverse micelles to solubilize the solutes (Yu et al. 2003). However, more impurities may be extracted together due to the higher solubilization capacity of the reverse micellar phase. Final volume reduction can be achieved by using a smaller volume of aqueous stripping phase relative to the reverse micellar phase (Gaikaiwari et al. 2012b). This is useful to obtain concentrated products for easier subsequent processing. However, longer contact time is needed to obtain a high recovery. Very low stripping phase to organic phase volume ratio should be avoided due to difficulty to achieve complete phase separation.

Initial concentration of target solute in the feed phase will affect the extraction efficiency. At fixed volumes, a higher initial concentration of solute is capable to offer greater driving power for the extraction but the efficiency of solute transfer is found maximum at the lower initial concentration of solute (Mohd-Setapar et al. 2012). Lower overall extraction percentage is obtained at high initial solute concentration because only a portion of the solutes can be extracted by the partial amount of available reverse micelles. Besides that, a high concentration of biomolecules such as protein and enzyme in the solution can cause the development of emulsion throughout the extraction process. Process of reverse micelles having low solubilization capacity requires a high feed solution of diluted aqueous media to elude emulsification. Therefore, crude extracts of biomolecules usually need to be diluted before extraction to ensure a smooth extraction process (Wan et al. 2016).

Besides optimizing various extraction parameters, a kinetic study is another important aspect to further improve a reverse micelle extraction. Kinetic models are often developed by measuring the concentration of solute over the duration of a reverse micelle extraction. These models are useful for predicting mass transfer coefficients, portioning of solutes, and rate-limiting steps during the extraction. The most popular basis used to describe reverse micelle extraction is the two-film theory. According to the theory, solutes will pass through three main regions during the forward and backward extraction. These regions are aqueous film, liquid–liquid interface, and organic film, with each of them presenting a resistant to the mass transfer process. Therefore, the rate-limiting steps are identified among diffusion in an aqueous phase, diffusion in an organic phase, and solute solubilization or release at the liquid–liquid interface. The model development starts from a simple mass balance and rate transfer equation. Several common assumptions made for the modeling procedures include no reaction occurred, negligible phase volume change, a steady state extraction, and the system is in equilibrium. The final form of kinetic equations may differ between researchers depending on the mathematical manipulations and simplifications involved. Nonetheless, they should still have a similar mathematical structure. Equations (3) and (4) show the final form of kinetic models obtained by Nishiki et al. (1998) describing forward and backward extraction respectively.

$$\ln\left|1-\left(1+1/m_{\mathrm{f}}\right)\left(C_{\mathrm{org}}/C_{\mathrm{aq,i}}\right)\right|=-\left(A/V\right)\left(1+1/m_{\mathrm{f}}\right)K_{\mathrm{f}}t \tag{15.3}$$

$$\ln\left|1-\left(1+m_{\mathrm{b}}\right)\left(C_{\mathrm{aq}}/C_{\mathrm{org,i}}\right)\right|=-\left(A/V\right)\left(1+m_{\mathrm{b}}\right)K_{\mathrm{b}}t \tag{15.4}$$

where m_{f} is forward extraction equilibrium partition coefficient, m_{b} is backward extraction equilibrium partition coefficient, C_{org} represents organic phase concentration of solute, C_{aq} denotes aqueous phase concentration of solute, $C_{\mathrm{aq,i}}$ represents aqueous phase initial concentration of solute, $C_{\mathrm{org,i}}$ represents organic phase initial concentration of solute, A is the interfacial area (usually unknown), V is aqueous phase volume, K_{f} represents the coefficient of overall mass transfer in forward extraction (including the two diffusion and the interfacial resistances), K_{b} is coefficient of overall mass transfer in backward extraction, and t is time. The value of the overall mass transfer coefficient can be calculated by making ln versus time plots. By comparing K values at different extraction conditions (different surfactant concentration or solution pH) and making corresponding linear plots, coefficients of individual mass transfer which can be assessed. The rate-limiting steps can then be identified by comparing those individual mass transfer coefficients.

Theoretically, during forward extraction with excess reverse micelles available compared to solutes, the solubilization process at the liquid–liquid interface is instantaneous and its resistance can be neglected. Thus, diffusion of aqueous and organic phase is the main limiting rate process during forward extraction. The rate of K_b is always lesser than K_f indicates that forward extraction is an easier process compared to backward extraction. The resistance at the liquid–liquid interface becomes dominant during backward extraction because the process requires the destabilization of reverse micelles to release the encapsulated solutes. Thus, the releasing of solutes at the liquid–liquid interface is always identified as the main rate limiting steps of backward extraction. Besides the two-film theory, researchers also used other basis such as association reaction (Xun et al. 2001), ion exchange mechanism (Cardoso et al. 1999; Pandit and Basu 2004), reversible pseudo-first order reaction (Cadar et al. 2018), and adsorption model to describe the kinetics of reverse micelle extraction. Langmuir isotherm and Freundlich isotherm are reported to provide good fitting of reverse micelle extraction depending on used surfactant concentration (Mohamad-Aziz et al. 2019b). Other proposed models are also useful for identifying the main resistance and predicting the extraction yield. In addition, all kinetic studies show that backward extraction is a harder process. Understanding the kinetics is very helpful for finding potential methods to improve the efficiency of extraction and designing the best extraction system.

Reverse micelles process has been proven to be a good extraction method for biomolecules. Nevertheless, several improvements need to be considered to make it more competitive with many other separation techniques available. Difficulty of backward extraction due to strong attractive interactions between solutes and reverse micelles may lead to low recovery or long extraction time. Therefore, various approaches had been suggested to enhance backward extraction efficiency. Addition of alcohol as a cosolvent is often effective to increase the recovery yield (Peng et al. 2012). Alcohols can penetrate into reverse micelles to destabilize them and reduce the attractive interactions between solutes and reverse micelles. Alcohols with shorter chains have better penetrating ability than long chain alcohols and thus are more effective at enhancing recovery yield (Pawar et al. 2017). Addition of oppositely charged surfactant during backward extraction can neutralize the charge of reverse micelles and causes them to collapse, releasing the encapsulated solutes into the stripping phase (Imm and Kim 2009). This method will prevent reuse of the reverse micellar phase due to the difficulty to separate the two oppositely charged surfactants. Higher temperature increases the frequency of collisions between reverse micelles and phase interface (Guo et al. 2015). Reverse micelles are also destabilized easier at higher temperatures. Thus conducting backward extraction at higher temperatures can enhance the recovery yield. Nonetheless, the temperature must not be too high to avoid denaturation of heat-sensitive biomolecules.

Reverse micelle process experiments are mostly carried out in the laboratory at a small scale with less sample size involved. A study reported that when the ratio of phase volume is maintained to 1:1, the same purification and recovery fold will be attained when sample volumes are increased (Imm and Kim 2009). Another study showed that more than 80% activity recovery of bromelain is obtained with 5 L extraction solution (Hebbar et al. 2011). Nevertheless, more scale-up experiments are essential to confirm the applicability of the extraction of reverse micelle at an industrial scale. Since micellization is a reversible process, the reverse micellar phase obtained after backward extraction can be collected and reused in forward extraction again. Although, the efficacy of extraction may not be as high as the fresh reverse micellar segment due to high impurities are predictable to store after every run, it helps to reduce chemical costs. Several studies showed extraction efficiencies only dropped slightly for at least the first recycle of reverse micellar phase (Hemavathi et al. 2010; Peng et al. 2012). The extraction efficiencies usually dropped significantly after the third recycle (Peng et al. 2012; Zhang et al. 2016).

Continuous operation is another aspect that is desired to be considered to make reverse micelle extraction more suitable for industrial applications. To reduce the cost and process automation, continuous operation can be conducted. Reverse micelle process is a type of liquid–liquid extraction process. Due to the surfactant present in the system, this process is entirely different from the conventional liquid–liquid extraction at an optimum concentration. Kinetics and physical properties are important in choosing and designing the extraction equipment. Some equipment had been proposed for the continuous reverse micelle process over the past few decades. For the extraction of protein, reverse micelle extraction was employed and used centrifugal extractor to avoid the emulsion formation and confirm short residence time (Lu et al. 1998). The extraction efficiency is affected by flow rate, phase volume ratio, and speed of the rotor. When the high speed of the rotor is used, the purity of the phase increased as well as the dwelling time. Raining bucket and Graesser contactor are proposed for biotechnology application as it offers solutions to several key drawbacks in other contactors like emulsion formation, low interfacial area, and stagnant droplets formation (Jarudilokkul et al. 2000). Although high extraction yield can be obtained, the Graesser contactor is not promising in case of backward extraction owing to extensive settling time (Jarudilokkul and Stuckey 2001). Packed column is one of the most commonly used equipment and is also suggested for reverse micelle extraction (Hasmann et al. 2007; Nishii et al. 1999). The flow rates and phase ratio greatly affect extraction efficiency. Spray column is the other commonly used equipment that had been suggested (Lye et al. 1996). It does not require high investment and operational costs but a high number of circulations may be required during backward extraction (Han et al. 1994). Other extraction equipment suggested includes a rotating disc contractor that can provide better mixing to increase the interfacial area for mass transfer (Carneiro-da-Cunha et al. 1996) and pulsed caps column that offers a gentler mixing mechanism to avoid emulsion formation (Fileti et al. 2010; Rodrigues and Tambourgi 2001). However, there is a lack of new studies in recent years. Continuous reverse micelle extraction using state-of-the-art equipment and design technology is a largely unexplored area thus more researches about this topic is highly encouraged.

Reverse micelle process had been used for removal or pre-concentration of various biomolecules. It has various advantages such as easy to operation, maximum extraction yield, high selectivity, optimum operating conditions, as well as scale-up potential, recycling of solvents, and continuous operation. This extraction method is comparatively superior to a conventional liquid–liquid extraction process in many ways such as faster extraction time, protein activities preservation, formation of reduced emulsion, and safe use of solvents. It can be combined with other separation techniques such as ultrasound to further enhance the extraction efficiency. Due to increasing environmental awareness, biosurfactants had been investigated as the replacement of chemical surfactants. These biosurfactants reverse micellar systems significantly reduce environmental impacts, produce safer products, and potentially give better extraction performance compared to chemical surfactants.

5 Biosurfactants

Nowadays there is a general trend to synthesized biotechnology materials chemically due to many reasons such as demand for a safer or environmental friendly process, manufacturing the renewable resources increases, method of conventional processing replacement with new generation biotechnological process, and manufacture of innovative biotechnology products with a novel feature or improved performance as compared to conventional counterparts (Muller et al. 2012). In this regard, biosurfactants have received great attention as the replacement of chemical surfactants. Biosurfactants refer to the surfactants obtained from natural sources, mainly microbial origins. Nevertheless, with today's technology, some simple biosurfactants can be synthesized in the laboratory. Various types of biosurfactants had been discovered to date, including glycolipids, lipopeptides, phospholipids, polysaccharide protein, polymeric surfactants, particulate surfactants, and fatty acids. They have widely different chemical structures and physicochemical properties. In general, low molecular weight biosurfactants possess better surface activities while biosurfactants with high molecular weight which are also recognized as bioemulsifiers and its better in stabilizing emulsions (Varjani and Upasani 2017). Biosurfactants also have a wide range of hydrophilic–lipophilic balance (HLB) values. Biosurfactants with low HLB are better at stabilizing water-in-oil emulsion while those with high HLB are good for stabilizing oil-in-water emulsion. Therefore, biosurfactants can be used to solubilize many substances with low solubility. Diversity of biosurfactants makes them attractive for many applications like detergent, pharmaceuticals, cosmetics, food, environmental, and petroleum. The benefits of biosurfactants are extraordinary biodegradability, high specificity, less toxic, biocompatible, environmentally friendly, and stable at extreme conditions (pH, temperature, and salinity). They can be formed from renewable and cheap resources such as agriculture wastes. They can also be specifically tailored to have a higher binding affinity toward specific compounds (Sun et al. 2018). This is very useful for enhancing solubilization and extraction of specific solutes. Among the wide variety of biosurfactants, several had been studied for micelle-based extraction as discussed in the following subsections.

5.1 Rhamnolipids

Rhamnolipids belong to glycolipids biosurfactants and are the most extensively studied biosurfactants. Their general molecular structure consists of one or two rhamnose groups and one or two hydrophobic hydrocarbon tails. These are mostly made by *Pseudomonas aeruginosa* strains. Microbial rhamnolipids are typically formed as mixtures of rhamnolipids homologs. Compositions of the rhamnolipids mixtures are mainly affected by microbial strains, carbon source, and culture conditions. Rhamnolipids produced using different substrates have different homologs compositions, characteristics, micellization properties, and potential applications (Guo and Hu 2014). For example, Zhao et al. (2020) reported that rhamnolipids produced using glucose as a substrate have a CMC of 50 mg/L and are capable to diminish water surface tension to 26 mN/m. On the other hand, rhamnolipids produced using soybean oil have a CMC of 60 mg/L and are capable to diminish water surface tension to 28 mN/m. In addition, glucose-based rhamnolipids show improved surface as well as a good antimicrobial activity while soybean oil-based rhamnolipids exhibit better emulsifying activity.

Crude rhamnolipids can be used directly to reduce costs. Nevertheless, they are usually isolated to obtain rhamnolipids with more consistent characteristics. Among the homologs, mono-rhamnolipids and di-rhamnolipids are the most commonly separated rhamnolipids. Mono-rhamnolipids have one rhamnose group on each molecule while di-rhamnolipids have two rhamnose groups. They have low CMC, often reported to be lower than 100 mg/L, with di-rhamnolipids usually having lower CMC than mono-rhamnolipids. This indicates that di-rhamnolipids have better surface activity compared to mono-rhamnolipids. A study showed that mono-rhamnolipids have a higher mass transfer rate while di-rhamnolipids have a higher solubilizing capacity for 17α-ethinylestradiol (Guo and Hu 2014). The study also showed that micelle size increases and shape change is greater for di-rhamnolipids after solubilization.

Rhamnolipids can ease water surface tension to around 27 mN/m and oil–water interfacial tension to less than 1 mN/m. Besides that, they have low toxicity, high solubilization of water, good biodegradability, and good environmental compatibility (Peng et al. 2014). They also possess antimicrobial, antiproliferative, and other biological activities. Rhamnolipids are well-tolerated by human skin so they can be useful in dermal drug delivery (Muller et al. 2017). They can significantly enhance solubilization and biodegradation of PAHs (Czaplicka and Chmielarz 2009; Posada-Baquero et al. 2019). With their many outstanding properties, it is no wonder that rhamnolipids gained a lot of attractions in recent years for applications in industries including agriculture, bioremediation, cosmetics, enhanced oil recovery, food, and pharmaceuticals (Madrid et al. 2020).

Rhamnolipids are the most frequently studied biosurfactants in micelle-based extraction owing to their good micellization properties. Rhamnolipids are anionic biosurfactants with pKa range of 4.8–5.6. Thus, they are a good candidate to replace chemical surfactants such as AOT and SDS in reverse micelle extraction. For example, rhamnolipids in isooctane/n-hexanol reverse micellar phase had been used for the extraction of laccase from *Coriolus versicolor* crude extract (Peng et al. 2012). Through optimization of important factors, up to 92.7% activity regaining and 4.79 purification were achieved. These values are higher than those obtained when using AOT and Tween 80 for the same reverse micelle process. In addition, the total amount of rhamnolipids used is significantly lower than the chemical surfactants. The rhamnolipids reverse micellar phase was also recycled and reused three times with an acceptable drop in extraction performance. Later, similar rhamnolipids were used in the reverse micellar system for a simultaneous extraction of extracellular manganese peroxidase and lignin peroxidase from *Phanerochaete chrysosporium* (Peng et al. 2014). Highest activity recovery obtained after process optimization is 93.5% for lignin peroxidase and 88.8% for manganese peroxidase. Lignin peroxidase has higher activity recovery due to its smaller size that allows it to be encapsulated and easily released using reverse micelles. Mixed rhamnolipids and Tween reverse micellar systems were investigated for the extraction of cellulase (Peng et al. 2016). Addition of nonionic surfactants can increase flexibility in terms of physicochemical properties of the reverse micellar system. The study showed that the chain length of Tween surfactants affected the sensitivity of the systems to solution pH and temperature. Rhamnolipids/Tween 80 mixed reverse micellar system was reported as the most efficient and able to provide purer cellulose than shorter chain Tween surfactants.

Rhamnolipids also take a role in the development of environmentally friendly analytical methods. Haeri (2016) designed biosorption-based dispersive liquid–liquid microextraction (bio-DLLME) using nano-aggregates formed by rhamnolipids as a pre-concentration method. The process involves mixing rhamnolipids and organic solvents like methanol into the samples, solubilization of analytes into micelles, and phase separation for subsequent steps. Methanol is used to promote the dispersion of rhamnolipids in an aqueous phase and induce clouding. However, a high volume of methanol increases the water solubility of rhamnolipids and solutes, which leads to incomplete phase separation. Mono-rhamnolipids are found to give better extraction performance than di-rhamnolipids because mono-rhamnolipids can form a more stable micellar phase due to their higher hydrophobicity (Haeri et al. 2017). Bio-DLLME greatly enhances extraction from liquid samples and solid samples. It is rapid, environmentally friendly, and uses nontoxic organic solvents. It can be combined with other techniques like adsorption or solid phase extraction as a two-step pre-concentration to improve extraction recovery and sample clean up. Several extraction recoveries reported using bio-DLLME are 98–103% for bisphenol A (Haeri 2016), 104% for methamphetamine (Haeri et al. 2017), and 96–104% for paracetamol (Abbasi et al. 2019).

Rhamnolipids micelles can solubilize various organic compounds, thus, they are used to extract organic contaminants. Madrid et al. (2020) reported that rhamnolipids can extract hydrophobic organic compounds including nonylphenol, pyrene, and phenanthrene better than water. Li et al. (2015) observed that rhamnolipids form liposome-like vesicles at pH < 6, lamellar or lipid aggregate at pH 6–6.6, and micelle at pH > 6.8. Increasing the pH allows more organic compounds to be solubilized. In addition, rhamnolipids promote biodegradation of the organic contaminants (Posada-Baquero et al. 2019). Many studies had shown that rhamnolipids are a good alternative to chemical surfactants for solubilization, extraction, and separation of biomolecules.

5.2 Sophorolipids

Sophorolipids are glycolipids biosurfactants and were the first microbial surfactant available in the market (Muller et al. 2012). Their general structure consists of a sophorose head group linked by the hydroxyl group through a glycosidic bond or hydroxylated fatty acid. These are usually formed from *Candida bombicola* strain which is a nonpathogenic yeast. The crude sophorolipids produced are a mixture of different variants of sophorolipids. Raw materials nature, yeast strain, and fermentation conditions affect the composition of sophorolipids produced. Commonly, surfactants like sophorolipids are categorized into two major sets namely acidic (anionic) and lactonic form (nonionic). It depends on the ring or opened structure. Lactonic sophorolipids showed superior surface tension, good antimicrobial actions, and reducing properties. Contrarily, the acidic nature of sophorolipids has improved solubility and foaming capacity as well as free carboxylic acid end (Shah et al. 2005).

Sophorolipids have good surfactant properties. Their CMC is between 11 and 250 mg/L, which magnitude is lesser than chemical surfactants. These have the capacity to diminish surface tension of water to 30–40 mN/m and water/n-heptane interfacial tension to less than 1 mN/m. Sophorolipids are more hydrophobic surfactants (Nguyen et al. 2010) that may dissolve polar solvents greatly such as methanol, ethanol, and ethyl acetate (Bluth et al. 2006; Hu and Ju 2001). Nevertheless, they can also dissolve well in water at pH 6 (Van Bogaert et al. 2011). Nevertheless, these are not appropriate for long run storage at pH above 7.5. Sophorolipids can act as fewer foaming surfactants (Hirata et al. 2009) and better wetting representatives (Develter and Lauryssen 2010). They also have good antimicrobial, antiradical, anti-inflammatory, and anti-elastasic properties (Van Bogaert et al. 2007). Due to their many interesting properties, sophorolipids have found applications in cosmetic, pharmaceutical, detergent, microorganism control, and nanoparticle production.

Good micellization properties of sophorolipids allow them to be applied in micelle-based extraction. A sophorolipids/isooctane reverse micellar system had been studied for the extraction of amoxicillin and erythromycin (Chuo et al. 2018). The study showed that significantly high forward extraction efficiency was achieved at much lower sophorolipids concentration as compared to AOT and Tween. The extraction efficiency of erythromycin is higher than amoxicillin probably due to the differences of antibiotics' structures that lead to the antibiotics having different interactions with the sophorolipids reverse micelles. A follow-up study revealed that the reverse micelle extraction process is rapid, where mass transfer equilibrium was achieved within 200 s (Chuo et al. 2019). Kinetics of the extraction and rate limiting steps were also investigated in the study. Sophorolipids show respectable prospective as alternatives to chemical-based surfactants in the reverse micelle process.

5.3 Lipopeptides

Lipopeptides are another class of biosurfactants produced by various microbes. Their molecular structures are commonly composed of a peptide group and a fatty acid with corresponding structural isomers. A notable lipopeptides biosurfactant is the surfactin. Surfactins are anionic biosurfactants mainly produced by *Bacillus subtilis* strains. Temperature, dissolved oxygen, foaming, pH, and broth media are some of the important factors during surfactin production (Chen et al. 2015; Ines and Dhouha 2015). General structure of surfactins contains a cyclic peptide group with 7 amino acid peptides and a hydrophobic hydrocarbon tail. They have very low CMC, around 23–25 mg/L or 0.01 mM, and can reduce water surface tension to 27 mN/m (Chen et al. 2015). It shows stability in a varied range of pH and temperature. They also show antibacterial, antiviral, and antifungal activity. Thus, they have great potential in many industrial uses like pharmaceuticals, improved oil recovery, and bioremediation (Kong et al. 2018). Their micellization behavior and interactions with various biomolecules had been studied (Zdziennicka et al. 2018; Zhang and Li 2018). Mixed micellar systems of surfactins and some anionic sodium cetyl benzene-sulfonate surfactants were studied (Kong et al. 2018). The mixed surfactants can have synergistic effects and different micellar size.

Amphisin is a type of cyclic lipopeptides and had been studied for the solubilization of BSA (Janek et al. 2018). The amphisin was metal chelated to alter their surface charge and conformation so that the self-assembly process can be enhanced. Stable lipopeptide–metal complexes were formed with different divalent metal ions to neutralize negative charge on amphisin and reduce electrostatic repulsions to enhance micelle formation. The CMC was lower and better BSA encapsulation was achieved. Taniguchi et al. (2019) tested two novel lipopeptide-based surfactants for solubilization of membrane protein photosystem I. The lipopeptides can solubilize the membrane protein without denaturation. These studies show that lipopeptides can form micellar systems for solubilization and extraction of biomolecules.

5.4 Saponins

Nonionic biosurfactants like saponins (plant-derived) which can be achieved from different portions of plants like flowers, leaves, bark, stems, as well as roots. Many extraction methods such as the conventional organic solvent process, supercritical CO_2 extraction, ultrasound, and microwave assisted extraction may be used to extract saponins from plant materials (Guo et al. 2018; Singh and Kaur 2018). Saponins are high molecular weight biosurfactants and their structures can be rather complex. General structures of saponins consist of a hydrophobic steroid aglycone or triterpene and one or more hydrophilic sugar chains. Saponins are mainly divided into three types based on their aglycone structures: triterpenoid saponins, steroid saponins, and steroidal–glycoalkaloid saponins. They differ in the number of carbon in their aglycone (30 carbons for triterpene and 27 carbons in steroid). Saponins with one sugar chain attached to their aglycone are known as monodesmosides while saponins with two sugar chains attached to aglycone are called bidesmosides. Likewise, tridesmosides have three sugar chains attached to their aglycones. CMC of Saponins can range from 0.11 to 1.81 g/L (Yu and He 2018) due to their wide structural variety. Saponins have the capacity to diminish water surface tension to 32–37 mN/m (Guo et al. 2018). Their properties include micelle forming, emulsifying, foaming, antimicrobial, antioxidant, insecticidal, and molluscicidal. They also have great potential for pharmaceutical applications because they are safe and able to enhance the solubilization of insoluble drugs (Dai et al. 2015). Besides that, they have wide applications in cleansers, beverages, and cosmetics (Liu et al. 2017).

Since saponins are nonionic surfactants that can form micelles, they can be used in micellar extraction. A simulation experiment was carried out to examine the solubilization of saikosaponin by ginsenoside (Dai et al. 2012). The interesting observation is that ginsenoside formed the main aggregates at low saikosaponin concentration while saikosaponin formed the main aggregates at high saikosaponin concentration. Mixed micelles were formed at intermediate saikosaponin concentration. A saponin/glycerol micellar system was studied for lycopene extraction from tomato waste (Amiri-Rigi et al. 2016). The sample was pretreated with ultrasound followed by an enzyme. The final extraction yield after optimization was 39%. Other studies also showed that saponins are able to solubilize more organic compounds than chemical surfactants (Zhou et al. 2011). They can effectively remove hydrophobic organic compounds, dyes, and heavy metals from soil and water (Liu et al. 2017; Samal et al. 2017). Saponins are widely available in plants and they can be easily extracted at a low cost, thus, they have better mass production capability compared to microbial-based biosurfactants. They can also be synthesized through enzymes and biochemical pathways. Saponins have good potential to replace chemical surfactants in many applications including micellar-based extraction.

5.5 *Other Biosurfactants*

Phosphocholines are phospholipid-based zwitterionic biosurfactants that are good for solubilizing membrane proteins. Wang et al. (2015) tested three phosphocholines of different tail lengths (12–16) for the solubilization of bacteriorhodopsin. Phosphocholines with intermediate chain length are most effective at solubilization. Phosphocholines with longer chain lengths have the strongest stabilization capacity but negligible solubilization at low concentration. Phosphocholines provide mild solubilization conditions to preserve bacteriorhodopsin structure. On the other hand, SDS and CTAB cause denaturation while Brij-35 has negligible solubilization of bacteriorhodopsin.

Bile salts are important amphiphilic molecules synthesized by livers. They are used to solubilize nonpolar complexes such as cholesterol, fatty acids, and vitamins. The bile salts structures are quite dissimilar from conventional surfactant molecules. Bile salts are a derivative of cholic acid and are based on the hydrophobic tetracyclic steroid ring system. The steroidal skeletal is marginally curved, with hydrophilic groups attached to the concave side, hydrophobic methyl groups attached to the convex side, and a carboxylated group (acidic group) attached to the top of the steroidal group (Peng et al. 2017). Bile salts are differentiated based on the position and number of –OH groups, as well as conjugated amino acid on the acidic groups. Due to their unique structure, bile salts have a hydrophobic side and a hydrophilic side instead of a conventional surfactant's hydrophilic head and a hydrophobic tail. Therefore, they have different micellization behavior than conventional surfactants. They show two stages of micellization when their concentration in solution is increased. First, they form smaller aggregates (multimers) mainly due to hydrophobic interactions, and then they form stable micelles mainly through hydrogen bonding. Madenci and Egelhaaf (2010) presented a detailed review of the micellization behavior of bile salts. Bile salts have many potential applications in pharmaceuticals, cosmetics, analytical science, and separation process.

Sodium salt of hyodeoxycholic acid was used for micellar extraction of gingerols, zingiberone, and shogaol from ginger (Peng et al. 2017). Ultrasound and microwave were incorporated in the micellar extraction to improve the yield. Microwave-assisted micellar extraction with 87–103% recovery was better than ultrasound-assisted micellar extraction in terms of yield and extraction time. Nevertheless, both methods were better than conventional solvent extraction. Another study used sodium deoxycholate and sodium cholate for solubilization of 2,4,6-trichlorophenol (Zeng et al. 2013). The solubilization was described using the allocation process and partition coefficients were calculated. The bile salts were able to solubilize trichlorophenol well.

There are still many other types of biosurfactants rarely studied for the solubilization of organic compounds (Czaplicka and Chmielarz 2009; Sun et al. 2018). More researches are encouraged to discover new biosurfactants that can be used to replace chemical surfactants in micellar-based extraction.

5.6 Limitations

The key limitation preventing a broader use of biosurfactants is their maximum production costs due to low production scale and low production efficiency. Production of biosurfactants usually begins from screening the producing microorganism, preparing suitable culture, biosynthesis of biosurfactants, biosurfactant extraction, purification, and characterization. Raw materials are generally considered to account for 10–30% of total production costs for biotechnological processes. On the other hand, downstream processing generally contributes to 60% of total production costs. Difficulty in separating biosurfactant homologs is another issue. Reducing the costs from each segment of biosurfactant production can bring down their price so that they can be more competitive economically. For the screening step, new producing strains had been continuously discovered to produce biosurfactants (Ma et al. 2012; Price et al. 2012). Strain modification and genetic engineering are also used to produce microorganisms that give high biosurfactant yield (Wu et al. 2019). Cheap substrates such as agricultural wastes and industrial residues are used for biosurfactant production to reduce raw material costs (Felse et al. 2007; Jiang et al. 2020; Yang et al. 2012). Optimization of the fermentation process by adjusting the important factors including temperature, pH, dissolved oxygen, and agitation is required to improve biosurfactant production (Varjani and Upasani 2017). Design of experiment strategy and statistical analysis like response surface methodology should be applied to optimize the fermentation process. Foaming is the main hindrance that reduces biosurfactant yield during fermentation, thus, a foam control strategy must be applied. Many downstream processing strategies had been studied for easier separation and purification of biosurfactants from crude fermentation broth. These strategies include in situ separation, membrane filtration, solvent extraction, foam fractionation, and adsorption (Chen et al. 2015; Liu et al. 2019). In addition, large-scale biosurfactant production is crucial to make them more competitive economically.

Biosurfactants showed good results for the extraction of biomolecules. However, there is a lack of detailed investigation on the mechanism of interactions between biosurfactants and biomolecules such as how the biomolecules are adsorbed and the localization of biomolecules in the micelles or reverse micelles. Micellization of biosurfactants can be studied in the laboratory through measurements of density, viscosity, conductivity, fluorescence intensity, and surface tension. Computer simulation like DPD can be used to study micellization and the interactions involved. These fundamental studies allow more understanding of micellization behaviors and are useful to determine their potential applications as well as to estimate their extraction efficiency.

6 Scope, Approach, and Applications

Nano-micelle-based extraction has great efficiency and potential for separation of biomolecules. Various molecules can be encapsulated by nano-micelles depend on the type of surfactants used. Nonionic surfactants are often used to extract neutral molecules while ionic surfactants are effective at extracting charged molecules. Micellar system is often used for the extraction of hydrophobic molecules. On the other hand, a reverse micellar system is used for the extraction of hydrophilic molecules. The extraction can be optimized easily by adjusting the operating parameters such as surfactant concentration, cosolvent concentration, ionic strength,

Table 15.1 Some recent studies on nano-micelle-based extraction of biomolecules using biosurfactants

Biosurfactant	Target molecule	Result/note	References
Rhamnolipids	Paracetamol	Recovery 96–104%	Abbasi et al. (2019)
Rhamnolipids	Methamphetamine	Recovery 104%	Haeri et al. (2017)
Rhamnolipids	Bisphenol A	Recovery 98–103%	Haeri (2016)
Rhamnolipids/tween 80/ isooctane/ n-hexanol	Cellulase	Activity recovery 83% Protein recovery 54%	Peng et al. (2016)
Rhamnolipids/ isooctane/n-hexanol	Lignin peroxidase Manganese peroxidase	Activity recovery 93.5% Activity recovery 88.8%	Peng et al. (2014)
Sophorolipids	Amoxicillin Erythromycin	Antibiotic recovery 0.4 g/L Antibiotic recovery 1.6 g/L	Chuo et al. (2018)
Saponin/glycerol	Lycopene	Yield 39% (assisted by ultrasound and enzyme)	Amiri-rigi et al. (2016)
Hyodeoxycholic acid sodium salt	Zingiberone, shogaol, gingerols	Recovery 87–103% (assisted by microwave)	Peng et al. (2017)
Amphisin	BSA	Metal chelating enhances micelle formation	Janek et al. (2018)
Phosphocholine	Bacteriorhodopsin	Better solubilization than SDS, CTAB, and Brij-35	Wang et al. (2015)

solution pH, extraction time, and temperature. In recent years, biosurfactants obtained from natural sources received great interest as an alternative to chemical surfactants. Studies were conducted to investigate their micellization and solubilization behaviors. Biosurfactants often showed better properties compared to chemical surfactants such as greater surface tension reduction, lower CMC, low toxicity, and protection of encapsulated biomolecules. Utilization of biosurfactants in nano-micelle extraction techniques can make the process more environmentally friendly. The extracts will also be safer for incorporation into final products. Biosurfactant nano-micelles can be used to extract various active compounds from plant materials. In addition, many studies showed that micellar-based extraction is a good pre-concentration technique for various molecules before subsequent processing. Nano-micelles can also serve as carriers for drugs and active ingredients. Some recent studies about biosurfactant-based nano-micelle for extraction of biomolecules are shown in Table 15.1.

7 Conclusion

Biosurfactants have many advantages like low CMC, good surface properties, stable at extreme conditions, highly biodegradable, low toxicity, and environmentally friendly. Many of them also possess good biological properties such as antimicrobial, antioxidant, anti-inflammatory, and antiproliferative activities. Many biosurfactants including rhamnolipids, sophorolipids, surfactins, phospholipids, saponins, and bile salts can form micelles or reverse micelles. The micelles can effectively extract hydrophobic biomolecules and separate them from the bulk aqueous phase. The reverse micelles are good for solubilizing water and various hydrophilic biomolecules. Therefore, they are a good replacement for chemical surfactants in micelle-based extraction. The advantages of micelle-based extraction are low organic solvent consumption, utilization of safe solvents, easy to operate, the fast extraction process, high selectivity, and high extraction efficiency. Reverse micelles can also preserve the activities of encapsulated biomolecules. Thus, micelle-based extraction is a good alternative for downstream processing or pre-concentration of biomolecules. For future studies, newer biosurfactants should be tested for micelle-based extraction. In addition, more detailed studies on micellization behavior of biosurfactants and their interactions with different solutes need to be conducted. Production costs reduction strategy for biosurfactants is also a crucial matter to make them more economically competitive.

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Chapter 16
Implications of the Nanoscopic Surface Modification on the Protein Adsorption and Cell Adhesion

Abshar Hasan and Lalit M. Pandey

Contents

1 Introduction

The amalgamation of material science, biological science and engineering has been crucial in the advancement of functional materials with improved biocompatibility for biomedical applications (O'brien 2011). Metallic implants (such as bone plates and rods), coronary stent, neurostimulator, artificial tooth and intraocular lens are

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widely used biomaterials implants. The biocompatibility of the implant is the most important criterion that decides the fate of biomaterial. Surface properties of implanted biomaterials play an important role in biocompatibility as this part of the implant material is exposed to the biological environment inside the body. Thus, interfacial characteristics of the implant surface and body fluids define the response of proteins, cells, tissue and organs (Dubiel et al. 2011). In this regard, employing surface engineering and material science tools, smart functional surfaces are developed to overcome the foreign body response (FBR) and minimize the implant rejections (Hench and Wilson 1984). Their tendency to imitating the extracellular matrix (ECM) exhibits an opportunity to support cell adhesion and proliferation. Protein adsorption followed by cell adhesion takes place immediately as implant surfaces come into the contact with the body fluids. Since protein adsorption is a bio-interface process, it is desirable to understand the underlying mechanism as it regulates cell adhesion and subsequently tissue integration. Several physical and chemical factors such as protein composition and charge, pH, ionic concentration, temperature, physio-chemical properties of surfaces regulating the protein behaviour on bio-interfaces have been previously studied and are discussed in detail in Sect. 2.

Cell adhesion on surfaces is a receptor mediated process that includes interactions between receptors (known as integrins) present on the cell surface and ligands (ECM proteins, functional groups) to provide intracellular connections with the extracellular environment (Bosman 1993). Integrins and cytoplasmic proteins assemble to form a complex network called focal adhesions, which regulates the interactions between cells and ECM, controls cytoskeletal dynamics and signalling. Integrins are trans-membrane heterodimeric proteins (comprises of α and β subunits), which recognises and bind to ECM proteins and cellular receptors to initiate a cascade of reactions for the different cellular functions such as the assembly of actin filaments for signal transduction (Plow et al. 2000; Hynes 2002). There exist 18 different types of α and eight types of β subunits, associated non-covalently in a heterodimeric fashion to form 24 integrins units that show specificity for the recognition and binding of the different proteins (as shown in Fig. 16.2) (Hynes 2002).

ECM is a three-dimensional scaffold that comprises various proteins, glycosaminoglycan and growth factors to support cell adhesion, cell migration and proliferation into tissues (Danen and Yamada 2001; Hohenester and Engel 2002). Major ECM proteins such as albumin, laminins, fibronectin and collagen play a central role in the integrin mediated binding for the cellular communication via intracellular signalling for the cell–surface interactions. These ECM proteins are folded and held by disulfide bonds and interact with surface topologies via hydrophobic interactions (Jin and Yuan 2011). Upon interaction with the surrounding environment, various cascades of signals are transmitted inside the cell that results in changing the cellular behaviour such as morphology, migrations and differentiation.

Overall, surface properties play a major role in regulating cellular behaviour, and hence, are of great interest for investigations particularly in tissue engineering, biosensors development, drug delivery and tools for diagnosis and therapy (Delaittre et al. 2012). The design of materials to mimic the natural environment of cells has been mainly addressed by carefully tailoring surface features such as surface morphology (surface roughness, topology and pattern size and shape), surface chemistry (surface potential, charge and energy) and mechanics (stiffness, elasticity) (Hasan et al. 2018a, b; Santos et al. 2014; Choi et al. 2010; Lord et al. 2010; Behera et al. 2020a, b, 2018; Hasan and Pandey 2016). One of the other disadvantages of the surface modifying systems have led to the improvement of the existing methods and development of new techniques. Effects of physio-chemical properties of surfaces on cell behaviour have been explained in more detail in Sect. 3 and correlated with the integrin expression for a better understanding of the chemical signalling cascade that occurs in cells while interacting with the foreign materials.

1.1 Scope of this Chapter

The purpose of the present chapter is to highlight the current understanding of the protein behaviour and the underlying mechanistic phenomenon as a function of the surface's physio-chemical properties. Efforts have been made to cover the essential parameters that regulate this process at both nano- and micro-scales. We have also tried to recapitulate and establish a synergy of how surface modification regulates the protein adsorption, which in turn governs cell responses on the solid surfaces. The chapter has been designed keeping in mind the young audience especially the beginners in the field of material science and surface engineering.

2 Protein Adsorption

2.1 Protein Composition (Hydrophobicity and Charge), pH, Temperature, and Ionic Concentration

Proteins are bio-macromolecules and composed of a mixture of amino acid subunits, which are polar, non-polar and charged based on the side chains. The net charge is the sum of positive and negative charges of these constituents (Gitlin et al. 2006). Proteins exhibit positive and negative charges if their isoelectric point (pI) is above or below the physiological conditions, respectively. In other words, proteins are positively charged if the pH of the surrounding environment is lower than pI ($pH < pI$), negatively charged if $pH > pI$ and neutral molecule if $pH = pI$. The charged, hydrophobic and hydrophilic moieties in the protein molecules regulate the interaction of proteins with the surfaces via ionic forces, hydrophobic interactions and hydrogen bonding, respectively (Hasan et al. 2018b; Pandey and Pattanayek 2013a, b). Protein adsorption is generally higher at pI value due to minimal electrostatic interactions resulting in less intermolecular repulsive forces which in turn results in dense packing of molecules at surfaces (Demanèche et al. 2009). Also, opposite charges in protein molecules and surfaces induce electrostatic interactions resulting in the enhanced adsorption rates due to the faster diffusion of molecules towards surfaces via electrostatic forces (Hartvig et al. 2011).

Temperature induced mobility of protein molecules regulates the thermodynamic and adsorption kinetic mechanisms at the solid–liquid interfaces. In terms of thermodynamics, higher temperature induces greater entropy change which results in the increased diffusivity of molecules towards surfaces causing more amount of protein adsorption (Rabe et al. 2011). This is also favoured by the release of surface bound water molecules resulting in the lesser steric hindrances otherwise imparted by surface adsorbed water molecules and salt ions. Hence, an increase in temperature results in higher adsorption rates.

The concentration of dissolved ions or ionic strength also regulates protein adsorption and is widely used to understand this complex phenomenon. It has been observed that under the higher ionic strength conditions, electrostatic interactions due to opposite charges between surface and protein get hindered, reducing adsorption rates whereas the adsorption to similarly charged substrates is increased (Jones and O'Melia 2000). Furthermore, protein molecules tend to aggregate under high ionic conditions.

2.2 Effect of Surface Properties

Protein adsorption on surfaces is common yet a complicated process to understand why they bind to almost all the surfaces, swiftly and persistently. Despite the considerable research in this area, many mechanistic aspects and regulating factors are still not well studied and understood. Due to the intricate structure and composition of protein molecules, their behaviour on surfaces is governed by many factors. Hence, their attachment and detachment on surfaces cannot be simply explained by certain adsorption and desorption principles, unlike other smaller molecules that behave like rigid entities (Rabe et al. 2011). Furthermore, due to the large sizes of the protein molecules, the interactions between surfaces and protein are nontrivial and may result in a change in the protein structure and conformation, which adversely affect the structure–function relationship. This results in the loss of protein functionality not only in diagnostics applications (such as antibodies and enzymes) but also in other biomedical applications such as implant surface in tissue engineering (immobilised ECM proteins) and antimicrobial (antimicrobial peptides and peptoids) surfaces (Ziółkowski et al. 2020; Toffoli et al. 2020; Nir et al. 2019; Hasan et al. 2020a, b).

As mentioned in the introduction section, when biological fluid comes into contact with biomaterials, protein adsorption takes place instantaneously. Interactions between surfaces and proteins molecules govern the cascades of reactions that determine the success of the biomaterials. Non-specific protein adsorption from the blood plasma results in biofouling, because of the alterations in the adsorbed protein conformation, which causes deterioration of biomaterial due to the platelet adhesion and activation leading to the thrombosis (Gorbet and Sefton 2004). Such unwanted biological responses can be controlled by carefully tuning the interfacial properties such as surface chemistry, topology (roughness), wettability and surface charge (Hasan and Pandey 2015). Modifications of ceramics, polymers, composites and metals via physical and chemical methods have been widely reported to control the protein behaviour and adsorption, and cell adhesion to circumvent such undesirable processes (Behera et al. 2018; Hasan et al. 2018b; Hasan and Pandey 2018; Hasan et al. 2018d, 2017; Saxena et al. 2018; Jawed et al. 2020; Kaur et al. 2014).

2.2.1 Physio-Chemical Surface Properties

Pioneer work by Whitesides on the systematic analysis of the structure–property relationship has helped to establish a set of empirical rules to design protein repellant self-assembled monolayers (SAMs) coatings (Ostuni et al. 2001; Chapman et al. 2000). The understanding of the key properties down from molecular level organisation and functionality can exhibit significant effects in regulating the protein adsorption and are now widely known as ‘Whitesides rules’. This includes the presence of (a) polar functional groups (hydrophilicity), (b) hydrogen bond acceptor groups, and the absence of (c) hydrogen bond donor groups, (d) net charge (Wei et al. 2014). In principle, surfaces modified based on the aforementioned rules should prevent protein adsorption. However, there exist exceptions as several polyglycerols and polysaccharides exhibit hydrogen bond donors (conflicting third rule) but impart exceptional hydrophilicity abiding by the first rule.

Surfaces are classified into hydrophilic, hydrophobic and super-hydrophobic based on how fluids interact with the surfaces. In the scientific community, surfaces are defined hydrophilic if the static water contact angle θ is $<90°$, hydrophobic if θ is in between 90° and 150° and super-hydrophobic when θ is $>150°$. Hydrophilic surfaces inhibit protein adsorption due to the presence of a hydration layer that prevents interactions between protein molecules and surfaces (Vogler 2012). Whereas hydrophobic surfaces are water repelling and hence lack hydration layer due to which a large number of protein molecules interact and bind with surfaces. While in the case of super-hydrophobic surfaces, the contact area between fluids and surfaces is the minimum, hence, negligible molecules get in contact with the surface preventing protein adsorption. Hydrophobic surfaces are also known to induce changes in protein’s conformation and secondary structures upon adsorption. During interactions between surfaces and proteins particularly in hydrophobic interactions, internal hydrophobic moieties in protein get exposed, causing protein denaturation (Karlsson et al. 2005). Many studies in the past emphasised that a higher mass of adsorbed protein is observed on hydrophobic surfaces as compared to hydrophilic surfaces. However, many critics in the scientific community contradicted this notion and demonstrated that hydrophobicity alone is not responsible for the higher adsorbed mass, in fact, other intrinsic factors such as protein size and protein charge are equally important (Vogler 2012). This has been extensively studied and verified by Hasan and coworkers using different proteins (serum proteins such as albumin, immunoglobulin-G, fibrinogen and ECM proteins such as fibronectin and collagen-1) on modified titanium surfaces (Hasan et al. 2018a, b; c; Hasan and Pandey 2020). For instance, albumin exhibit higher adsorbed mass on hydrophobic surfaces due to hydrophobic–hydrophobic interactions whereas fibronectin majorly adsorbs on hydrophilic/

charged surfaces primarily due to hydrogen bonding and ionic interactions (Hasan et al. 2018b).

Ideally, for the non-reversible protein adsorption, the secondary structure and conformation of adsorbed proteins should remain intact. However, protein molecules undergo changes in their secondary structure upon adsorption along with their orientation based on the adsorption behaviour of other proteins during competitive protein adsorption as shown in Fig. 16.1 (f1–f4). Proteins acquire different orientations based on the interactive forces between the protein molecules and surfaces.

Protein molecules adsorbed with end-on orientation are weakly bound to the surfaces and experience fewer interactive forces as compared to side-on orientation due to lesser surface area in contact. However, side-on orientation is more thermodynamically favoured. Hasan and coworkers explained the organisation of these orientations on surfaces from a single and binary mixture of protein solutions (Hasan et al. 2018c). It was reported that the loosely adhered small-sized protein molecules (e.g., bovine serum albumin (BSA)) in end-on orientation are exchanged by a larger sized protein (e.g., immunoglobulin G (IgG)) (Fig. 16.1f). Moreover, the larger sized IgG molecules may even partially dislodge the side-on oriented BSA molecules and finally bestow themselves into orientations that attain the least energy and higher stability.

2.3 Techniques to Study Protein Adsorption

Understanding protein behaviour at interfaces is undoubtedly intricate but is essentially required for designing various biomedical and biosensor devices. Many mathematical kinetic models have been designed to describe the mechanistic details of protein adsorption based on the experimental data gathered from the protein adsorption experiments conducted under the effect of different parameters. Developing a model is a cyclic procedure involving experimentation and designing a hypothesis until it gets refined to provide an adequate description of the adsorption kinetics and isotherms of the adsorption processes. Highly sophisticated and state-of-the-art techniques have been developed in the recent past to minimize the experimental errors and providing the molecular level precision. The following section provides an overview and introduction of the various techniques being widely used for analysing the protein interactions with other proteins, surfaces, and their secondary and tertiary structure post adsorption.

***Ellipsometry*:** A non-invasive optical technique mainly used in characterisation and analysis of thin films for investigating the dielectric properties. It relies on the principle of change in the polarisation of light upon reflection or transmission from flat surfaces with adsorbed protein layer and compares it with an established model. The change in polarisation is calculated in terms of the amplitude ratio (Ψ) and phase difference (Δ). Ψ and Δ describe the ratio of reflection coefficients and the difference in phase change, respectively between parallel and perpendicular polarised lights. These parameters are affected by several factors such as film thickness,

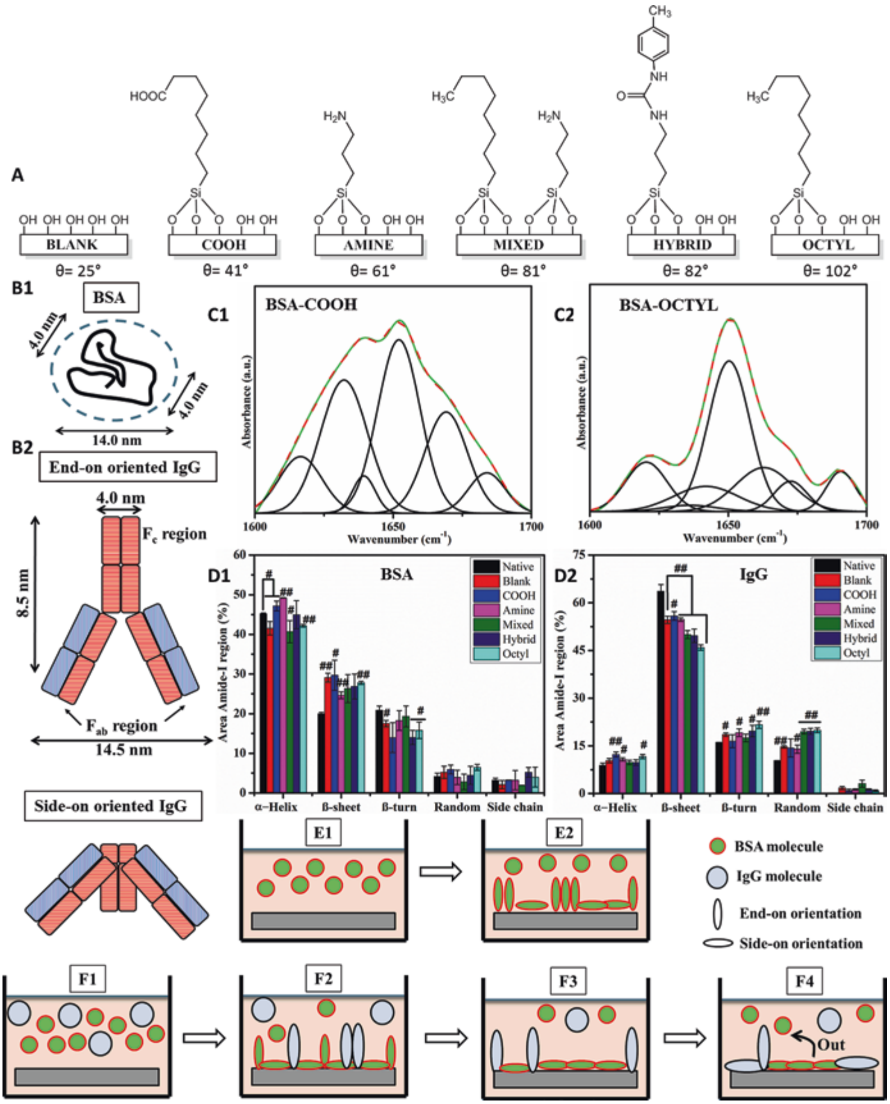

Fig. 16.1 (**a**) Formation of various SAMs to functionalise the surfaces. (**b1**) Heart-shaped BSA molecule and (**b2**) end-on and side-on orientations of IgG molecules. Fitting of the amide-I (1600–1700 cm^{-1}) region of the FTIR spectra of the BSA molecules on (**c1**) COOH and (**c2**) octyl surfaces for the secondary structure analysis. Percentage distribution of secondary structures of (**d1**) BSA and (**d2**) IgG adsorbed on various modified/functionalised surfaces. (**e1**, **e2** and **f1**–**f4**) Schematic representation of the competitive protein adsorption process from (**e1**, **e2**) a single and (**f1**–**f4**) binary (BSA and IgG) proteins mixture. (Adapted with permission from Langmuir 2018;34 (28):8178–8194. Copyright (2018) American Chemical Society)

refractive index, extinction coefficient, surface anisotropy and surface roughness. Ellipsometry has been widely used by many researchers to study adsorption kinetics of various protein molecules (Seitz et al. 2005; Malmsten 1995; Wasilewska et al. 2019).

Surface plasmon resonance (SPR): SPR is another non-invasive and one of the most powerful optical techniques widely used in analytical sciences with high sensitivity. SPR is a real-time monitoring system used for the label-free detection of interactions between surfaces and protein molecules and also between protein–protein molecules (Douzi 2017). It is widely used in pharmaceutical industries for analytical applications such as for analysing the binding, association and dissociation kinetics, affinity, and specificity. SPR measures the changes in the refractive index of the material based on the interactions at the interfaces (Patching 2014; Daghestani and Day 2010). It relies on the principle that when polarised light is incident at a certain angle (also called as resonance angle) on the metallic (gold) film–molecule interface, the field of light undergoes total internal reflection, excites and interacts with the oscillating electrons (or surface plasmons) at the surface. This generated electromagnetic wave or evanescent wave travels a short distance of around 300 nm into the vicinity. Based on the refractive indices of the vicinity, the time response of the plasmon resonance is recorded, which provides the information about the molecules present or interacting on the sensor surface (Patching 2014; Breault-Turcot et al. 2014). Apart from sensing, SPR is also used for studying the kinetics of the protein adsorption (Sota et al. 1998; Nguyen et al. 2015).

Quartz crystal microbalance (QCM): QCM is a microgravimetric device based on an acoustic sensor, which works on the principle of the inverse piezoelectric effect using a disk-shaped quartz crystal. This is a straightforward label-free technique that relies on the change in the oscillating frequency (Δf) of the quartz substrate when protein molecules come into contact with the surface. Protein adsorption on the surface of the oscillating QCM crystal causes a decrease in the frequency with respect to the mass of protein adhered to the crystal's surface. It has also been extensively used for studying both the competitive and non-competitive adsorption of proteins on various metallic, polymeric and silica surfaces (Pandey and Pattanayek 2013a, b; Pandey et al. 2013; Pandey and Pattanayek 2011; Ferreira et al. 2009; Teichroeb et al. 2008; Migliorini et al. 2018; Chandrasekaran et al. 2020). This technique also measures the dissipation energy due to the surface protein interactions, which deciphers the viscoelasticity of the adsorbed layers.

Optical waveguide lightmode spectroscopy (OWLS): OWLS is also a label-free technique based on a thin-film optical waveguide in which the incident of the laser beam at a specific incident angle propagates through the highly optically transparent substrate such as glass or quartz. It is highly sensitive and registers even small variations in the refractive index due to protein adsorption to calculate the adsorbed protein mass. It has also been commonly used for protein quantification and adsorption kinetics owing to its high sensitivity, real-time monitoring and user-friendly handling operations (Vörös 2004; Tie et al. 2003; Fulga and Nicolau 2006).

Attenuated total reflection–Fourier transform infrared spectroscopy (ATR-FTIR): FTIR is an infrared based spectroscopic technique widely used to study secondary structures such as α-helix, β-sheets, random coil, and turns in the specific amide bands of protein molecules. ATR mode is primarily used for analysing surface-induced changes in protein's secondary structure post adsorption. IR light is shined through high refractive index substrates such as Ge, ZnSe, or diamond crystals to generate evanescent waves at the interface. It also works similarly to OWLS except that the IR signal is measured here. It has been extensively used for analysing the protein behaviour on various surfaces (Hasan and Pandey 2020; Hasan et al. 2018a; b; c).

Atomic-force microscopy (AFM): It is a microscopic technique used for analysing samples with nanoscale features (topologies and roughness) with high molecular precision and is frequently used to image protein adsorption on smooth surfaces. It consists of a piezoelectric cantilever fitted with a sharp tip to scan over the surface either in contact or non-contact (tapping) mode (Migliorini et al. 2018). In the case of contact mode, the interactions between surfaces and tip result in an increase in the forces on the cantilever, which is regulated by the feedback loop to regulate tip movement and records the surface features. However, in tapping mode, the amplitude of the oscillating cantilever reduces when the surface is in close contact with the tip. For protein adsorption, AFM is used to study the protein–protein and protein–surface interactions particularly for determining the protein distribution, aggregation and orientation (Pellenc et al. 2008; Mulheran et al. 2008; Migliorini et al. 2018; Hasan et al. 2018c).

3 Cell Adhesion

3.1 Role of Integrins in Cell Adhesion

Integrins are the major cell adhesion heterodimeric proteins present on the cell membrane to transmit signals from the extracellular environment to the cell and vice versa (Hynes 1992). Except for erythrocytes, integrins are found in all metazoans and their number increases with increasing complexity. The extracellular regions of these heterodimeric receptors recognise and bind to the counter-receptors present on mammalian cells, bacterial membranes, coat proteins present in viral particles, and ECM proteins. While its intracellular domain is connected to focal adhesion elements that control cytoskeletal (actin) arrangement and also regulates the signalling pathways by contacting signal transduction machinery (Hynes 2002). The extracellular domains (~80–150 kDa) are generally larger than the transmembrane domain (~25–30 amino acid residues) and cytoplasmic domains (10–70 amino acids, except β4 integrin). Out of 18 α units, nine α units (α1, α2, α10, α11, αD, αL, αM, αX and αE) have extra inserted domain (called I or A domain, unknown function) of about 180 residues in the transmembrane region, while remaining α subunits have ~25–30 residues due to post-translational modifications (Hynes 1992). The detailed explanation of the integrin structure is out of the scope of this chapter, but we have tried to explain their classification and role in the cellular activities in brief.

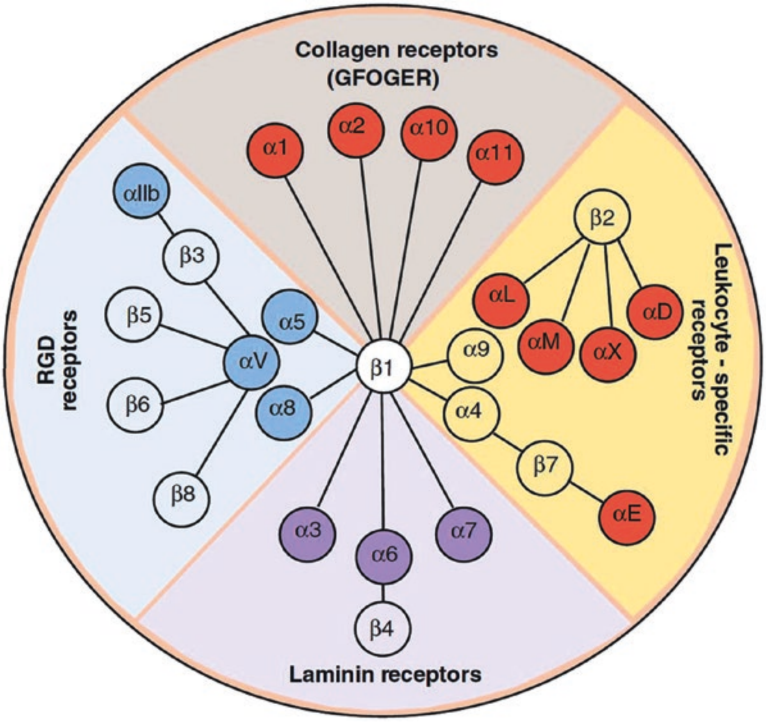

Fig. 16.2 Integrin family: the arrangement of different combinations of α- and β-subunits to form integrins that recognise different receptors in the extracellular matrix. (Adapted with permission from Cell and tissue research 2010;339(1):269. Copyright (2009) Springer Nature)

Arrangement of 18α and 8β subunits in 24 heterodimer integrin pairs have shown the specificity for different ECM proteins like fibronectin, laminins and collagens as shown in Fig. 16.2 (Barczyk et al. 2010). In vertebrates, all collagen receptors (α1, α2, α10 and α11); and leucocytes receptors (αD, αE, αL, αM, αX) have inserted domain known as I or A domain (Hynes 2002; Ruggiero et al. 1996; Camper et al. 1998). Integrins α3β1 and α6β1 majorly recognise laminin (TASHIRO et al. 1999) and other integrin receptors that recognise RGD tripeptide sequence in fibronectin are α5β1, α8β1 and αvβ6 (Van der Flier and Sonnenberg 2001; Hynes 2002). Fibronectin can be recognised by eight integrins including α3β1, α4β1, α5β1, α8β1, αvβ1, αvβ3, αvβ6 and αIIbβ3. Leukocyte specific receptors in vertebrates such as αDβ2, αMβ2 also recognise immunoglobulins receptors and arbitrate cell–cell interaction (Hynes 2002). Although integrins are known to be specific for the recognition and binding of the ECM proteins, there exists redundancy for some interactions. For example, α1β1 and α2β1 are key receptors for collagen but bind to laminins as well (Hynes 1992; Srichai and Zent 2010). Integrins like α4β1 and α9β1 not only recognises ECM fibronectin but also interact with membrane proteins of Ig superfamilies such as vascular cell adhesion molecule-1 (VCAM-1) and intercellular cell adhesion molecule (ICAM) for mediating the cell–cell adhesion. αvβ1 binds to both fibronectin as well as vitronectin (Hynes 1992, 2002). In each protein, integrin binds to a specific peptide sequence that serves as the binding site for integrins. RGD (Arg–Gly–Asp) was the first sequence to be found acting as the binding site in fibrinogen. The tripeptide sequence, that is, RGD present in adhesive proteins such as fibronectin and vitronectin is the major ligand binding site. But apart from RGD, other peptide sequences have been reported that serve as binding sites for different integrins. For example, αIIbβ3 recognises KQAGDV in fibrinogen, α2β1 binds DGEA in collagen, α4β1 binds EILDV sequence in fibronectin and QIDSPL in (VCAM-1) and αXβ2 binds to GPRP of fibrinogen (Hynes 1992; Loike et al. 1991).

3.1.1 Integrin Role Studied by Knockout Mice Models

A mouse whose specific gene have been 'inactivated' or 'knocked out' by replacing it with other genes for studying their function is called a knock out mouse. The researchers do so to study the effect of particular knocked out gene on mouse phenotype since human and mouse share a lot of gene similarity. These mice models have been used in diagnosing diseases like cancer, arthritis, anxiety, ageing and Parkinson's disease and for studying the effect of the drug and other therapeutics. Similarly, integrin knockout mice have made it possible to find the role of each integrin and their effect on phenotype in a constitutive or cell type-specific manner, ranging from normal mice to prenatal lethality (Bouvard et al. 2001). Human diseases like cancer and genetically transmitted diseases have been associated due to impairment of integrin causing altered integrin mediated cell adhesion and migration.

Mice with single gene (αD, αE, αL, α1, α3, α5, etc.) as well as double gene knockouts (α3/α4, α4/α5, β3/β5, etc.) have been used to find out phenotypic effects (Bouvard et al. 2001). For example, α5/αv knockout impaired fibronectin receptors that led to the death of mice with severe gastrulation defects (Yang et al. 1999). Similarly, mice deficient in integrin α8β1 lack stereocilia or contain malformed stereocilia (Evans and Müller 2000). β1 is the most shared integrin among all and takes part in at least 12 heterodimeric (αβ) integrin receptors like RGD, laminin and collagen receptors as shown in Fig. 16.2. Table 16.1 summaries various phenotypic defects for each integrin knockout in detail.

3.2 Focal Adhesion Kinase (FAK)

Integrin mediated interaction is important for the arrangement of the actin cytoskeleton at focal contacts, which is controlled by tyrosine phosphorylation of various signalling proteins. Integrin clustering due to ECM and cell interaction results in the activation of the various non-receptor protein kinases which further regulates the downstream signalling process by activating the signalling proteins. FAK is one of the non-receptor and non-membrane linked protein tyrosine kinase-2 (PTK-2), which plays a significant role in integrin and other intracellular signalling pathways. FAK was separately

Table 16.1 Types of integrin subunits (Alam et al. 2007), distribution (Bosman 1993), ligands (Hynes 1992) and their knockout phenotypes (Bouvard et al. 2013)

	Integrin subunit/gene knockout	Viability	Integrin distribution	Cytoplasmic proteins	Extracellular ligands	Knockout/defective phenotype
Collagen receptors	α1	V,F	Smooth muscle, fibroblasts endothelium, hepatocytes, activated T-cells, neural cells	F-actin	Collagen, laminin	Reduced tumour vascularisation in adults, hypocellular dermis, increased collagen synthesis, defective cell attachment
	α2	V,F	Various epithelia, endothelium, platelets, mesenchymal stem cells, leucocytes	F-actin	Collagen, laminin, E-cadherin, tenascin	Mildly impaired hemostasis, delayed platelet aggregation, skin infections, defective cell attachment
	α10	V,F	Chondrocytes, fibroblasts		Collagen, laminin	Mild cartilage phenotype, growth plate defects
	α11	V,F	Subsets of fibroblasts, cancer associated fibroblasts, odontoblasts, mesenchymal stem cells		Collagen	Defective incisor eruption, dwarfism, increased mortality
RGD receptors	α5	L,E10	Fibroblasts, endothelium, hepatocytes, platelets, lymphocytes		Fibronectin, osteopontin, fibrillin	Extra and intraembryonic vessel development defects, muscular dystrophy
	αv	E10/P,E12-birth	Endometrium, endothelium, osteoblasts, fibroblasts, glial cells, melanoma cells, keratinocytes	RACK1	Fibronectin, vitronectin, tenascin, osteopontin	Placental defects, cerebral vascular defects like cerebral haemorrhage, seizures, axonal degeneration
	α8	P	Mesenchymal cells, various epithelia, endothelium, brain	Talin	Fibronectin, vitronectin, osteopontin	Kidney and inner ear defects
	αIIb	V,F	Blood platelets, melanoma cells		Fibronectin, fibrinogen, vWF, ICAM	Glanzmann thrombasthenia, defective platelet aggregation, impaired hemostasis

	Integrin subunit/gene knockout	Viability	Integrin distribution	Cytoplasmic proteins	Extracellular ligands	Knockout/defective phenotype
Leucocyte receptors	αD	–	Macrophages and eosinophils		ICAM-3, VCAM-1	No obvious phenotype, mild T-cell phenotypic changes
	αE	V,F	Immune cells mostly		E-cadherin	Inflammatory skin lesions, defective gut-associated lymphoid tissue
	αL	V,F	Leucocytes		ICAM-(1-5), JAM-1	[1]Impaired leukocyte recruitment and tumour rejection, reduced lymph node size, reduced neutrophil adhesion
	αX	–	Monocytes, macrophages, dendritic cells, NK cells Granulocytes, activated lymphocytes		iC3b, fibrinogen	[2]No obvious phenotype, affects monocyte firm adhesion
	αM	V,F	Granulocytes, monocytes, macrophages, NK cells, neutrophils		iC3b, fibrinogen	[2]Defective development and function of the mast cell, impaired phagocytosis and PMN apoptosis; obesity
Laminin receptors	α3	L,Birth	Various epithelia, endothelium	BIN1	Collagen, laminin, fibronectin	[3]Defects in kidneys, lungs, and cerebral cortex; skin blistering
	α6	L,Birth	Various epithelia, fibroblasts, neurons		Laminin	[4]Defects in cerebral cortex and retina; skin blistering
	α7	V,F	Muscle cells, melanoma cells		Laminin	Muscular dystrophy, defective placenta formation
	α4	L, E11–E14	Tumour cells (some), developing muscle, leucocytes Activated leucocytes	Paxillin	Fibronectin, VCAM-I, MAdCAM	Defective placentation and cardiac haemorrhage
	α9	L, perinatal				[5]Defective lymphatic system development

(continued)

Table 16.1 (continued)

	Integrin subunit/gene knockout	Viability	Integrin distribution	Cytoplasmic proteins	Extracellular ligands	Knockout/defective phenotype
	β1	L, E5.5	Almost all vertebrate cells (fibroblasts, leucocytes, platelets, myocytes, endothelial cells)	Talin, Filamin A, B, α-Actinin, Skelemin	Collagens, laminins, fibronectin, VCAM-1	ICM deterioration, complete block of peri-implantation development
	β2	V,F	Leucocytes, keratinocytes, endothelial cells	Filamin A, B, α-Actinin	ICAM-1,2, fibrinogen, iC3b	[6]Defective leukocyte recruitment, T cell proliferation, skin infections
	β3	V,F	Platelets	Talin, myosin, skelemin	Most of ECM proteins	[7]Defective platelet aggregation, osteosclerosis
	β4	P	Epithelial cells	Plectin/HD1, p27(BBP/eIF6)	Laminin	Defective epithelial tissue, severe blistering of the skin
	β5	V,F	Keratinocytes, epithelial cells, fibroblasts, osteoclasts, monocytes	Nischarin, Talin	Vitronectin fibronectin	No obvious defects in development, reproduction and healing of cutaneous wounds
	β6	V,F	Basal airway epithelial cells		Fibronectin, tenascin C, ADAM, osteopontin	[8]Skin and lung inflammation and impaired lung fibrosis
	β7	V,F	Lymphocytes	Filamin A, B	Fibronectin, VCAM-1, MAdCAM	[9]Impaired GALT formation such as Peyer's patches and mesenteric lymph nodes
	β8	E10/P	Diffusely expressed on basal cells		Vitronectin, laminin, TGF b-LAP	Placental defects, defective CNS

Human associated diseases: 1 = Psoriasis; 2 = Systemic lupus erythematosus; 3-Interstitial lung disease, nephrotic syndrome, epidermolysis bullosa; 4 = Epidermolysis bullosa; 5 = Bilateral chylothorax; 6 = LAD1, leukocyte adhesion deficiency; 7 = Glanzmann's disease, excessive bleeding; 8 = Asthma; 9 = Inflammatory bowel disease. V = Viable; F = Fertile; L = Lethal; E# = Embryonic lethal # month

MAdCAM mucosal addressin cell adhesion molecule, *iC3b* inactivated complement component, *ICM* Inner cell mass, *GALT* Gut-associated lymphoid tissue, *vWF* von Willebrand factor, *TGF b-LAP* transforming growth factor b latency-associated peptide, *ADAM* a disintegrin-like and metalloproteinase-containing protein identified and reported as a highly tyrosine-phosphorylated protein by researchers during 1991–1992 and was for the first time linked their role in the integrin associated signalling (Hanks et al. 1992; Schaller et al. 1992; Guan et al. 1991; Kornberg et al. 1992). Since this protein is found to be co-localised at focal adhesion points inside the cell, it was named as focal adhesion kinase (Schaller et al. 1992). FAK plays a central role in the maturation and turnover of focal adhesions (or focal contacts) and acts as signalling kinases as well as a scaffold protein, tethering various signalling molecules of different intracellular pathways into complexes. Mesodermal cells from FAK knockout embryos (FAK−/−) exhibited round topology with ventral surface carrying an abnormally large number of focal adhesions resulting in slower migration rates, which finally lead to embryonic lethality.

3.2.1 Structural Divisions of FAK

FAK is a 125 kDa protein consisting of three important domains, N terminal FERM (protein 4.1, ezrin, radixin and moesin homology) domain, a central kinase domain and C terminal focal adhesion targeting (FAT) domain as shown in Fig. 16.3 (Lee et al. 2015). There lies one protein rich sequence (PRS) in the N terminal domain, that is, between FERM and kinase domain and two PRSs between FERM and FAT domain in the C terminal region. These PRSs serve as an attachment site for different signalling proteins like p130Cas, CAP, GRAF (GTPase regulator associated with FAK). It is interesting to note that FAK lacks Src homology 2 (SH2) or SH3 protein interaction domains, although it is one of the important intracellular signalling proteins. SH2 and SH3 are structurally conserved domains found in the adaptor proteins, which have high affinity to be docked at phosphorylated tyrosine residues in other proteins and hence facilitates signalling processes. FAKs are actively recruited at the integrin clustering sites as well as growth factor receptor sites at the cell membrane and are engaged in growth factor mediated cell migration. Sieg and co-workers demonstrated for the first time that N terminal FERM domain which,

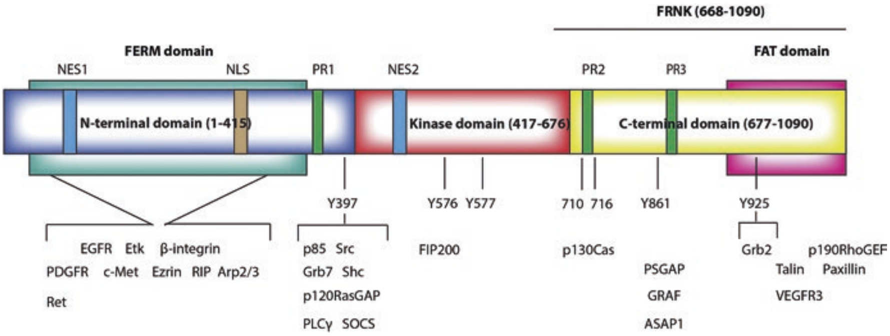

Fig. 16.3 FAK structural domains. FERM domain of FAK is associated with integrin RTK (e.g., EGFR, PDGFR) linked signalling by GFR activation. (Adapted with permission from Pharmacology & Therapeutics 2015; 146:132–49. Copyright (2015) Elsevier)

upon exogenous expression, was found to be associated with receptor tyrosine kinase (RTK) such as growth factor receptors (GFR) like epidermal growth factor receptor (EGFR) and platelet derived growth factor receptor (PDGFR) (Sieg et al. 2000). was evidenced that the deletion of the FERM domain resulted in the disruption of the FAK–EGFR complex. A central kinase domain contains three major tyrosine phosphorylation sites, that is, Y397, Y576 and Y577 for regulating the FAK activation in cell motility. Y397 serves an important site as a number of signalling events are associated with its auto-phosphorylation. Binding of signalling proteins like p85 subunit of phosphatidylinositol-3-kinase (PI3K), Shc adaptor protein and Src family PTKs are facilitated by Y397 (Chen et al. 1996; Schlaepfer et al. 1998). Y576 and Y577, present in kinase regulatory/activation loop, are phosphorylated by Src mediated transphosphorylation to promote the maximum FAK activation (Hanks et al. 2003). C terminal region has two protein rich sequences, which serves as the binding sites for the SH3 domain containing adaptor proteins like p130Cas. Phosphorylation of p130Cas promotes other adaptor protein (Crk and Nck) binding and their further phosphorylation. Cascade of such processes results in the activation of Rac at membrane extensions for promoting cell migration (Hanks et al. 2003; Chodniewicz and Klemke 2004). C terminal FAT domain (~160 aa) promotes fusion proteins localisation to FAK at focal adhesion points. FAK is indirectly associated with integrins through the FAT domain, as it contains an attachment site for integrin associated proteins such as paxillin and talin. Phosphorylation of FAK at Y925 site mediated by Src family kinase promotes the binding of another adaptor protein, Grb2 via SH2 domain. Grb2 leads to Ras/ERK2/MAPK (extracellular regulated kinase/mitogen activated protein kinase) activation signal which promotes cell survival, proliferation and migration. Streblow et al. reported fibronectin stimulated Grb2 binding to FAK and its role in ERK2/MAP activation in the cell motility (Streblow et al. 2003).

It is important to note that a balanced expression of N and C terminal domains are mutually responsible for FAK activation. Since, overexpression of the N terminal FERM domain inhibits FAK activation and negatively affected G-protein stimulated cell migration (Streblow et al. 2003), whereas overexpression of the C terminal FAT domain promotes dephosphorylation of Y397 and disruption of FAK–EGFR complex (Sieg et al. 2000).

Y576 and Y577 are major phosphorylation sites by Src family PTK.

Phosphorylated p130Cas upon binding with Ras adaptor protein results in Ras activation, lamellipodia formation and cell migration.

3.2.2 FAK Regulation: Activation/Inactivation

Recruitment of FAK at focal contacts is important for the focal contact maturation in cell adhesion. FAK activation/inactivation cycle mediates focal contacts assembly and disassembly for the cell adhesion and migration. FAK interacts with various signalling molecules and hence, is considered to be a major mediator that actively participates in the integrin mediated signalling pathways. Various phosphorylation sites present in FAK serve as attachment sites for intracellular proteins like Grb7, Shc, Src, PLC-γ via the SH2 domain. SH3 domain containing proteins like p130Cas binds to the proline rich sequences, which are found upstream of Y397. Src binding to Y397 via the SH2 domain results in phosphorylation of p130Cas, which stimulates cell migration and association of other Src family PTKs at this binding site. This has also been evidenced while studying the disruption of FAK binding to Src or p130Cas, which resulted in reduced cell migration due to improper p130Cas phosphorylation (Cary et al. 1998, 1996). SH3 domain oriented binding of p130Cas takes place at second (out of three) proline rich sequence (PRS-2) located at 711–717 residues and it has also been revealed in the mutational studies that PRS-3 (872–879 residues) also serve as a binding site as well (Polte and Hanks 1995, 1997). The maximal FAK activation triggers the phosphorylation of Y567/577, which are present in the activation loop of kinase domain (Calalb et al. 1995). Grb2 adaptor protein binds via the SH2 domain at phosphorylated Y925, which directly contributes to the activation of an ERK2/MAP kinase cascade, leading to the cell migration (Schlaepfer et al. 1994).

3.3 Effect of Surfaces on Integrin Activation/Inactivation

Surface chemistry plays a vital role in integrin facilitated cell adhesion and migration as revealed by immunostaining and biochemical analyses. It is important that synthetically modified surfaces must mimic ECM so as to modulate the structural and molecular composition of cell matrix adhesions and regulate intracellular signalling pathways. It is well known that the cell adhesion is mediated by adsorption of several serum proteins like albumin, fibronectin, fibrinogen, immunoglobulins and vitronectin. It should be noted that protein upon adsorption must not lose its orientation and properties, which is primarily controlled by surface chemistry. Improper and disoriented protein adsorption will negatively affect the desired cell adhesion kinetics and migration. Although substrate stiffness plays an important role in regulating cellular behaviour, it may change due to changes in surface chemistry, functional groups and attached ligands. Cell culture studies on polyacrylamide hydrogel with a higher degree of compactness (hence stiffness) revealed the strong cell adhesion due to the increased focal adhesion and integrin activation (Pelham and Wang 1997). Several matrices like protein gels, synthetic hydrogels, scaffolds, silane self-assembled monolayers (SAMs) modified substrates, cell adhesive ligands modified gels and scaffolds have been explored for determining the cellular behaviour (Hasan et al. 2018a; Santos et al. 2014; Liu et al. 2012).

Protein based gels like Matrigel, collagen type-1 and fibrin undergo self-assembly to generate nanoporous and fibrous structures that mimic natural ECM and regulate the integrin signalling. Physical properties of such gels like stiffness can be easily tailored by changing the content of protein in the starting gel solution. Crosslinking agents for collagen gels like ribose, glutaraldehyde and carbodiimide; photochemically crosslinked fibrin regulates the chemical composition and stiffness of gels

(Rault et al. 1996; Syedain et al. 2009). Synthetic polymers (PEG, dextran, poly (pentafluorophenyl methacrylate), poly (tetrafluoroethylene) and polypyrrole, etc.) based hydrogels have been proved effective in differentiating the effect of surface properties on cell adhesion and migration. The patterned rigidity gradient revealed lower lesser cell adhesion on the surfaces with lesser rigidity in comparison to the surface having higher rigidity.

Various surface modifications of synthetic polymers have been employed which were cohesive with material chemistry without affecting their integrity. Protein and cell repellant polymers, as well as specific cell binding polymers, were designed by incorporating ECM proteins/peptides (Sreejalekshmi and Nair 2011; Perlin et al. 2008; Hersel et al. 2003), peptidomimetic molecules (Hersel et al. 2003), carbohydrates (Hersel et al. 2003; Biltresse et al. 2005) growth factors serving as cell-binding motifs (CBMs). These are specifically used for the controlled cell adhesion. In-depth details are available in some exhaustive reviews on CBMs based biofunctionalisation of synthetic polymers (Delaittre et al. 2012; Hersel et al. 2003). CBMs based surface modifications rely on the fact that these motifs induce cell–surface interactions. ECMs proteins and biopolymers are functionalised either on the surface of the polymer or in the polymeric matrix. ECM proteins, for example, fibronectin, collagen, elastin and laminin contain signalling domains (short peptide sequences) that serve as binding sites during the cell adhesion. However, immobilisation of ECM proteins in comparison to the short sequences of cell binding motifs on polymeric matrices is disadvantageous in the following ways; (a) proteins are highly susceptible to degradation and structural deformation, (b) difficult to attach on surfaces and (c) short peptides are easily synthesised, attached and are less prone to the degradation.

In this section, we have mainly focused on the immobilisation of ubiquitously used short CBMs on polymeric surfaces for the specific and controlled cell adhesion applications as shown in Fig. 16.4. Among various CBMs used for the cell adhesion, short peptide sequences are the most widely used cell binding domains recognised by the transmembrane cell receptors (mainly integrins) present on the cell surface. RGD tripeptide sequence was the first recognised in ECM protein fibronectin (Pierschbacher and Ruoslahti 1984) and later in other ECM proteins such as collagen, laminin and vitronectin (Frantz et al. 2010; Hynes 2009; Ruoslahti 1996). RGD alone as well as different linear RGD sequences with flanking amino acid residues have been synthesized to improve the cell adhesion (as summarised in Table 16.2). However, linear RGD sequences undergo slow degradation due to enzymatic effects hence, cyclic RGD derivatives (such as cRGDfK) were designed to overcome this problem (Hersel et al. 2003; Massia and Hubbell 1991; Kantlehner et al. 2000). It should be noted that the linear and cyclic structures of RGD sequences affect their activities by addressing different integrin receptors (Hersel et al. 2003).

Apart from RGD peptides and their derivatives, various other peptide sequences such as IKVAV and YIGSR and derivatives have also been used for inducing the cell–surface interactions. These sequences are derived from laminin protein, which shows specificity against integrins like α1β2, α2β1 and α6β2. Moreover, IKVAV and YIGSR sequences when attached to polymeric surfaces induce the neuronal cell adhesion as laminin is the most dominant ECM protein

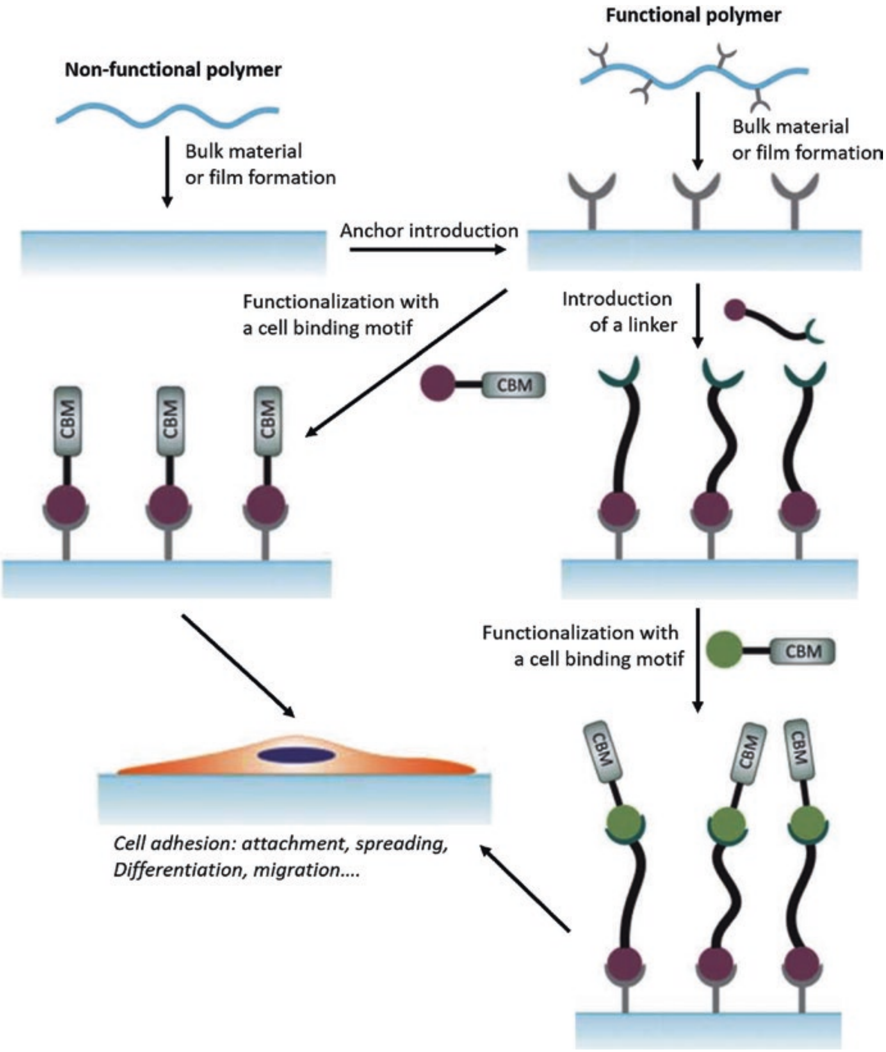

Fig. 16.4 Different approaches of modifying polymeric surface (with and without linker groups) by CBMs for enhanced cell attachment, spreading and proliferation. (Adapted with permission from Soft Matter, 2012, 8, 7323)

Table 16.2 Bio-functionalisation of polymeric surfaces using CBMs

Polymer	CBMs	Functional anchor and linker groups	Cell type	Results	References
PCL	GRGDY	NH_2, C_6-NH-C_5	NIH3T3 fibroblast	GRGDY conjugated surfaces showed better adhesion and spreading of NIH3T3 cells	Causa et al. (2010)
	RGDC	NH_2	Bone marrow stromal cell (BMSC)	PCL-RGDC showed significant FAK phosphorylation as compared to PCL-NH_2 and PCL alone	Zhang and Hollister (2009)
	GRGDSPC	COOH, acrylic acid	Keratinocytes (NCTC 2544)	Electron beam induced graft polymerisation; COOH group activation, EDC/NHS coupling; cells showed the spreaded round morphology on peptide coupled surfaces	Sun et al. (2004)
PDMS	GRGDS, PHSRN, YIGSR, and GEFYFDLRLKGDK	NH_2, star shaped isocyanate-terminated-PEG	Human–skin keratinocytes and fibroblasts	PEG coating prevents non-specific cell adhesion and CBMs promotes specific cell binding and spreading	Salber et al. (2007)
	RGDS, PHSRN, PDSGR	OH, allyl alcohol	Corneal epithelial cells	Plasma induced polymerisation; multiple peptides showed greater cell adhesion property than single peptides only	Aucoin et al. (2002)

(continued)

Table 16.2 (continued)

Polymer	CBMs	Functional anchor and linker groups	Cell type	Results	References
PET	GRGDY and GYIGSRY	OH	HUVECs	PET-OH is less cell adhesive while PET-CBMs showed enhanced adhesion even in the presence of only albumin and no other serum proteins	Massia and Hubbell (1991)
	RGD Peptidomimetics	OH and COOH, triethylene glycol	Caco-2 cells	RGD peptidomimetics can replace the use of RGD peptides and vitronectin; cost-effective synthetic protocol	Biltresse et al. (2005)
PHPC based PU	GRGDSP	Direct grafting	Endothelial cells	GRGDSP grafting density controlled cell adhesion and spreading; can be used for the fabrication of artificial small-diameter blood vessels	Li et al. (2008)
PS	RGDS and RGD	COOH, acrylic acid	Mouse fibroblasts cells	RGDS immobilised films were more heat and pH resistant with better cell adhesion as compared to fibronectin immobilised films	Ito et al. (1991)
	RGDS	COOH	NIH3T3	Patterned biofunctionalisation of polymers using electron beam induced COOH for immobilisation of RGDS and insulin for enhanced cell adhesion and proliferation	Hatakeyama et al. (2007)

PCL poly(caprolactone), *PDMS* polydimethylsiloxane, *PEG* polyethylene glycol, *PET* poly(ethylene terephthalate), *PU* polyurethane, *PHPC* poly(1,6-hexyl-1,5-pentylcarbonate), *PS* polystyrene, *PNiPAAm* poly(N-isopropylacrylamide), *EDC* 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC), *NHS* N-hydroxysuccinimide found in neuronal cells (Ranieri et al. 1994, 1995; Tong and Shoichet 1998; Shaw and Shoichet 2003). Different other peptide sequences such as KRSR (proteoglycan-binding from bone material), REDV (from fibronectin), DGEA (from collagen-I), SVVYGLR (from osteopontin), and VAPG (from elastin) have not been used much with synthetic polymers and hence can be explored for the potential applications.

Polymeric surface modification approaches: Two different widely used modes of anchoring CBMs on the polymeric surfaces are: (a) pre-functionalisation of polymer base material; in this method, the surface of the polymeric material is functionalised with CBMs, which does not alter the characteristic properties of the bulk material. It is not a widely used approach since most of the polymers used in biological applications are inert and hence, makes it difficult to anchor CBMs while there are few exceptions that contain reactive groups such as hydroxyl (PVA, polyvinyl alcohol; PHEMA, poly(hydroxyethyl methacrylate); PPF, poly(propylene fumarate)) and carboxylic groups (poly1-2-carboxyethyl pyrrole and PET, polyethylene terephthalate) (Massia and Hubbell 1990; Matsuda et al. 1989; Lee et al. 2009; 2006a; Biltresse et al. 2005). Lee and co-workers prepared a polypyrrole derivative, poly(1-(2-carboxyethyl)pyrrole) (PPyCOOH) which is carboxylated at N position of polymer backbone making it possible to conjugate with various biological moieties such as RGD tripeptide (Fig. 16.5a) (Lee et al. 2006a). (b) Post processing functionalisation of polymeric matrices; it is a simple procedure of incorporating CBMs on the surface of polymeric matrices. Although the protocol is simple, sometimes the implementation of the harsh treatments such as hydrolysis, UV or electron irradiation, and plasma treatment may cause the breakage of polymer backbone resulting in the altered substrate topology (Sidouni et al. 2001).

In a scheme shown in Fig. 16.5c, Sun and Onneby described a simple method of generating carboxylic functional groups on the PCL surface via hydrolysis for conjugating the cell adhesive peptide (Sun and Önneby 2006). While in another scheme Fig. 16.5d, aminolysis of PCL surface by hexanediamine for generating the amine groups on the surface via nucleophilic reaction is shown. The generation of amine groups on the surface was dependent on the reaction temperature and time (Santiago et al. 2006; Causa et al. 2010). Santiago and co-workers showed the bioconjugation of laminin derived peptide sequences, CBMs (RGD, YIGSR, and IKVAV) on the aminated–PCL surface for the adhesion of adipose-derived stem cells (ASC) and found that IKVAV was the most suitable CBM for the attachment and proliferation (Santiago et al. 2006). Several other peptides sequences have also been reported that enhance the cell adhesion and spreading on various CBMs modified polymers as shown in Table 16.2. Nucleic acid (DNA and RNA) based aptamers have been used for various applications such as the development of sensors (Song et al. 2013; Wen et al. 2011) and tools in biotechnology (Iliuk et al. 2011), but have not been applied much in the polymeric surface modification. Biofunctionalisation of such molecules can be of great help in bio-sensing industries and explored more for accessing their stability and efficiency.

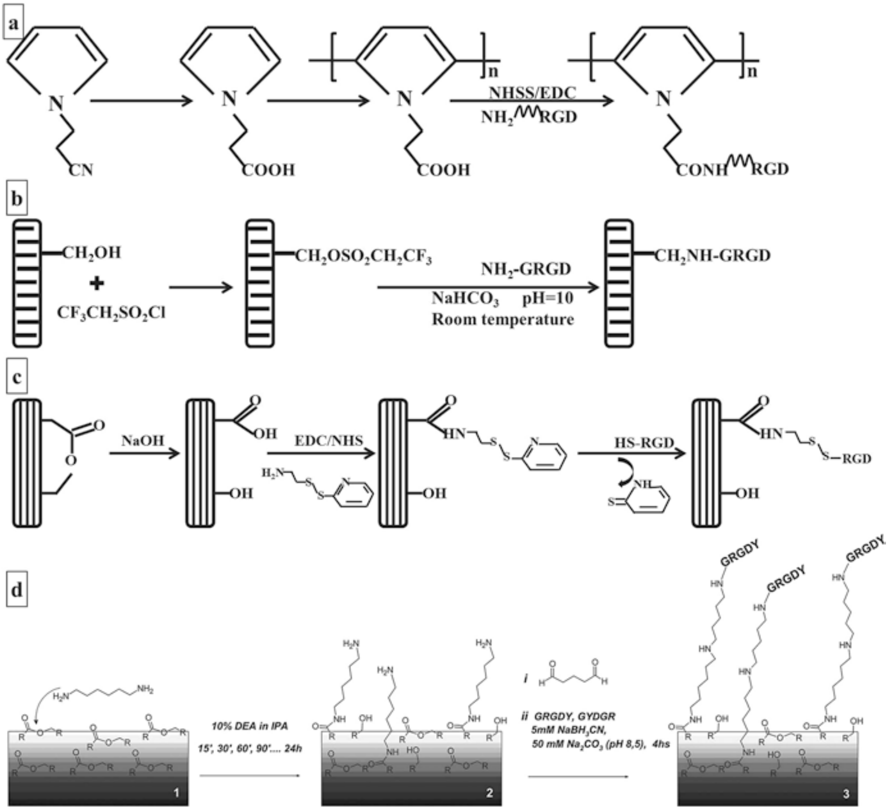

Fig. 16.5 (**a**) Schematic representation of carboxylation of polypyrrole for chemical conjugation with RGD tripeptide for enhanced attachment and spreading of human umbilical vascular endothelial cells (HUVECs) (Lee et al. 2006a), (**b**) Coupling of GRGD peptide to hydroxymethylated PET film, (Massia and Hubbell 1990) (**c**) Attachment of pyridyl disulfide group onto hydrolysed polycaprolactone (PCL) followed by addition of cysteine-containing RGD via disulfide linkage (Sun and Önneby 2006), (**d**) Hexanediamine (aminolysis/amination) treatment of PCL surface followed by covalent linkage of GRGDY pentapeptide via glutaraldehyde (Causa et al. 2010). ((**a**) Adapted with permission from Biomacromolecules 2006;7(6):1692–1695. Copyright (2006) American Chemical Society. (**d**) Adapted with permission from Langmuir 2010;26(12):9875–9884. Copyright (2010) American Chemical Society)

4 Factors Affecting Cell Adhesion

4.1 Surface Characteristics

Biomaterial implantation may either be done as a permanent implant for a specific function (ex. heart stent) or as a temporary implant to support the growth of ruptured or new tissues (ex. bone plate, screws, etc.). In both cases, surface characteristics play a vital role in determining cell–implant interactions. Hence, it is essentially required to have a clear understanding of the cell–implant interactions in order to engineer the directed cell response. The improper implant performance in the human body is the result of the non-integration of the implant with tissues, which finally causes implant rejection. Physical surface characteristics like roughness, surface potential, material porosity and wettability direct the cellular functions such as cell adhesion, proliferation and differentiation. Topological and chemical properties of biomaterial surfaces not only regulate cellular functions but also modulate genotypic as well as phenotypic differentiation (Kasemo 2002). Rosales-Leal and co-workers classified surfaces on the basis of the degree of surface information, as (a) height/spatial distribution, (b) topology and (c) morphology (Rosales-Leal et al. 2010). The height/spatial distribution gives the measurement of the surface roughness in the nanometer scale using amplitude or horizontal lengths. The topology of the surface is described as a property correlated to structures like connectedness and compactness giving random roughness organisation at the biomaterial surface. Morphology is basically the microscopic structure at the surface giving detailed information about surface topology at a higher resolution performed by scanning electron microscope (SEM).

4.1.1 Topography

Significant progress in tissue engineering from the last few decades has resulted in remarkable research findings on the bio-interface engineering for the controlled cell responses to material surfaces. Surfaces have been tailored to provide the physical and chemical cues for cell proliferation and differentiation for the successful integration of the implant in surrounding tissues. Surface topology is one among the other important surface properties substantially affecting the macroscopic behaviour of biomaterial and controlling the quantity and quality of cells adhered to the implant surface.

In bone tissue engineering, it is important to evaluate topology as it modulates biological events during the osteointegration at the bone–implant interfaces. Nanoscale surface topographies are the current trends in the biomaterial research, as it is hypothesised to resemble ECM and control the various events at molecular and cellular levels (Lord et al. 2010). Days are gone when microscale surface topologies of biomaterials were designed and studied for cellular behaviour. With the advancement of technologies in the era of nanotechnology, surfaces bearing nanoscopic topologies have been recently designed and revealed that such topologies produce considerable effects on the protein adsorption and cell adhesion.

4.1.1.1 Lithography

It is one of the most ancient and widely used patterning techniques for producing features with controlled dimensions and specific shapes. It was first used by Brunette and co-workers for producing grooved surfaces with excellent uniformity to study the cellular interactions at surfaces (Brunette et al. 1983). Different topological features like grooves, grooves and pits, ridges, steps, waves, poles and spheres have been fabricated using photolithography supplemented with reactive ion etching, glow discharge, anisotropic etching and wet etching (Brunette 1986; Den Braber et al. 1996; Chesmel et al. 1995; Flemming et al. 1999). Other techniques such as glancing angle deposition, laser ablation and deposition, replica moulding of X-ray lithography masters, imprint lithography, micro-contact printing (μCP) and etching, and inkjet printing have also been extensively used for one or the other advantages depending upon the substrate used (Robbie and Brett 1997; Phillips and Sauerbrey 1993; McClelland et al. 1993; Xia et al. 1996). Optical lithography is a well-established patterning technique in the field of microelectronics, used for the fabrication of integrated circuits. Photoresists used in this technique are generally made of polymers, whose chains undergo molecular rearrangement, folding or degradation when exposed to the external energetic sources. Due to limitations like patterning of limited functional materials, little functional group modifications are possible and failure in producing 3D patterns has prompted the development of other patterning techniques. Not very old technique of generating arbitrary patterns, known as writing, whose resolution can be controlled from macroscopic size to atomic level. Writing techniques can be used to produce patterns induced by physical, chemical, mechanical, electrical or their combinations, as per the substrate and required applications. Depending on these mentioned patterns inducing ways, separate methods have been designed. For example, micromachining is a mechanical method of surface modification, requires direct contact of the stylus with the surface (Abbott et al. 1994). The stylus moves on the surface generating a pattern in relief. Scanning tunnelling microscope (STM) and atomic force microscopy (AFM) with ultra-sharp tips (nanometer range) are employed for writing the high-resolution patterns. Photons beam may also be used as an energetic source for producing the physical and chemical changes. μCP based on laser assisted ablation relies on radicals generated in the gas, which causes removal of the material from the substrate. Focused beams of electrons used in electron-beam lithography also serve as an important tool along with SEM for the high throughput patterning. Depending on the chemical nature of resists, polymers, inorganic materials and self-assembled monolayers (SAMs) have been widely used for generating patterns in different applications.

Laser induced chemical vapour deposition (LCVD) is an attractive add-on writing method used for patterning (via deposition) planar as well as non-planar surfaces that are not compatible with resist or etching. Photolytic and pyrolytic are the two major variants used for the writing via cleavage of chemical bonds by photon adsorption and thermal induction, respectively. Inkjet printing (IJP) is a smart alternative technique, which relies on small volume (10–20 pL) deposition of liquid ink using nozzles of micrometer diameter (20–30 μm) onto surfaces with good spatial control. Being a soft technique, it had been a method of interest in developing the polymeric features and exploited widely in biochips fabrication. High resolution dip-pen nanolithography (DPN) technique had gained a lot of interest due to its salient features of patterning biomolecules such as protein and DNA on substrates. AFM tip dipped in the liquid ink is moved on the substrate to deliver the material via a thin film formed between tip and surface.

Nanoscience is an important area of research, which proved to be an important tool for discovering various techniques for developing surface nano-topologies and to study their role in solving the complex interactions between surfaces and biomolecules. Techniques like photon and electron based lithography, nano-imprint lithography (NIL), etching and glancing angle deposition (GLAD), combined with etching and deposition techniques, have opened ample of the opportunities and challenges for researchers to explore new methods of surface modification for advanced biomaterials. Although these sophisticated techniques produce desirable nano-topologies but widely suffer from one or the other drawbacks like high processing cost and time, toxic byproducts, such post process may hinder biomaterial performance hence, making such processes unsuccessful for commercialisation.

4.1.1.2 SAMs Pattern

Fabrication of micro and nanoscale patterns using photolithography requires a photoresist for selective etching of the material. Properties of the photoresists are important as it decides the pattering mode (positive or negative), controls the dimensions, resolution and stability of the etched surface. Since then, polymer science has played a crucial role in photoresist formulation and is a field of intense interest in the regeneration of better quality photoresists. Silane and thiol based resists layers are the latest trends in photoresist formulation. Their ability to form a thin monolayer helps in improving resolution (Azuma et al. 1996). SAMs were for the first time used as an alternative for photoresists in 1991. SAMs consisted of phenyltrichlorosilane (PTCS), benzyltrichlorosilane (BTCS), N-(2-aminoethyl-3-aminopropyl) trimethoxysilane (APTMS) and were used for the deep ultraviolet photo-patterning using different UV sources (Dulcey and Georger Jr 1991). Since then, various organosilane and SAMs patterning techniques like e-beam lithography, scanning probe lithography, micro-contact printing, latex bead projection patterning and nanoimprint lithography have been introduced for serial as well as parallel patterning as summarised in Table 16.3. Techniques like ion or electron beam lithography are highly desirable for serial fashion patterning by destroying SAMs using irradiation resulting in the high resolution nanopatterning.

Organosilane SAMs have been widely exploited in studying protein adsorption and cell adhesion on the modified surfaces. Immunoassay-based diagnostic devices have been developed as an outcome of extensive research on immobilisation of biomolecules (protein, nucleic acid) in a controlled manner and without losing their structural and functional properties (Karyakin et al. 2000; Turkova 1999; Crampton et al. 2005). Utmost care is taken during the fabrication of such surfaces since changes in surface characteristics may alter adhesive properties resulting in an overall change in the behaviour of adsorbing biomolecules and cells. This may be important since the detection of target molecules with high sensitivity and selectivity are the major features of such diagnostic devices (Johnson and Martin 2005; Tsang et al. 1995). Recently it was reported that controlling chain length in growing SAMs helps in the passivation of nanopatterns. On combining such tailorable SAMs with nanosphere

Table 16.3 Types of SAMs and patterning techniques

SAM type	Fabrication method	Substrate	Feature dimensions	Observations	Reference
APTES	E-beam lithography	PMMA onto Si/SiO_2 substrate	NA	Au NP patterned on SiO_2 surface for single-electron transistor applications	Coskun et al. (2009)
	μCP	SiO_2	2.5 nm height pattern	Au NP on APTES served as a template for the growth of ZnO nanostructures, immobilisation of lectin on APTES pattern	Li et al. (2009)
OTS	UV irradiation, particle lithography, CVD	Gold	Nanopatterns of 3.7 nm height, 246 nm diameter with inner ring pore area of 46 nm, spaced 321 nm apart from each other	Particle lithography with CVD developed highly periodic OTS nanostructures of uniform height. UV irradiation improved surface wettability	Li and Garno (2009)
	Latex bead projection	SiO_2 glass substrate	Hexagonal geometry with 2.8 nm OTS monolayer on 6 nm diameter gold NP	Multifunctional SAM nanostructures with controlled dimensions to tailor binding properties of the structure	Herzer et al. (2008)

APTES (3-aminopropyl) triethoxysilane, *OTS* octadecyl trichlorosilane, *CVD* Chemical vapor deposition

lithographic technique, resulted in highly selective nanopatterns showing specificity for the single protein adsorption. By varying the size and distance of gold nanostructures, it was possible to regulate the size of focal adhesion, and influencing the fibronectin formation by human dermal fibroblasts cells (Niepel et al. 2013).

4.1.2 Surface Roughness

Surface roughness can be classified into three divisions based on topological irregularities on the surface such as macro-roughness (>100 μm), micro-roughness (<100 μm) and nano-roughness (<100 nm) (Vagaská et al. 2010). Nanoscale changes in surface topology may significantly alter the protein adsorption and cellular behaviour. Several topological research studies have reported that altering surfaces at micron- and nanoscale, leads to the enhanced cell differentiation and ECM production in vitro (summarised in Table 16.4). A recent study by Gittens and co-workers have predicted a higher level of osseointegration of bone implant due to similarity with bone hierarchical complexity with micro- and nano-scale modified implant surface (Gittens et al. 2011). However, it is important to note that the vertical and lateral character of the roughness parameter should be considered while modifying the surfaces and hence

Table 16.4 Effect of surface functionalisation on physico-chemical properties and cell behaviour

Substrate type	SAM-group	Water contact angle (deg)	Surface roughness (nm)	Cell line studied	Type of integrin	Results	Reference
Glass	NH_2, CH_3, COOH, Hybrid[a], Mixed (NH_2-CH_3)	NH_2-60° CH_3-103° COOH-45° Hybrid-79° Mixed (NH_2-CH_3)-81°	NH_2-0.95, CH_3-0.51, COOH-1.14, Hybrid-0.46, Mixed (NH_2-CH_3)-1.12	L929-mouse fibroblast cells	NA	Surface coverage rate by cells: Hybrid > NH_2 > COOH	Hasan et al. (2018a)
	OH, NH_2, EPOXY, COOH, CF_3, SO_3	NH_2-65°, CF_3-85°, EPOXY-40°	NA	Dermal fibroblasts	α5β3	Integrin expression trend: NH_2 > OH > EPOXY >SO_3 > COOH>CF_3	Altankov et al. (2003)
Gold	Mixed NH_2/COOH	NA	< 2	NIH3T3	NA	Cell attachment and proliferation increased with increasing surface potential.	Chang et al. (2014)
	CH_3, NH_2, COOH, OH	CH_3-108°, OH-24°, COOH-30°, NH_2-47.5°	NA	Endothelial cells	α 2,α5, αV, β1, β3	– COOH-α 2,α5, αV, β3 higher expression while β1 lesser expression – CH3-αV and β1 higher but α 2,α5,β3 lesser – NH2 and OH –intermediate expression	Shen et al. (2015)
	CH_3, COOH, OH, PL	CH_3-101°, COOH-18°, OH-7°	NA	HeLa	α1,α2, α3, α4, α5, αV, αVβ3	– increased expression of αV and αVβ3 – decrease of α2, and α3 on PL surfaces than TCPS indicate migration of HeLa cells rather than proliferation on PL – Negatively charged surfaces with WCA ~20° offer better cell adhesion and proliferation	Santos et al. (2014)
	CH_3/OH, CH_3/NH_2, CH_3/COOH	CH_3/OH-40 CH_3/NH_2-50 CH_3/COOH-50	NA	HUVECs, HeLa	NA	CH_3/OH—Maximum HUVECs adhesion. CH_3/OH and CH_3/COOH-maximum HeLa adhesion. – Results indicate cell adhesion depends on surface chemistry and cell type	Arima and Iwata (2007)
	OH, COOH, NH_2, CH_3	NA	NA	MC3T3-E1	α5β1 and αVβ3	Integrin expression pattern: α5β1- OH > NH_2 = COOH > CH_3 αVβ3- COOH > NH_2> > OH=CH_3	Keselowsky et al. (2004)

Substrate type	SAM-group	Water contact angle (deg)	Surface roughness (nm)	Cell line studied	Type of integrin	Results	Reference
Silicon	OH, COOH, NH_2, CH_3	OH-44° COOH-27° NH_2-41 CH_3-103°	OH-0.27 COOH-0.21 NH_2-0.24 CH_3-0.25	K562	α5β1	COOH surface with pre-adsorbed Fn interacted more strongly with α5β1 in comparison to Fn-NH_2 and Fn-CH_3 surfaces	Lee et al. (2006b)
Ti6Al4V	NH_2, CH_3, COOH, Hybrid[a], Mixed (NH_2-CH_3)	NH_2-63° CH_3-105° COOH-42° Hybrid-82° Mixed (NH_2-CH_3)-86°	NH_2-720, CH_3-740, COOH-710, Hybrid-750, Mixed (NH_2-CH_3)-830	L929	NA	Hybrid surface with pre-adsorbed Fn showed better cell adhesion and spreading	Hasan et al. (2018b)
	Hybrid[a]	82°	3.2	MG63	α1,α2, α3, α4, α5, αV, αVβ3	Higher expression of α1 and α2 integrins on hybrid surfaces with pre-adsorbed Col-I	Hasan and Pandey (2020)

NA Not available, *PL* Poly-L-lysine, *TCPS* tissue cultured polystyrene, *HUVECs* human umbilical vein endothelial cells, *Fn* Fibronectin, *K562* Erythroleukemia cell line

aHybrid contains both NH_2 and CH_3 groups on the same molecule; MG63, human osteosarcoma cell line there is no empirical formula to define the best universal roughness for the enhanced cell response. For example, Wu and co-workers reported better response of hFOB osteoblast cells on plasma-sprayed titanium surfaces as compared to satin finished surfaces due to the microscopically smooth and macroscopically rough surfaces offered by a plasma-spraying (Wu et al. 2011). Furthermore, rough topology induces enhanced expression of β_1, β_3 and α_5, integrins mediated fibrillar adhesions (Lüthen et al. 2005) and $\alpha_2\beta_1$ mediated cell proliferation (Luo et al. 2018).

4.1.3 Surface Potential

Surface potential in combination with other factors like wettability and surface roughness plays a significant role in cell adhesion and proliferation via integrin expression. Altankov and co-workers used siloxane SAM-modified glass surfaces for studying the effect of surface potential along with wettability (Altankov et al. 2003). It is interesting to note that cell adhesion and spreading decreased in the order of $-NH_2 > -OH >$ EPOXY $> -SO_3 > -COOH > -CF_3$, which was opposite to the order of the negative surface potential. This indicates that positive surface potential favours cell adhesion and spreading and was also evidenced by the fluorescence microscopy results. Increasing α5β1 integrin expression also follows the same order of cell adhesion ($-NH_2 > -OH >$ EPOXY $> -SO_3 > -COOH > -CF_3$). Chang and co-workers also obtained a similar effect of the surface potential on cell adhesion and proliferation (Chang et al. 2014). It was also found that the rate of cell proliferation increased with the increasing incubation time and surface potential. The better cell–cell interactions and cell adhesion were observed on surfaces with positive surface potential, but lesser proliferation rate when seeded at higher density. It was concluded that contact inhibition is a major reason for the lesser proliferation rate at higher seeding density in comparison to lower density. Kirby and co-workers also showed that lesser cell adhesion on decreasing zeta potential of polyacrylamide films attached to SAMs on the silica micro-channels (Kirby et al. 2003). Hence, it is a well-established fact that by engineering surfaces one can easily modulate their zeta potential for a particular application.

5 Conclusions

Physio-chemical properties of surfaces such as surface topography (patterns), roughness, surface wettability, energy and surface potential play a critical role in regulating the protein behaviour, which in turn controls cell response. Various surface modification techniques such as physical, chemical, biological, biochemical and physio-chemical have been employed to obtain the desirable effects, which may vary from application-to-application. For example, certain applications require no protein adsorption (anti-fouling surfaces), while in some applications such as biosensors, surfaces require specific conformation of adsorbed proteins for optimum sensing and also recognition for the integrin mediated cell adhesion.

Many such strategies have been successful in tailoring the surface properties to tune the desired bio-interfacial interactions. However, the underlying mechanisms that regulate protein adsorption and cell behaviour remain uncertain and require further mechanistic investigations.

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Part III

Nanotechnology for Plant and Environmental Applications

Chapter 17

Nanotechnology as Effective Tool for Improved Crop Production under Changing Climatic Conditions

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1 Introduction

The Intergovernmental Panel on Climate Change (IPCC 2001, 2007) defined the climate as "the average weather at a given period of time, whereby it is described in terms of mean and variability of weather elements such as temperature, precipitation, and wind over a specified time". "Climate change" is a change that can be identified using statistical methods and that has persisted for more than a decade. This change can be caused not only by natural phenomena (e.g., modulation of the solar cycle or volcanic eruptions) but also due to long-term anthropogenic activity manifested, for example, in the composition of the atmosphere or land use. In contrast, the United Nation Framework Convention on Climate Change (UNFCCC) defines "climate change" as "a change of climate that is attributed directly or indirectly to human activity that alters the composition of the global atmosphere and that is in addition to natural climate variability observed over comparable time periods" (United Nations Framework Convention on Climate Change 1992). Anthropogenic activities connected with the increase of heat trapping greenhouse gases (GHGs), water vapor, CO_2, CH_4, N_2O, and O_3, which absorb and emit radiant energy within the thermal infrared range in the atmosphere, contribute to global warming. At present 72% of the anthropogenic greenhouse effect could be contributed to CO_2 because of its stronger absorption band for infrared heat. Atmospheric carbon burden (concentrations of CO_2 + CH_4) increased significantly by about 260 ± 5 Pg from approximately 1750 (i.e. from the beginning of the Industrial Revolution) to 2015 due to the widespread use of fossil fuels for energy, cement production, conversion of land use and deforestation. The total amount of CO_2 emitted into the atmosphere is proportional to the global temperature increase (Rogelj et al. 2015), and it was estimated that the temperature of the air above the land rises faster than the temperature in the oceans; during the twentieth century, it increased on average by 0.75 °C (IPCC 2007; Hansen et al. 2006). It could be mentioned that beside GHGs emitted to the atmosphere by burning fossil fuels, the contribution of agricultural emissions (CO_2, CH_4, and NO_x) is related to livestock production and these emissions consist of approximately 27% CO_2, 44% CH_4, and 29% N_2O (Gerber et al. 2013; Food Emissions 2020). Globally, CH_4 and N_2O emissions from livestock production in 2010 were ca. 9% of total GHG emissions, with global livestock GHG emissions increasing by 51% during 49 years (1961–2010) (Caro et al. 2014).

Change of climate associated with the frequent occurrence of diseases and pests, as well as increased abiotic stresses (floods, drought, enhanced temperature, increasing soil salinity), could decrease crop yields by 10–20% (Jones and Thornton 2009). Climate change-induced fluctuations in weather patterns represent a serious threat to crop yield sustainability (Porfirio et al. 2018). Since global food requirements should increase by 70–100% by 2050 due to human population growth (Burney et al. 2010), it is inevitable not only to reduce GHGs emissions but also enhance resilience on climate change using alternative approaches in agriculture practice, including climate smart agriculture (FAO 2013; Campbell et al. 2014; Venkatramanan et al. 2020,

2021) and sustainable land management (Lal 2004) to maximize the economic profits from the land but also to maintain and/or enhance the ecosystem services that land resources provide (Ussiri and Lal 2017). In addition, reducing CO_2 emissions will contribute to a more stable agricultural system that can reduce food insecurity more effectively (Porfirio et al. 2018). In December 2018, the United Nations General Assembly declared 2020 the International Year of Plant Health (IYPH), which aims to increase global knowledge of how healthy plants can protect the environment, reduce hunger and poverty, and promote overall economic development.

It will be necessary to pay increased attention to mechanisms and processes securing good plant performance under limiting resources in order to obtain sustainable crop yields in a broader range of environmental conditions and design mitigation strategies which enable to combat efficiently with the adverse impact of much more frequent extreme weather events on agricultural production (Tubiello et al. 2008; Rojas-Downing et al. 2017; Kulshreshtha and Wheaton 2018; Raza et al. 2019; Pareek et al. 2020). The use of effective crop protection technologies will contribute to the adaptation to altered climatic conditions as well.

Nanotechnologies focused on the design of materials with unique particle sizes and thus, unique properties allow to expand the range of uses of existing materials can be considered key technologies of the twenty-first century (e.g., Sekhon 2014; Jampílek and Kráľová 2015, 2017a, b, c, 2018a, b, c, 2019a, b, c, 2020a, b; Jampílek et al. 2019, 2020; Prasad et al. 2017) being one of the effective tools capable to cope with the adverse impact of abiotic stresses caused by climate change. The US National Nanotechnology Initiative defines nanoparticle (NP) size by a range of 1–100 nm (U.S. National Nanotechnology Initiative 2004). The European Commission adopted a definition where "nanomaterial means natural, incidental or manufactured material containing particles, in unbound state or as an aggregate or as an agglomerate, and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1–100 nm" (European Commission 2011). Beneficial effects on plants growth and crop yields of nanoscale materials used in nanopriming or as fertilizers applied foliarly or in soil were frequently observed and described by a lot of scientists (e.g., Masarovičová et al. 2014; Liu and Lal 2015; Jampílek and Kráľová 2017b, 2018a, 2019b, c; Elemike et al. 2019; Juárez-Maldonado et al. 2019; Shang et al. 2019). On the other hand, also the use of nanosized formulations of insecticides, bactericides, or fungicides in plant protection can significantly contribute to better yields, and the application of nanoscaled herbicides killing harmful weeds has great importance for improved agricultural production as well (Abd-Elsalam and Alghuthaymi 2015; Fraceto et al. 2016; Jampílek and Kráľová 2015, 2017a, 2018a, 2019a, 2020a, b; Jampílek et al. 2019, 2020; Worrall et al. 2018; Azamal and Iqbal 2019; Raliya 2019; Sun et al. 2020). The use of biologically active NPs in agriculture is favorable because compared to their bulk counterparts for the same effect lower dose is required, the nanoformulations show controlled and targeted release of the active compounds and are less toxic to nontarget organisms (Jampílek and Kráľová 2017a, b, 2019a, b, c; Jampílek et al. 2020; Camara et al. 2019; Lichtfouse 2020). These advantages of NPs for improved agricultural production can be utilized also under climate change conditions. In addition, it seems that the application of NP can significantly help reduce abiotic stresses in plants. Potential use of nanoparticles/nanoformulations under changing climatic conditions is shown in Fig. 17.1.

The aim of the contribution is to provide a comprehensive view of the adverse impacts of abiotic stresses on crops when climatic conditions change, which affect also the spreading of weeds, noxious insects, and plant diseases. The positive impact of various nanoparticles/nanoformulations applied as priming agents and fertilizers ameliorating the growth, yield, and nutritional quality of crops, their important role in crop protection against harmful insects, fungal diseases, and weeds as well as in mitigation of some abiotic stresses (heat, drought, UV radiation, excess salinity, and flood), which could help to achieve improved crop yields under climate change conditions are discussed.

2 Nanoscale Materials Used for Improved Plant Growth

2.1 Nanopriming

Seed priming is defined as the pre-sowing treatment of seeds leading to a physiological state enabling more efficient seed germination. In water-based seed priming, the seeds are partially hydrated without allowing emergence. While at hydropriming the seeds are soaked in pure water and subsequently dried to original moisture content prior to sowing, at the osmopriming the seeds are soaked in an osmotic solution instead of pure water. On the other hand, at hormopriming, the plant growth regulators present in an aqueous solution can affect directly the seed metabolism during seeds imbibition. Biopriming involves seed imbibition together with bacterial inoculation of seeds and at halopriming specific salts are applied. Also, the application of various chemical compounds in their bulk or nanosized form used as priming agents can exhibit beneficial effects on plant germination and growth (Suman et al. 2010; Singhal et al. 2017). At nutripriming, that is, soaking of seeds with solutions containing the limiting nutrient (e.g., essential metals such as Zn, Cu, Mn, or Mo) instead of pure water, the supply of nutrients for early growth is reflected in improved germination, seedling vigor, and root system development. A comprehensive overview focused on the seed priming-induced modifications was presented by Lutts et al. (2016), while new perspectives related to seed priming were summarized by Paparella et al. (2015).

In aged germinating rice seeds nanoprimed with AgNPs stimulation of the upregulation of aquaporin genes and increased formation of reactive oxygen species (ROS) was estimated. Hence, nanopriming could result in the nanopores formation for increased water uptake, rebooting ROS/antioxidant systems in seeds, production of harmful $HO^{\bullet}$ species causing loosening of the cell wall and NPs can act as nanocatalysts for starch hydrolysis (Mahakham et al. 2017). The beneficial impact of priming of safflower seeds with 40 ppm AgNPs was reflected in seed yield 2180.63 kg/ha (being by one third higher than the control), while application of

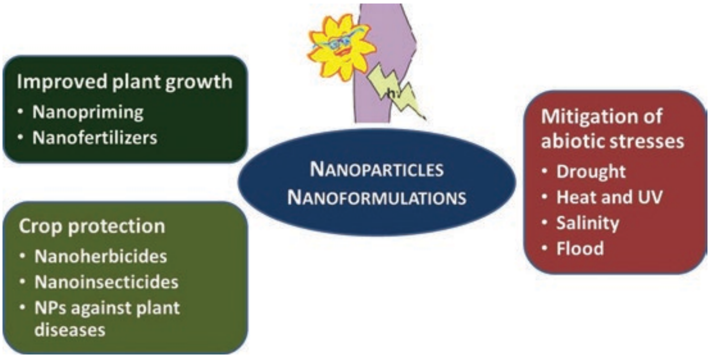

Fig. 17.1 Potential use of nanoparticles/nanoformulations under changing climatic conditions

20 ppm AgNPs resulted in 30.8% higher oil yield (522.87 kg/ha) compared to untreated plants (Zari et al. 2015). Zn–chitosan (CS) NPs (0.01–0.16%) applied via seed priming or by foliar treatment effectively stimulated maize growth, controlled Curvularia leaf spot disease, and ensured fortification of *Zea mays* plant with Zn. The favorable impact of Zn–CS NPs was connected with improved activities of antioxidant and defense enzymes, and higher lignin accumulation (Choudhary et al. 2019).

Comparison of the impact of seed priming and foliar application of CS NPs and carbon nanotubes (CNTs) applied as fertilizers on French bean plants either alone or loaded with NPK showed ameliorated growth, yield and antioxidant system of plants and biochemical content of yielded seeds was improved as well. However, the foliar treatment was found to be more effective and it resulted even in a significant reduction of days to harvest without reducing yield compared to control and seed priming treatment (80 vs. 110 days) (Abdel-Aziz et al. 2019). Some examples of favorable effects of priming with metal- and carbon-based NPs on crops are shown in Table 17.1.

2.2 Nanofertilizers

Climate change accompanied by temperature anomalies results in increased agricultural emissions from nitrogen fertilizers. For reducing of adverse effects of these temperature anomalies mainly increased inputs of fertilizers are frequently applied resulting in enhanced emissions from nitrogen fertilizers (Erbas and Solakoglu 2017). Due to anthropogenic activity, the rate of nitrogen input into the terrestrial nitrogen cycle was doubled and the global concentration of N_2O, a potent greenhouse gas as well as other NO_x increased (Vitousek et al. 1997). The rise of atmospheric N_2O concentration from 270 ppb in the preindustrial period to approx. 319 ppb in 2005 could be attributed mainly to agriculture (IPCC 2007) and according to Mosier (2001) animal and crop production is responsible for 70% of annual

Table 17.1 Beneficial effects of priming with nanoparticles on crops

NPs	Applied NPs concentration	NPs size (nm)	Applied seeds	Beneficial effects of priming on plants	References
Ag	10 mg/L 20 mg/L	5 10	Rice (aged)	↑ Germination performance, seedling vigor, α-amylase activity, plant growth	Mahakham et al. (2017)
Au Ag	5.4 ppm 31.3 ppm	116.2 93.7	Onion	↑ Germination, emergence, growth, and yield	Acharya et al. (2019)
Au	5 and 15 ppm	10–30	Maize	↑ Emergence percentage, vigor index; improved physiological and biochemical characteristics of plants	Mahakham et al. (2016)
ZnO	25–100 mg/L	34.4	Wheat	↑ Growth, photosynthesis, plant biomass, Zn levels in plants organs and grains	Munir et al. (2018)
ZnO	10 ppm	30–40	Wheat	↑ Plant growth and biomass, number of spikelets per spike, spike length, number of grains per spike, TPC levels, Fe content in grains	Mansoor et al. (2019)
ZnO Fe	25–100 mg/L 5–20 mg/L	20–30 50–100	Wheat	↑ Plant growth, Chl contents, Fe and Zn concentrations and ↓ oxidative stress, electrolyte leakage, and Cd content in plants grown under Cd stress	Rizwan et al. (2019)
CuFeCo	3–5 mg/L	30 70	Maize	↑ Germination rate, plant growth, SOD and APX activities, yield over three seasons	Hoang et al. (2019)
FeCuCoZnO	50 mg/L	40–60	Soybean	↑ Germination, root growth acceleration, and ↑ growth of leaves, cell division at root tips	Hoe et al. (2018)
Fe	20 mg/L	33.8	Aromatic rice cultivar	↑ Length of roots and shoots, biomass, the content of assimilation pigments, activities of hydrolytic and antioxidant enzymes, and root dehydrogenase enzyme activity	Guha et al. (2018)

(continued)

Table 17.1 (continued)

NPs	Applied NPs concentration	NPs size (nm)	Applied seeds	Beneficial effects of priming on plants	References
Fe_2O_3	20–160 mg/L	19–30	Watermelon	Modulated 12-oxo phytodienoic acid levels, ↑ nonenzymatic antioxidant potential, induced jasmonates-linked defense responses	Kasote et al. (2019)
Multi-walled CNTs	70–90 mg/L	diameter 13–14	Wheat	Early germination, excessive root hairs, denser stomata, ↑ root length, and yield	Joshi et al. (2018)

anthropogenic N_2O emissions. It could be emphasized that the global warming potential of N_2O emissions is 298 times greater than that of CO_2, considering 114 years as a lifetime and 100 years of time horizon (Forster et al. 2007). The contribution of increased emission of N_2O to the global warming was found to be 6.2% compared to 76% and 16% contributions of CO_2 and CH_4, respectively, although there are also cooling effects caused by altered concentrations of tropospheric O_3 and CH_4 due to emissions of NO_x and formation of NO_x and NH_3 aerosols (Fagodiya et al. 2017). The overuse of nitrogen fertilizers is connected with their increased accumulation in the soil and rivers and strong increases in nitrogen fluxes due to anticipated changes in precipitation patterns are expected by the end of the twenty-first century resulting in increased eutrophication (Sinha et al. 2017; Yao et al. 2020). However, climate change accompanied by increased temperatures and longer drought periods has an adverse impact on plant performance, and therefore appropriate fertilization of crops with macro- and micronutrient is inevitable.

Maintenance of soil fertility and improved yields and quality of crops require nutrient fertilization using effective fertilizers ensuring high nutrient use efficiency, whereby nanofertilizers could be considered as a useful tool for sustainable soil management (Sanivada et al. 2017; El-Ramady et al. 2018; Zulfiqar et al. 2019; Prasad et al. 2014; Bhattacharyya et al. 2016; Sangeetha et al. 2017a, b). Plant mineral nutrition is a prerequisite to reach higher agricultural productivity and can be applied via foliar and soil routes. Plants absorb nutrients from fertilizers and while nutrient use and uptake efficiency of most conventional fertilizers are low, nutrient nanofertilizers are designed to be target oriented and not easily lost (Elemike et al. 2019).

The efficiency of nutrient utilization in crops in intensive agriculture is less than 50% under all agroecological conditions (Baligar and Fageria 2015). Nutrients applied either alone or in combination, which are bound to nanoscale adsorbents, are characterized with considerably protracted nutrient release than conventional fertilizers (Zulfiqar et al. 2019). Mineral nanofertilizers and CNTs are characterized by controlled release and better targeted delivery efficiency than their bulk counterparts (Chhipa and Joshi 2016; Chhipa 2017). Due to smart delivery mechanisms and controlled release of active ingredients the nanofertilizers can minimize excess runoff to water bodies and reduce the environmental impact of agricultural practices and improve plant productivity, which is exceedingly desirable with respect to the rising global population and need for increasing food demand (Raliya et al. 2018; Saldivar et al. 2018; Adisa et al. 2019). Besides improving crop production, the nanofertilizers could also secure biofortification of crops with nutrients (Elemike et al. 2019). Beneficial as well as adverse effects of nanofertilizers applied foliarly and by soil routes to plants, their impact on plant microorganisms associated with plants, and effectiveness in controlling agricultural pests was summarized by Achari and Kowshik (2018) and Feregrino-Perez et al. (2018). Kah et al. (2018) presented a critical evaluation of nanofertilizers and nanopesticides compared to their conventional analogs. Nanofertilizers for precision and sustainable agriculture were discussed by Raliya et al. (2018). However, it could be emphasized that the wide use of nanofertilizers in agricultural practice requires their large-scale industrial production (Dimkpa and Bindraban 2018).

Nanofertilizers could be classified into (a) macronutrient nanofertilizers (e.g., $Ca_5(PO_4)_3$ NPs, $CaCO_3$ NPs, and MgO NPs), (b) micronutrient nanofertilizers (e.g., Fe_3O_4 NPs, MnO NPs, ZnO NPs, and CuO NPs), (c) nutrient-loaded nanofertilizers (zeolites, SiO_2 NPs, and CNTs), and (d) plant growth-stimulating nanomaterials (TiO_2 NPs, and CNTs) (Liu and Lal 2017).

Materials used as nanosize carriers of macronutrient (N, P, and K) fertilizers were comprehensively reviewed by Jampílek and Kráľová (2017b). Hydrotalcite-like layered double hydroxide structure ([Mg-Al]-LDH) was found to release PO_4^{3-} ions into water over a tenfold longer period, compared to release from KH_2PO_4 and during short periods it was able to secure comparable level of phosphate nutrition as other typical sources, while maintained higher availability of phosphate over longer periods (Bernardo et al. 2018). NPK nanosized fertilizer prepared by loading these macronutrients into CS NPs (300–750 nm; zeta potential of $\approx$50 mV) was able to enhance uptake of nutrients, improved photosynthesis, and growth of coffee plants, and increased the levels of macronutrients in leaves (Ha et al. 2019). A pronounced increase in total saccharide content, as well as K and P contents in grains of *Triticum aestivum* plants treated with 10% nanosized chitosan NPK fertilizer was observed, the effects being most significant in plants cultivated in clay–sandy soil (Abdel-Aziz et al. 2018).

Faster germination rate of *Asparagus officinalis* was observed with the application of rod-shaped hydroxyapatite NPs nanofertilizer showing the length of approx. 86 nm and diameters of 20–25 nm incorporating micronutrient composition consisting of Ag, Zn, Cu, Co, and Fe (Phan et al. 2019). By coating of nanosized hydroxyapatite with urea using urea to hydroxyapatite ratio of 6:1 by weight, nanohybrid fertilizer with a nitrogen weight of 40% was fabricated showing slow release, which can maintain the crop yield at a reduced amount of urea (Kottegoda et al. 2017). Effective nanofertilizer formulations using SiO_2 were reported by Sun et al. (2016), Sharifi-Rad et al. (2016), or Kheyri et al. (2018).

Several metal micronutrients are essential for the growth and development of plants because they are involved in numerous crucial processes: as catalytic active cofactors they activate enzymes, act as electron carriers in photosynthetic electron transport, and contribute to enhanced resistance of plants to abiotic and biotic stresses. On the other hand, low concentrations of Se, Si, Na, Ni, Co, V, and Al when applied at low concentrations also exhibit beneficial impact on plant growth (Hänsch and Mendel 2009; Marschner 2012; Dalcorso et al. 2014; Tripathi et al. 2014, 2015; Hasanuzzaman et al. 2018). Positive impact of several nanosized metals applied at low concentrations on plant growth was comprehensively overviewed by several scientists (Masarovičová et al. 2014; Liu and Lal 2015; Fernández-Luqueño et al. 2015; López-Valdez et al. 2018; Jampílek and Kráľová 2019b, c). Based on many published results it was stated that low ZnO NPs concentrations (ca. 50 mg/kg) have a favorable impact on plants, while the effects of concentrations exceeding 500 mg/kg could be detrimental (Pullagurala et al. 2018b). Application of TiO_2-based nanomaterials as antimicrobial, growth-regulating, and fertilizer-like agents in sustainable agriculture was overviewed by Rodriguez-Gonzalez et al. (2019). Also carbon-based nanomaterials such as single-wall carbon nanotubes (SWCNTs), multi-walled carbon nanotubes (MWCNTs), fullerenes, carbon NPs, and carbon nanohorns (CNHs) with appropriate size when applied at optimum doses positively affect plant growth resulting in improved crop production (Khodakovskaya et al. 2012; Husen and Siddiqi 2014; Liu and Lal 2015; Mukherjee et al. 2016). According to Lahiani et al. (2013), the MWCNTs could act as regulators of germination and plant growth because the coating of seeds with MWCNTs led to increased gene expression encoding several types of water channel proteins compared to uncoated control seeds. Favorable effects of some nanosized metal- and carbon-based fertilizers on plants are presented in Table 17.2.

3 Nanoscale Materials Used for Crop Protection

3.1 Nanoherbicides

Chemical agents used to control the unwanted vegetation, i.e. herbicides, are widely used in modern agriculture and land management. According to Oerke (2006), the greatest potential crop yield losses overall were caused by weeds (34%), while those caused by animal pests and diseases represented only 18% and 16%, respectively. However, it is needful to develop herbicidal compounds showing higher effectiveness in general, which are more effective for specific weed species but less damaging to desirable vegetation, and besides this have lesser adverse impact on the environment. In the recent climate change conditions increased CO_2 levels will have a positive impact on photosynthetic processes and growth of C_3 weeds, the stomatal aperture will be diminished and water use efficiency of weeds (C_3 and C_4 as well) will be enhanced. Due to better adaptation ability of C_3 plants to increased CO_2 levels, they will compete with weeds, especially with C_4 weeds (Korres et al. 2016). However, northward expansion of weeds and aggressive species originating from southern tropical/subtropical regions could be expected (Patterson 1995). To the

Table 17.2 Beneficial effects of nanosized metal- and carbon-based fertilizers on plants

NPs	Plant	NPs size (nm)	Applied NPs conc.	Beneficial effects of nanosized fertilizers on plants	References
Cu	Pigeon pea	20–30	20 ppm	↑ Height, root length, fresh and dry weights, and performance index of seedlings	Shende et al. (2017)
CuO	Cucumber	< 50	200 mg/L	↑ Fruit fresh weight	Hong et al. (2016)
MgO	Maize	40	50 mg/L; 100 mg/L	↑ Biomass shoot-root growth, Chl content	Jayarambabu et al. (2016)
FeS	*Brassica juncea*	100	4 ppm	↑ Growth and seed yield, Fe content in seeds; activation of C and N assimilatory pathways	Rawat et al. (2017)
γ-Fe_2O_3	Tomato	27	0.5 M	↑ Contents of Chls and carotenoids, crop yield, resistance to chlorosis	Pavani et al. (2016)
α-Fe_2O_3; $5Fe_2O_3{\cdot}9H_2O$	Maize	100	1–4 g/L; 1–6 g/L	↑ Growth and Chl content	Pariona et al. (2017)
ZnO	Habanero pepper	12–24	1000 mg/L; 2000 mg/L	↑ Plant height, stem diameter, Chl content, fruit yield, biomass ↑ Total phenols, total flavonoids and capsaicin, and dihydrocapsaicin contents	Garcia-Lopez et al. (2019)
ZnO	Rice	50	0.5–5.0 g/L	↑ Growth and yield parameters and Zn contents in the plant	Bala et al. (2019)
ZnO	Cilantro	24	100–200 mg/kg soil	↑ Photosynthetic pigments, improved defense responses of plants, ↓ lipid peroxidation	Pullagurala et al. (2018a)
ZnO	*Melissa officinalis*	29.3	100 mg/L; 300 mg/L	Enhanced development of lateral roots, ↑ K content in roots and contents of ascorbate, Fe and soluble phenols in leaves, expression of rosmarinic acid synthase and hydroxy phenylpyruvate reductase genes	Babajani et al. (2019)
ZnO	Coffee	15–137	10 mg/L	↑ Fresh and dry weight of plant organs, net photosynthetic rate, and Zn content in leaves	Rossi et al. (2019)

Ag	*Brassica rapa* ssp. *rapa*	2–10	1.0 mg/L	↑ Fresh biomass	Thiruvengadam et al. (2015)
Ag	Wheat	10–20	25 ppm	↑ Number of seminal roots, leaf area, root biomass, fresh weight and dry weight, yield, Chl content	Razzaq et al. (2016)
Gum arabic–Ag	*Phaseolus vulgaris*	22	5–60 ppm	↑ Height, root length, number of leaves per plant, the leaves' area, total fresh and dry weights of plants, seed yield, amounts of IAA, GA3, GA3/ABA, and total cytokinins	El-Batal et al. (2016)
TiO_2	Tomato	30–50	0.5–2 g/L	↑ Plant growth, photosynthesis, Chl content; ↑ P and ↓ Fe contents in roots and leaves	Tiwari et al. (2017)
TiO_2	Maize	2–6	25 mg/L	↑ Fresh and dry weights of shoots and roots, Chl*a*, Chl*b*, and carotenoids contents	Yaqoob et al. (2018)
TiO_2	Rapeseed	27	0.5–4 g/L	↑ Root length, plant height, fresh biomass, Chl content, nitrate reductase activity, and improved antioxidant system	Li et al. (2015)
Single-wall carbon nanohorns	Tobacco	50–100	50 mg/L; 100 mg/L	↑ Fresh weight of callus	Lahiani et al. (2015)
MWCNT	*Satureja khuzestanica*	Diam: 5–15; length: 50000	50 μg/mL	↑ Calli growth and contents of rosmarinic acid, caffeic acid, phenolics, and flavonoids	Ghorbanpour and Hadian (2015)
Fullerol	Bitter melon	1.5–5.0	0.94–47.2 nM	↑ Biomass yield, fruit yield, and contents of cucurbitacin-B, lycopene, charantin, and insulin	Kole et al. (2013)
Water soluble carbon nanodots	Wheat	20–100	150 μg	↑ Root and shoot growth	Tripathi and Sarkar (2015)

climatic factors that affect the invasive traits of weeds that degrade ecosystems and adversely affect plant and animal biodiversity belong not only atmospheric temperature and soil temperature but also precipitation, evaporation, and CO_2 concentration (Kathiresan and Gualbert 2016). Considering the increased temperature scenario in the weed management perspective, C_4 weeds will cause serious yield losses. However, the competitive balance between crops and some weed species will also be altered due to recurrent and unforeseen droughts reducing water availability and will result in intensified crop-weed competition pressure (Ramesh et al. 2017). Consequently, species showing better use of resources will displace to varying degrees species using resources with lower efficiency.

The majority of ca. 2000 known weed species in the world are C_4 plants and according to the composite list of weeds by the Weed Science Society of America (WSSA), 146 weed species possess C_4 physiology. From 250,000 plant species on our planet the number of C_4 plants is less than 1000, however, among weed species the portion of C_4 weeds is 17-fold greater (Elmore and Paul 1983). According to Korres et al. (2016) increased temperature will result in the expansion of the geographical range of C_4 weeds such *as Rottboellia chochinchinensis*, *Imperata cylindrica*, and *Striga* sp., while according to underwater or nutrient shortage scenarios C_4 weeds such as *Amaranthus palmeri*, *Digitaria sanguinalis*, *Sorghum halepense*, and *Euphorbia* sp. will most likely dominate. Therefore, it would be indispensable to select crop species, which will ensure not only desirable yields under changing climatic conditions but are able to compete with weeds as well.

The current state of weed management and perspectives of application of sustainable weed management in Pakistan, including progressive techniques considering the local agroecological conditions, were summarized by Matloob et al. (2020). The researchers also mentioned that the advanced weed management in Pakistan could by supported by adopting some precautions such as “vision guided machines for site-specific weed management, recognition and application modules, development of air inclusion nozzles, nanoherbicides, water based formulations with fewer hydrocarbons, herbicide-resistant transgenic crops, robotics to monitor and spray weeds, decision support systems and predictive modeling”. Considering the increasing number of crops resistant to synthetic herbicides and ongoing climate change, desirable crop yields could be achieved only as a result of effective cooperation between scientists and efficacious contacts of researchers with farmers (Chauhan et al. 2017).

The increased effectiveness of herbicides could be achieved by using suitable herbicidal formulations enabling controlled release and targeted delivery of the bioactive compound along with reducing toxic effects on nontarget organisms and bioavailable amounts of herbicide in the soil. In this context, the use of nanotechnologies represents a valuable tool for this purpose (Yadav and Srivastava 2015; Amna et al. 2019) and nanoformulations with encapsulated herbicides could be successfully used also under changing climatic conditions. For effective weed management, specific herbicide molecules encapsulated in NPs targeting specific receptors in the roots of individual weeds are favorable; they penetrate weed roots and then target the parts, which inhibit glycolysis of food reserves in the roots. Consequently, the weed plant will starve for food until it will be killed (Ali et al. 2014; Jampílek and Kráľová 2015, 2017a).

For example, the toxic effects of herbicides can be reduced by the application of herbicide-loaded NPs showing improved efficacy and environmental safety. An overview focused on the perspectives in the development of nanoencapsulated pesticides and efficient nanoscaled carrier systems for sustainable agriculture, which could serve as an alternative for conventional pesticide applications, was presented by Grillo et al. (2016). A review paper focused on various carriers applied in pesticide preparations, ensuring sustained release and slow mobility of herbicide in soil was presented by Yusoff et al. (2016).

Atrazine (ATZ) loaded lignin microparticles incorporated within alginate (ALG) beads exhibited controlled release of herbicide and were found to be non-phytotoxic in contrast to commercial ATZ preparation (Busatto et al. 2019). The field evaluation of metsulfuron methyl-loaded pectin NPs showing sizes of 50–90 nm, zeta potential value of −35.9 mV, and the herbicide encapsulation efficiency (EE) of 63 ± 2%, tested on *Chenopodium album* plants exhibited improved efficacy and environmental safety (Kumar et al. 2017). Chitosan nanospheres loaded with herbicide tebuthiuron, which is used for controlling and combating weeds in sugarcane plantations, showed a controlled release of herbicide with the best pH range for release ranging from 6.3 to 7.2 (de Oliveira and Andrade 2018). The ALG/CS NPs loaded with paraquat altered not only its release profile but also its interaction with the soil suggesting that the use of such carrier systems is suitable to reduce effectively the negative environmental impact of paraquat (Silva et al. 2011). The herbicides imazapic and imazapyr encapsulated in ALG/CS and CS/tripolyphosphate (TPP) applied at preemergence treatment were found to be less toxic to the target weed species *Bidens pilosa* and showed reduced genotoxicity compared to unencapsulated herbicides (Maruyama et al. 2016). Paraquat encapsulated in CS/tripolyphosphate (TPP) NPs showed less cytotoxicity and genotoxicity than the pure herbicide, but it preserved the herbicidal effectiveness against *Zea mays* and *Brassica* sp. (Grillo et al. 2014). In *Allium cepa* exposed to paraquat encapsulated in CS/TPP NPs reduced damage of chromosomes compared to conventional bulk paraquat herbicide was observed as well (Nishisaka et al. 2014).

Solid lipid nanoparticles (SLNPs) with encapsulated herbicides ATZ and simazine (SIM) applied in pre- and postemergence treatment exhibited efficient herbicidal activity against the wild radish weed but did not reduce the growth of the nontarget maize plants suggesting that SLNPs reduced the toxicity of the herbicides (de Oliveira et al. 2015).

Superb encapsulation efficiency (> 84%) of ametryn, ATZ, and SIM showed poly(ε-caprolactone) (PCL) nanocapsules exhibiting controlled release of triazins mediated mostly by relaxation of the polymer chains (Grillo et al. 2012) or pretilachlor (Diyanat et al. 2019) showing less toxicity than free herbicides. Treatment with ATZ-loaded PCL nanocapsules was reflected in immense damages in *B. pilosa* weed even after application of tenfold lower dose compared to the application of bulk herbicide suggesting the suitability of nanoencapsulation in the preemergence treatment with ATZ. However, in contrast to the equally great toxic effect to *Glycine* *max* plants observed in a short-term (17 days) experiment, at the application of tenfold lower concentration of nanoformulated herbicide compared to that of bulk herbicide (200 g/ha vs. 2000 g/ha), in an experiment lasting 60 days, the soybean plants were partially recovered from the toxic impact of ATZ suggesting that a safe span from use of nanoencapsulated ATZ formulation to sowing could be respected (Preisler et al. 2020).

While the application of diclofop-methyl (DM) at concentration 1.0 mg/L did not show a pronounced impact on the fresh weight of shoots of *A. thaliana* as well as on the content of total Chls and anthocyanin, treatment with 0.5 mg/L AgNPs caused serious oxidative damage in plants reflected in an adverse impact on plant growth and Chl synthesis. However, at combined treatment reduced release of Ag^+ ions from AgNPs was reflected in lower Ag^+-content in plant organs by 15.2% (shoots) and 9.4% (roots) compared to the plants exposed to AgNPs alone, and such treatment positively impacted the *A. thaliana* growth (Li et al. 2018).

Preparation of controlled release formulations, in which the phenoxyherbicides were intercalated in Zn–Al-layered double hydroxide serving as the matrix, was reported as well (Sarijo et al. 2010a, b). According to Hussein et al. (2005), the release of 2,4-dichlorophenoxyacetate (2,4-D) from the Zn–Al-layered double hydroxide matrix results from the ion exchange process between intercalated 2,4-D anion and CO_3^{2-}, Cl^- and OH^- anions in the aqueous solution.

Besides organic herbicides, adverse impacts on plants also exhibit metal- and metal-based compounds in ionic, bulk, and nanoscale form applied at higher concentrations (e.g., Masarovičová and Kráľová 2013; Masarovičová et al. 2010, 2014; Jampílek and Kráľová 2019b, c; Kráľová et al. 2019). However, because in many cases they even target crops besides weeds, their thoughtless application as herbicides could endanger the nontarget plant species and lower crop yields.

3.2 *Nanoinsecticides*

Insects comprise the vast majority of animal diversity on this planet. Beside harmful insect species exhibiting adverse impact on crops, other insects such as the pollinators (e.g., bees, bumblebee, and butterflies) are indispensable for the maintenance of both wild and agricultural plant communities (Künast et al. 2013; van der Sluijs and Vaage 2016; CBD 2018; Bris et al. 2019; IPBES 2020). However, the biodiversity of insects is endangered globally and due to its strong drop, 40% of insect species on our planet could disappear in a few decades (Sanchez-Bayo and Wyckhuys 2019).

In general, the pronounced reduction in diversity and abundance of terrestrial insect species accompanied with local extinctions across Europe are not only due to agricultural intensification causing habitat loss, use of fertilizers and harmful pesticides resulting in environmental pollution but also because of climate change, increasingly intense urbanization, and increased traffic volume. Therefore to reestablish Europe's insect diversity more nature-friendly land-use practices are necessary (Habel et al. 2019).

As poikilothermic animals, insects are very susceptible to warming connected with climate change and because the regulation of their physiological functions depends on environmental temperature, global warming represents a serious threat for insects. For survival in drought conditions, the size of insects plays a role, whereby smaller species respond to higher temperatures more sensitively (low thermal inertia), but bigger species are losing water much faster through respiration (Jakubec 2014). The physiological mechanisms regulating insect responses to heat and providing them tolerance against higher temperatures were overviewed by Gonzalez-Tokman et al. (2020). Insects show splendid resilience to dehydration, can withstand great water deficits, and are capable to revive and survive upon rehydration. Desiccation tolerance can contribute to avoiding the adverse consequences of changing hydroperiodicity patterns (Thorat and Nath 2018). Rapid adaptation of insects to changing environmental conditions is mediated via several mechanisms including both phenotypically plastic and evolutionary responses (Garnas 2018).

In a review paper, Kellermann and van Heerwaarden (2019) discussed how different traits (stress, fitness, and phenology) might contribute to shaping the insect responses to changing climatic conditions and examined the potential for adaptive genetic and plastic responses.

Temperature increases during the growing season adversely impact crop species resulting in yield losses. However, at climate warming, these yield losses will be pronouncedly enhanced by harmful insects. While nowadays approx. 5–20% of major grain crops are consumed by insects, according to the analysis of Deutsch et al. (2018) rising of the yield lost for the basic grain crops (*T. aestivum*, *Oryza sativa*, and *Zea mays*) caused by insects will achieve 10–25% with a temperature increase of 1 °C, and the temperate zone will be affected at most. With temperature rise, clear shifts in a range of insect species will be observed due to improved development and survival of insects in mid to high latitudes. Moreover to the rapid increase of insect species population at increasing temperatures, will contribute their relatively short life cycles, high reproductive capacity, high degree of mobility, and higher winter temperatures accompanied with lower mortality of insect species will result in poleward range expansions (Stange and Ayres 2010). However, changes in the cropping patterns induced by changing climatic conditions will have an impact on geographical distribution, diversity, and abundance of insect pests as well. Consequently, crucial insect pests such as cereal stem borers, the pod borers, aphids, and whiteflies may move to temperate regions causing serious damage in cereals, grain legumes, vegetables, and fruit crops. On the other hand, at global warming conditions, the effectiveness of pest-resistant cultivars, natural enemies, biopesticides, and synthetic pesticides will be reduced (Sharma and Dhillon 2018). Therefore, it is necessary to develop effective and economically feasible technologies in crop protection able to minimize the negative impact of harmful insects on crop yields. However, it could be also mentioned that at changing climate conditions, an increase in allergenic insect species could be expected resulting in increased frequencies of various allergies caused by stinging insects globally (Vega and Castro 2019).

With increasing CO_2 and temperature and plant infection with pathogens, modified plant defense responses will affect insect fertility, feeding rate, survival, population size, and dispersion, and altering host plant quality due to increased CO_2 (e.g., C:N ratios in C_3 plants) will have an adverse impact on insect pests (Trebicki et al. 2017). Elevated CO_2 or O_3 decrease the plant nitrogen content and affect the vector insects by altering salicylic acid- and jasmonic acid-mediated signaling pathways (Guo et al. 2017). In plant disease management, the use of NPs, whether alone or as nanocarriers for compounds showing insecticidal or fungicidal effects can reduce the toxicity, improve the shelf-life, and enhance the bioavailability of pesticides characterized by low aqueous solubility (Worrall et al. 2018; Abd-Elsalam and Prasad 2018, 2019). Rai and Ingle (2012) overviewed the strategies usually used for the management of harmful insects and highlighted the advantages of the use of nanosized materials.

Essential oils (EOs), that is, the volatile secondary metabolites found in a large number of vascular plants, exhibit repellent, insecticidal or growth-reducing effects against many insects. They could inhibit acetylcholinesterase (AChE), stop up the γ-aminobutyric acid-gated chloride channels, or function as agonists of octopamine receptor causing neurotoxic effects to insects (e.g., Regnault-Roger et al. 2012; Jampílek et al. 2020). However, the stability of EOs significantly depends on light, temperature, and oxygen availability (Turek and Stintzing 2013), and therefore the protection of EO active constituents using encapsulation is desirable. Use of botanical insecticides consisting of EOs, plant extracts, or their constituents instead of chemical insecticides can attenuate the toxic impact on pollinator insects (e.g., Santos et al. 2018; Seixas et al. 2018) as well as on predators of noxious insect species (e.g., Gupta et al. 2017; Chellappandian et al. 2018).

Insecticidal effects of EOs from several plant families against Coleopteran insect pests were summarized by Ebadollahi and Sendi (2015). Encapsulation of botanical insecticides contributes to increased agricultural productivity and reduced adverse impact on the environment (de Oliveira et al. 2014). Generally, 656 plant species were reported to have considerable insecticidal activities, whereby 17 species of plant families *Lamiaceae* and *Apiaceae* were especially effective against leaf-cutting ants (Boulogne et al. 2012). Secondary metabolites of plants showing insecticidal activity were overviewed by Rattan (2010).

(*E*)-Anethole, a constituent of *Pimpinella anisum* EO, is capable to penetrate throughout the cuticle causing irritations and strong damage to various body parts of the insect and its application in form of nanoemulsion (NE) to *Tribolium castaneum* Herbst resulted in a considerable reduction in beetle progeny number (Hashem et al. 2018). Onion EO NEs with particle size 93.4 nm showed acaricidal activity against the olive mites *Aceria oleae* Nalepa (LC_{50}: 298.225 μg/mL) and *Tegolophus hassani* (Keifer) (LC_{50}:309.634 μg/mL) (Mossa et al. 2018). Larvicidal activity of rosemary EO NEs against *Aedes aegypti* was observed by Duarte et al. (2015).

The ingestion and penetration of *Melissa officinalis* L. EO with main active compounds geranial and β-caryophyllene encapsulated in CS NPs (362 nm) strongly damaged the midgut region of *T. castaneum* Herbst, which induced feeding deterrence action leading finally to the suppression of further feeding. The toxic impact of the encapsulated EO was caused predominantly by oxidative stress, although no change in insect AChE activity was observed (Upadhyay et al. 2019).

Nanoformulation of patchouli EO containing as active constituents sesquiterpene hydrocarbons prepared using polyoxyethylene efficiently killed the worker of three leaf-cutting ants (EC_{50} ranging from 1.06 to 2.10 μL/L) and ants were dying within 42 h; workers of *A. opaciceps* and *A. sexdens rubropilosa* treated with this EO showed reduced displacement and velocity in totally treated arenas (Rocha et al. 2018).

Insecticidal activity against beetles of extracts of EOs of *Artemisia absinthium* or *Citrus* spp. and their active components such as α-chaconine, or α-solanine including mode of action of these plant products were discussed by Spochacz et al. (2018).

The use of traditional insecticides against noxious mosquitoes transmitting human diseases can result in the development of insecticide resistance and therefore it is desirable to replace them with natural products showing insecticidal activity (Benelli et al. 2016).

Using appropriate nanocarriers can ensure a controlled release of the active compounds and ameliorate their stability (Chaudhary et al. 2017). Neem oil can be successfully used in safer control of insect populations instead of synthetic pesticides (Morgan 2009; Campos et al. 2016; Chaudhary et al. 2017). Neem oil-loaded zein NPs with the size 198 ± 6 nm, and EE > 80% used in pre- and postemergence treatments did not show a negative impact on *Phaseolus vulgaris* plants, however, caused mortality of *Bemisia tabaci*, and *Tetranychus urticae* and were much more effective against *Acanthoscelides obtectus* pest than the plain neem oil (Pascoli et al. 2020). The benefits connected with the application of *Azadirachta indic*a oil and *A. indic*a cake by-products in the control of arthropod pest, with particular focus on mosquito vectors, which threatens the health of human population were summarized by Benelli et al. (2017a).

Benelli et al. (2017b) also analyzed the possibility to potentiate the predation rates of biological control agents against mosquitoes by addition of minor doses of 1–3 ppm biosynthesized metal NPs to the aquatic environment, which could reduce the motility of mosquito larvae and underlined the need to develop large-scale production of eco-friendly nanoscale mosquitocides. An updated overview of the current mosquito and tick research scenario in a rapidly changing world, including the development of nanoformulations containing highly effective repellents and acaricides against ticks, was presented by Benelli (2019), while a review paper of Barabadi et al. (2019) summarized the findings related to the effects of green synthesized NPs on major vectors of malaria. As effective insecticides against different mosquito species also metal NPs (mainly AgNPs) synthesized using plant extracts could be used (Benelli 2016).

Besides nanoscale bioinsecticides for plant protection, nanoformulations encapsulating effective synthetic pesticides are also used (e.g., Jampílek et al. 2020). However, when these pesticides are used in excess, they exhibit a negative impact on the environment causing, for example, a reduction in the population of beneficial insect pollinators and a threat to endangered species and habitat of birds, and therefore, the nanoformulations of active substances have significant importance especially for the possibility of targeted delivery and controlled release, thereby reducing toxicity to nontarget organisms (Jampílek and Kráľová 2018a, 2019a; Jampílek et al. 2020).

Besides insecticides containing NPs as carriers of active insecticidal ingredients, some NPs were found to be effective insecticides (Athanassiou et al. 2018). Natural minerals such as diatomaceous earth (Gao et al. 2018; Van den Noortgate et al. 2018), zeolites (Van den Noortgate et al. 2018), SiO_2 NPs (Debnath et al. 2011; Shoaib et al. 2018; Caceres et al. 2019) as well as Al_2O_3 NPs (Lazarevic et al. 2018; Lopez-Garcia et al. 2018) were found to exhibit pronounced insecticidal effects. Insecticidal activity of carbon-based nanomaterials such as graphene quantum dots (Murugan et al. 2017), fullerenes (nC_{60}) (Waissi-Leinonen et al. 2015), graphene oxide NPs (Martins et al. 2019), and single-walled carbon nanotubes (SWCNTs) (Liu et al. 2009) or oxidized MWCNTs (Martins et al. 2019) was reported as well. The insecticidal activities of above mentioned formulations against concrete insects were comprehensively described and discussed in a review paper of Jampílek et al. (2020).

3.3 Nanoformulations to Handle Plant Diseases

There are 270,000 fungal species attacking plants and causing crop losses worldwide, including genera *Botrytis*, *Sclerotinia*, *Aspergillus*, *Fusarium* and *Verticillium* and about 200 species of phytopathogenic bacteria, (Agrios 2005), which cause tremendous crop losses globally (Jampílek and Kráľová 2018a, Jampílek and Kráľová 2020a, b, 2021). Moreover, the most widespread toxigenic fungi from the genera *Aspergillus*, *Fusarium*, *Alternaria*, and *Penicillium* growing on diverse crops produce toxins that adversely affect the health of humans and animals, and consequently, it is necessary to prevent the entry of mycotoxins in food and feed using efficient management focused on the elimination of toxigenic fungi not only at the field but also in postharvest management as well as in food processing (Morris and Potter 2013; Jampílek and Kráľová 2018a, 2020a, b; WHO 2018). Fungi destroy up to 30% of crop products through disease and spoilage processes, and therefore, control of fungal growth belongs to crucial challenges under changing climate conditions (Avery et al. 2019). Plant-associated microbial communities show a beneficial impact on the growth of plants and their resistance to various environmental stresses and it is inevitable to investigate the impact of changing climate on soil microbial communities and plant–microbe interactions as well (Dubey et al. 2019). Increased frequencies of long drought periods and severe rainfall events caused by climate change increase the vulnerability of crops to soil-borne diseases, in particular, due to reduced resistance to pathogen attacks (Meisner and de Boer 2018). It was predicted that within a century in Europe, there will be an increase in the incidence of hepatocellular carcinoma associated with exposure to aflatoxins due to expected climate change (Assuncao et al. 2018).

Global warming will affect not only the contamination of cereal crops in the field but also the geographical distribution of certain cereals, mycotoxigenic fungi, and their mycotoxins (Medina et al. 2017a). In the future, the global risk of the occurrence of maize diseases caused by *Puccinia sorghi* and *Puccinia polysora* in common areas could be extremely harmful to crops (Ramirez-Cabral et al. 2017). Acclimatization of mycotoxigenic fungal pathogens to increased temperatures and CO_2 levels as well as drought stress will contribute to increased plant diseases and perhaps mycotoxin contamination of staple cereals (Medina et al. 2017b).

Under global warming, the thermotolerant and thermophilic fungi will be prevalent compared to the conventional mycotoxigenic fungi. For example, *Aspergillus fumigatus*, a serious human pathogen, will appear more frequently, because it is thermotolerant and also attacks the crops (Paterson and Lima 2017). A mean poleward shift of 2.7 ± 0.8 km/year since 1960 was reported due to global warming, although considerable variations among taxonomic groups were observed (Bebber et al. 2013). In recent years approximately 100% yield losses of susceptible wheat cultivars were observed even at favorable weather conditions due to new virulent races of *Puccinia graminis* f. sp. *tritici*. At climate change conditions warming with lower relative humidity will result in a 40% rise in the urediniospore emitting potential of an infected field as a global average. The overwintering areas of the fungus will expand as well. However, in drier conditions in fields without irrigation, the infection originating from deposited spores will be diminished (Prank et al. 2019). Juroszek et al. (2020) summarized the findings published by researchers during the past 30 years related to the impact of potential climate change on plant pathogens and crop disease risks.

A useful tool to combat plant fungal diseases biotechnology using genetic engineering and the application of advanced techniques in order to create plants able to adapt to these new climatic conditions (Jain et al. 2015; Ricroch et al. 2016) or nanobiotechnology using NPs (e.g., carbon-based NPs, CS NPs, AgNPs, SiO_2 NPs, and alumino-silicates) and nanosized biopesticide formulations enabling better effectiveness in the control of plant diseases (Alvarez et al. 2016; Jampílek and Kráľová 2019a; Jampílek et al. 2019; Prasad 2016, 2017; Prasad et al. 2018; Abdel-Aziz et al. 2018) could be used. Application of NPs in inhibition of toxicogenic fungi producing mycotoxins was overviewed by Jampílek and Kráľová (2020a, b) and Jogee and Rai (2020).

Technologies suitable for the microencapsulation of fungi and the green fabrication NPs with special emphasis on *Trichoderma harzianum*, suitable for the biological control of pathogens were overviewed by Fraceto et al. (2018). As effective fungicides also bio-based NEs encapsulating plant EOs can be used. For example, NEs of crude citronella and *A. indic*a oils showed antifungal activity against *Rhizoctonia solani* and *Sclerotium rolfsii* (Ali et al. 2017a), NEs with encapsulated cinnamon leaf EO suppressed the mycelial growth and spore germination of *Aspergillus niger* (Ribes et al. 2017), while clove oil NE mitigated growth of *Fusarium graminearum* as well as production of trichothecene mycotoxin (Wan et al. 2020), thyme EO NE showed antifungal activity against *Penicillium digitatum* (Ahmadi and Jafarizadeh-Malmiri 2020), a synergistic NE containing clove and lemongrass EO NE reduced the severity of tomato *Fusarium* wilt incidence (Sharma et al. 2018), eugenol EO NE was found to protect cotton seeds from *Fusarium* wilt infection (Abd-Elsalam and Khokhlov 2015), clove and lemongrass EOs inhibited the growth of *Botrytis cinerea* (Gago et al. 2019), cinnamon EO NE showed pronounced antifungal activity against *Botrytis cinerea* (Naserzadeh et al. 2019), CS/citral EO NEs showed antimicrobial activity against *Erwinia carotovora*, *A. niger* and *Rhizopus stolonifer* (Marei et al. 2018) and eucalyptus EO emulsions with particle sizes 1.071–1.865 μm exhibited antimicrobial activity against *Pseudomonas aeruginosa* in less than 1 min (Clavijo-Romero et al. 2019).

After 7 days of incubation, the AgNPs phytosynthesized using medicinal plant *Ocimum kilimandscharicum* completely inhibited *Fusarium oxysporum* and *Colletotrichum gloeosporioides* at concentrations 75 and 100 ppm, respectively (Singh et al. 2019). Green synthesized AgNPs using aqueous leaf extract of *Justicia peploides* and *Withania coagulans* showed effective antifungal activity against *F. oxysporum*, *F. solani*, *F. lateritum*, and *F. phylophillum* suggesting that they could be used to mitigate plant diseases (Hashmi et al. 2019). Roughly spherical AgNPs with diameters < 40 nm, green synthesized using the ethanolic extract of neem leaves, was found to inhibit the growth of *Pseudomonas nitroreducens*, a biofilm-forming bacterium, and *Aspergillus unguis* (NII 08123) fungus (Ulaeto et al. 2020). AgNPs fabricated using *T. harzianum* inhibited *Sclerotinia sclerotiorum*, whereby new sclerotia were not developed (Guilger-Casagrande et al. 2019). At high exposure times (20–30 h), the three effective lethal doses of AgNPs (14–100 nm) related to spore viability, the ED_{50}, ED_{90}, and ED_{100} values, ranged from 1 to 30 μg/mL for all the studied toxigenic *Fusariu*m spp. species producing harmful mycotoxins (Tarazona et al. 2019).

AgNPs and ZnO NPs biosynthesized using *Fusarium solani* KJ 623702 efficiently inhibited the growth of the multidrug-resistant (MDR) bacteria *P. aeruginosa* and pathogenic fungus *F. oxysporum*, whereby minimum inhibitory concentration (MIC) estimated for ZnO NPs against *F. oxysporum* was 24.7 μg/mL, while that of AgNPs against *P. aeruginosa* was 21.33 μg/mL (El Sayed and El-Sayed 2020). Monodispersed AgNPs and CuNPs with mean sizes of 2.5 and 17 nm, respectively, showed antifungal and anti-fumonigenic activities toward *F. verticillioides* with MIC values of 125 and 75 mg/L for CuNPs and AgNPs, respectively, whereby complete inhibition of fumonisin B1 was observed at ≥ 100 mg/L CuNPs and ≥ 20 mg/L AgNPs (Perez-de Leon et al. 2020).

The in vitro testing of antifungal activity of Cu/Cu_xO NPs against *F. oxysporum* showed that NPs of relatively small size and a higher proportion of Cu_2O phase effectively inhibited the radial growth (Herrnida-Montero et al. 2019). CuO NPs prepared using tea extract with particle sizes < 80 nm were found to inhibit ca. 90% of the mycelium growth of *F. solani* using a dose of 80 μg/mL (Khatami et al. 2019). Combined treatment involving seed coat and foliar spraying of *Eleusine coracana* plants infected with *Pyricularia grisea* with Cu–CS NPs increased the yield by ca. 89%, suppressed the blast disease development, and ensured approximately 75% protection of treated plants compared to control (Sathiyabama and Manikandan 2018).

Investigation of in vitro antimicrobial effect of ZnO NPs, CuO NPs, and Fe_2O_3 NPs with mean sizes of 20, 46, and 30 nm against *F. oxysporum* and *Alternaria* *solani* showed that application of 1000 mg/L of ZnO NPs and CuO NPs caused 99% and 95% mycelial growth inhibition of *A. solani*, while Fe_2O_3 NPs did not suppress its mycelial growth. On the other hand, CuO NPs more effectively inhibited the mycelial growth of *F. oxysporum* than ZnO NPs (96% vs. 91%) (Vera-Reyes et al. 2019).

MnO NPs exhibited significant antibacterial activity against phytopathogen *Ralstonia solanacearum* with MIC and MBC (minimum bactericidal concentration) of 200 and 250 μg/mL, respectively. MgO NPs directly attached to the surfaces of *R. solanacearum* cells caused physical damage to the cell membranes and reduced motility and ability of biofilm formation of the pathogen. Moreover, the antibacterial action of MnO NPs also contributed to ROS accumulation inducing DNA damage (Cai et al. 2018).

Spherical mycogenic SeNPs (60.48–123.16 nm) synthesized using *Trichoderma atroviride* showed superb in vitro antifungal activity against *P. grisea*, and doses 50 and 100 ppm were able to inhibit the infection of *Colletotrichum capsici* and *A. solani* on leaves of chili and tomato plants (Joshi et al. 2019).

Foliar exposure of *Solanum lycopersicum* plants cultivated in soil infested with *F. oxysporum* f. sp. *lycopersici* to 250 mg/L CeO_2 NPs caused an increase of the fruit dry weight and lycopene content compared with the untreated control infested with *F. oxysporum*, suppressed *Fusarium* wilt disease and practically did not impair the nutritional value of tomato fruit (Adisa et al. 2020).

CS NPs inhibited the growth of *C. gloeosporioides*, *Phytophthora capsici*, *S. sclerotiorum*, *F. oxysporum* and *Gibberella fujikuori*, whereby they exhibited the highest suppression of *F. oxysporum* mycelial growth. Moreover, CS NPs pronouncedly suppressed the growth of the investigated bacterial strains, *Erwinia carotovora* subsp. *carotovora* and *Xanthomonas campestris* pv. *vesicatori*a (Oh et al. 2019). Treatment with oleoyl-CS NPs (2 mg/mL) strongly suppressed the mycelial growth of *Verticillium dahliae*, caused degenerative alterations, and damaged cell membranes (Xing et al. 2017). CS NPs loaded with protocatechuic acid showed a strong antifungal effect against *Pyricularia oryzae* (Pham et al. 2019).

One hundred days after a single treatment with 500 mg/L SiO_2 NPs (with or without a CS coating) of healthy *Citrullus lanatus* seedlings and seedlings infected by *F. oxysporum* f. sp. *niveum* at the seedling stage reduced disease severity by ca. 40% and 27%, respectively, as well as expression of some stress-related genes was observed. Exposure of uninfected seedlings to a single dose of CS-coated SiO_2 NPs ensured improved fruit yield by 70% (Buchman et al. 2019).

The graphene oxide (GO)-AgNPs, which were tested against phytopathogen *F. graminearum*, showed MIC of 4.68 μg/mL and exhibited a three- and sevenfold increase of inhibition efficiency over pure AgNPs and GO suspension, respectively. The GO-AgNPs damaged the spores and hyphae and their synergistic effect induced physical injury and ROS generation (Chen et al. 2016).

4 Nanoparticles Used for Mitigation of Abiotic Stresses

4.1 Drought Stress

Drought can be defined as a physiological form of water deficit characterized by insufficient soil water content available to the plant having a negative impact on the plant's metabolism and causing considerable losses in yields of crops. Drought stress is manifested by a drop in leaf water potential, reduced stomatal opening, impaired availability of CO_2 and photosynthesis, loss of turgor, or changes in membrane fluidity. The responses of plants to water deficit could be morphological, physiological, molecular, or biochemical (Fathi and Tari 2016; Sourour et al. 2017; Kumar et al. 2018; Wang et al. 2018; Ye et al. 2020).

At water deficit conditions abscisic acid (ABA) activates stomatal closure. Stomatal closure is promoted by the ion- and water-transport systems across membranes, which control turgor pressure changes in guard cells and at acclimation to this abiotic stress plants accumulate also proline (Pro), dehydrins, heat shock proteins, or osmolytes (Chaves et al. 2003; Osakabe et al. 2014; Kumar et al. 2018). The effects of drought stress on the mechanisms of plant's resistance and appropriate management strategies suitable to mitigate its adverse impact were overview by Kumar et al. (2018).

Valliyodan and Nguyen (2006) in their review paper focused on the success of genetic or metabolic engineering achieved in enhancing of the tolerance of crops to water deficit, while Ye et al. (2020) reported about quantitative trait loci in late maturing *Glycin max* genotypes regulated by slow canopy wilting, which are associated with drought tolerance and support water use efficiency and conservation. Nutan et al. (2020) highlighted that in the seed development of *A. thaliana* and *Oryza sativa* and stress tolerance OsGATA8 transcription factor played an important role.

Frequencies of droughts, which are predicted to increase at changing climatic conditions, could have a significant adverse impact on food production and the use of nanoparticles can contribute to the mitigation of the harmful impact of water deficit on crops (e.g., Das and Das 2019; Jampílek and Kráľová 2019c, 2021; Khan et al. 2019a, b, 2020).

Soil and foliar treatments of wheat plants with CS NPs using a dose of 90 ppm were found to attenuate the negative impact of drought in the plants, which was reflected in enhanced leaf area, relative water content (RWC), Chl levels, improved photosynthesis rate, higher activities of CAT and SOD, and increased yield and biomass of plants grown at water deficit conditions compared to control plants (Behboudi et al. 2019). After spraying with *S*-nitrosoglutathione (GSNO) encapsulated in CS NPs the sugarcane plants cultivated in hydroponium under drought stress ensured higher photosynthetic rates compared to plants treated with free GSNO under the same conditions and increased root/shoot ratio after application of the encapsulated NO donor suggested that it contributed to better tolerance of plants to water stress (Silveira et al. 2019).

Treatment with TiO_2 NPs (500–2000 mg/L) and sodium nitroprusside (100 μM) alone or in combination pronouncedly mitigated the adverse effects of drought stress (−0.4 and −0.8 MPa) on seed germination and early growth of *T. aestivum* plants. This was manifested with ameliorated germination, prolongation of roots and shoots, and root fresh biomass of plant organs as well as improved vigor index and pronounced reduction of mean germination time (Faraji and Sepehri 2019). Application of TiO_2 NPs at doses of 30–50 ppm to Moldavian balm plants cultivated under drought stress at 75% field capacity increased the phenol bioactive compounds of this medicinal plant suggesting that controlled drought stress and TiO_2 NPs in the culture of *Dracocephalum moldavicum* could be used to enhance the production of phenolics also in practice (Kamalizadeh et al. 2019). Pretreatment of cotton plants, which were subsequently exposed to water stress, with 50 ppm TiO_2 NPs and 3200 ppm SiO_2 NPs mitigated the drought stress, what was reflected in an increase of assimilation pigment contents as well as levels of soluble sugars and proteins, phenolics, free amino acids (AAs) and Pro; improved activities of antioxidant enzymes and enhanced yield characteristics were observed as well. It was concluded that foliar application of these NPs could improve the tolerance of cotton plants to drought (Shallan et al. 2016).

Prunus mahaleb (Mahaleb) seedlings irrigated (or not) with 50 and 100 mg/SiO_2 NPs for 45 days, and subsequently, for 19 days irrigation regimes evoking severe drought stress (no irrigation) was used, showed a less adverse impact on gas exchange, photosynthesis, stomatal conductance, transpiration rate, and dry mass compared to controls, they maintained the root length as well as N, P, and K concentrations at comparable levels than in well-irrigated plants (Ashkavand et al. 2018). SiO_2 NPs supplemented in soil or applied by foliar treatment at three stages of wheat plant growth using doses 30 and 60 ppm were found to suppress the harmful impact of drought stress on *T. aestivum* plants. Soil supplementation with SiO_2 NPs increased the RWC by 84.04% and yield by 17.81%, while at foliar SiO_2 NPs application the yield increased by 25.35%. However, it could be mentioned that under the same irrigation regimes the increase of plant height and biomass was higher using soil application of SiO_2 NPs than at foliar application (Behboudi et al. 2018). Sun et al. (2018) encapsulated ABA in mesoporous SiO_2 NPs with diameters approx. 20 nm and pores showing sizes of ca. 2.87 nm and then covered the pore entrances of mesoporous SiO_2 NPs with decanethiol gatekeepers through glutathione (GSH)-cleavable S–S bonds. In this intracellular GSH responsive phytochemical delivery system the controlled release of ABA from the pores in treated *Arabidopsis* seedlings grown at water deficit conditions resulted in a considerable reduction of the leaf stomatal aperture, suppressed water loss, and better resistance to drought.

Accumulation of excess Cd in soil together with drought stress could represent a serious threat to sustainable agriculture production. Khan et al. (2020) supplemented to the soil SiNPs (25, 50, and 100 mg/kg) 1 week before of wheat sowing and after 50 days of seed sowing, introduced water supply corresponding to 70% and 35% soil water-holding capacity for the remaining growth period. They found that without as well as with drought stress the treatment with SiNPs improved the growth characteristics and photosynthesis but decreased Cd concentrations in *T. aestivum* tissues and grains due to reduced H_2O_2 production, electrolyte leakage, and malondialdehyde (MDA) levels; increased activation of SOD and POD in leaves was observed as well. ZnO NPs application to Cd-contaminated soils besides stimulating wheat productivity can successfully reduce soil Cd contamination either alone as well as under water-deficient conditions (Khan et al. 2019b).

In the experiment of Dimkpa et al. (2019), 4 weeks after sorghum seed germination in soil supplementation with ZnO NPs (1–5 mg Zn/kg) under drought conditions corresponding to 40% of field moisture capacity were introduced. The ZnO NPs were able to reduce the delay of flag leaf and grain head emergence caused by drought (4–5 vs. 6–17 days) and improved grain yield under drought stress by 22–183%. Moreover, at the application of 5 mg/kg ZnO NPs grain N translocation increased by 84% relative to the untreated drought-stressed plants, and N levels corresponded to those of the non-drought condition; lower total P acquisition under drought by 11–23% was observed as well. Using this dose of ZnO NP also enhanced total K acquisition (16–30%) and K content in grains (123%) and pronouncedly increased grain Zn levels in plants exposed to drought stress was estimated.

Spraying of *Phaseolus vulgaris* L. plants with 75 kg pure N in form of nano ZnFeMn, gradually providing the plants with its essential nutrients, improved the yield under both water sufficient and deficient conditions (Aghajani and Soleymani 2017). Application of γ-Fe_2O_3 NPs stabilized by yttrium doping to *Brassica napus* plants cultivated in soil via irrigation reduced the adverse impact of drought on plants reflected in lower H_2O_2 and MDA levels as well as in improved growth rate of leaves and increased Chl level compared to control plants, whereby the beneficial effect of tested NPs was higher than that of chelated iron fertilizer (Palmqvist et al. 2017). Sunflower plants grown in compost pre-amended contaminated soil supplemented with nanomaghemite (NM) and later exposed to drought showed enhanced dry weight compared to control and did not enhance the accumulation of Pro or total AAs in the plants grown at water deficiency conditions. NM was recommended as a superb soil amendment during phytoremediation procedures due to its ability to immobilize trace elements in the soil and preserve the plant water balance (Martinez-Fernandez et al. 2015).

Foliar treatment of *Sorghum bicolor* (L) Moench plants, in which drought stress was imposed at the booting stage by withholding water for 21 days with CeO_2 NPs (10 mg/L), reduced leaf $HO^•$ and H_2O_2 levels by 41 and 36%, respectively, and cell membrane lipid peroxidation by 37%, while leaf carbon assimilation rates, pollen germination and seed yield per plant increased more than by 30%. Hence, higher grain yield was achieved using CeO_2 NPs, which provided the protection of sorghum plants against oxidative damage under drought stress (Djanaguiraman et al. 2018a).

Priming of *B. napus* L. seeds with fullerol at doses 10 and 100 mg/L greatly stimulated germination under 15% PEG treatment, while foliar treatment of plants under drought stress improved dry biomass of stems and photosynthesis of rapeseed plants and was accompanied with suppression of ROS formation, and increased activities of antioxidant enzymes in plant leaves. The use of fullerol at doses 1–100 mg/L resulted in an enormous increase of the leaf ABA level and induction of ABA biosynthesis by downregulating the expression of the ABA catabolic gene CYP707A3 under drought was observed (Xiong et al. 2018). Foliarly applied fullerenol NPs to *Beta vulgaris* L. plants under drought stress suppressed the accumulation of Pro in plant organs caused by water deficiency, they acted as intracellular binders of water that enabled the creation of additional water reserves permitting to withstand the drought stress (Borisev et al. 2016).

Besides NPs also the plant growth promoting rhizobacteria (PGPR) colonizing the rhizosphere/endo-rhizosphere of plants could enhance drought tolerance of plants: they improve root architecture, enhance the efficiency of water use, and produce exopolysaccharides, phytohormones (ABA, salicylic acid and indole-3-acetic acid) and volatile compounds (Prasad et al. 2015). PGPR could also suppress the negative impact of drought stress via enhanced accumulation of osmolytes and antioxidants and up- or downregulation of stress responsive genes (Ali et al. 2017b). Treatment with CuO and ZnO NPs did not impair the tolerance to drought stress in wheat plants induced by the beneficial bacterium, *Pseudomonas chlororaphis* O6 (PcO6) colonizing the roots. On the contrary, the PcO6-colonized plants responded to the application of these NPs with systemic increases in the expression of genes associated with drought tolerance (Yang et al. 2018).

The results of an experiment performed by Hasan et al. (2019) who treated *Moringa oleifera* and *Moringa peregrina* plants with magnetic water using various watering regimes (100%, 50%, and 20% field capacity) it was found that the treated plants under water stress recovered from growth inhibition, chlorosis, and ion disruption and showed lower accumulation of Na^+ ions and improved Na^+/K^+ ratio suggesting that magnetic water attenuated the negative impact of drought in tested plants.

4.2 Heat and UV Radiation Stress

Intergovernmental Panel on Climate Change (2018) stated that in the period 2030–2052 due to global warming the global temperatures could be increased by 1.5 °C and will adversely affect plant growth and crop production (Hussain et al. 2019; Priya et al. 2019). According to prediction, each increase in global mean temperature by 1 °C will result in a 4–6% reduction in average global yields of wheat (Asseng et al. 2015). Elevated temperatures adversely affect properties of biological membranes causing increased fluidity and permeability, modified lipid composition, and interactions of lipids with specific membrane proteins (Yue and Yun 2018).

Under high temperature stress morphology, anatomy, physiology, and biochemical parameters of plants are changed. The adverse impact of heat on respiration and photosynthesis shorten the life cycle and reduce plant productivity, ROS formation is induced, proteins are denatured, and changes in water relations, as well as hormonal changes, are accompanied with decreased yield (Waraich et al. 2012; Bita and Gerats 2013; Gupta et al. 2018).

At increased levels of UV-B radiation (280–315 nm) due to reduced O_3 layer in the stratosphere overproduction of noxious ROS is induced negatively affecting photosynthesis and causing denaturation of proteins, damages of DNA, lipids, and membranes, which is manifested in impaired growth and yield of plants (Hollósy

2002). In contrast, UV-A radiation (315–400 nm) can suppress but also improve biomass accumulation and morphology in plants (Verdaguer et al. 2017; Chen et al. 2019).

Using NPs, the damages caused by heat and UV irradiation in crops could be attenuated. For example, carbon NPs reduced the UV absorbance by plant providing a UV shield and protecting the leaves from cell damages caused by radiation (Swapna et al. 2017).

Beneficial effect of AgNPs on *T. aestivum* plants exposed to higher temperatures was reported by Iqbal et al. (2017, 2019a, b). Foliarly applied TiO_2 NPs to tomato plants under mild heat stress were able to protect photosystem (PS) II and increased regulation, while decreased nonregulated PSII energy dissipation (Qi et al. 2013). Also, SeNPs applied at the booting stage of sorghum plants protected the plants exposed to heat stress against oxidative damage (Djanaguiraman et al. 2018b).

A radioprotective effect of ZnO NPs (500 and 2000 mg/L) in the mitotic-meristematic root tips of *Vicia faba* plants cultivated from seeds treated with γ-rays (20, 50, 100 Gy) was reflected in the attenuated adverse impact of γ-radiation on the phenotypic and cytogenetic markers and adverse ultrastructural changes in the chloroplasts and nuclei (Al-Harbi et al. 2019).

Protective effect against oxidative stress induced by UV-B radiation was ensured by pretreatment of hydroponically cultivated wheat seedlings with SiNPs (Tripathi et al. 2017). The surface redox Ce^{3+}/Ce^{4+} reactivity of CeO_2 NPs embedded in transparent SiO_2 hydrogels with entrapped living *Chlorella vulgaris* cells exposed to UV radiation reduced damage in the photosynthesizing organism caused by oxidation stress (Sicard et al. 2011). The anionic poly(acrylic acid) CeO_2 NPs of 10.3 nm with a low Ce^{3+}/Ce^{4+} ratio (35.0%) pronouncedly reduced leaf ROS (H_2O_2, $O_2^{\bullet-}$, $HO^{\bullet}$) levels and improved the photosynthesis of *A. thaliana* plants exposed to 35 °C for 2.5 h (Wu et al. 2017).

4.3 Salinity Stress

Erratic rainfall, high evapotranspiration rates, and the great amounts of soluble salts contribute to soil salinization in drylands resulting in land degradation processes connected with adverse impact on crop yields. However, also at the application of inadequate irrigation practices using insufficient water application or use of saline water, secondary salinization occurs when salts accumulate in the root zone and can reduce yields even by 30%. The high osmotic pressure of the soil solution embraces the water uptake by plants at enhanced salinity levels and inhibits the growth of most plants (Parihar et al. 2015).

At changing climatic conditions the salt leaching ability of rainfall will be reduced and increased temperature will result in enhanced evapotranspiration and higher rates of evapotranspiration of shallow groundwater could also contribute to increased salinity in drylands. However, at climate change conditions besides changing weather patterns, also sea-level rise will be accelerated resulting in increased inundation and saline contamination of soils in coastal regions and such progressive salinization will have an adverse impact on agriculture and humans inhabiting low-elevation coastal zones (Wheeler 2011; Dasgupta et al. 2015).

To improve osmotic balance at the cellular level plants under salt stress synthesize osmolytes and accumulate osmotic adjustment substances. Due to increased ROS levels observed in plants exposed to elevated salt concentrations peroxidation of lipids in the cell membrane takes place (Liang et al. 2018). Responses of plants to salt stress were overviewed by Negrão et al. (2017) and the review paper of Mbarki et al. (2018) focused on strategies able to attenuate the adverse impact of salinity excess on photosynthesis and crops yield.

Positive impact of nanoscaled materials on plants exposed to salt stress were reported previously (e.g., Jampílek and Kráľová 2019c, 2021). Stimulation of molecular defense mechanisms in plants against environmental stresses, including salt stress, was discussed by Almutairi (2019), while the effects of various NPs on plant growth and stress tolerance under various abiotic stresses, including salinity, was analyzed by Zhao et al. (2020).

At combined application of priming of *T. aestivum* seeds with AgNPs and salt stress, higher levels of Pro, soluble sugars and POD activity, while lower CAT activity in salt-stressed plants was estimated compared to the treatment with AgNPs alone, indicating that AgNPs improved the salt tolerance in *T. aestivum* plants (Mohamed et al. 2017). Foliar spraying of tomato plants with CuNPs (250 mg/L) cultivated in the presence of 50 mM NaCl increased the phenols and activities of antioxidant enzymes in the leaves, while the fruits showed considerably higher levels of ascorbic acid (AscA), GSH, and phenols compared to control fruits (Perez-Labrada et al. 2019). Treatment with CS-polyvinyl alcohol (PVA) and CS-PVA + CuNPs was found to improve plant growth, enhanced the concentrations of AscA and lycopene, respectively, and stimulated expression of jasmonic acid (JA) and SOD genes in tomato plants exposed to salinity stress, likely via attenuation of the negative effects of excess salt by regulating oxidative and ionic stress (Hernandez-Hernandez et al. 2018a). The treatment with CS-PVA and CuNPs was assumed to induce mechanisms of tolerance to salt excess, whereby combined treatment activated the enzymatic defense mechanism of plants (Hernandez-Hernandez et al. 2018b).

Treatment of *S. lycopersicum* plants exposed to excess NaCl with SeNPs (1–20 mg/L) alleviated the adverse impact of salinity, caused a considerable rise in the levels of both enzymatic and nonenzymatic compounds in the leaves and fruits suggesting their beneficial impact on the nutritional quality of tomato (Morales-Espinoza et al. 2019). Foliar application of SeNPs (10 and 20 mg/L) on strawberry plants exposed to salt stress ameliorated their growth and yield compared to untreated plants. Tomato plants exposed to SeNPs showed higher levels of key osmolytes and higher activities of antioxidant enzymes leading to a lower extent of lipid peroxidation and increased accumulation of indole-3-acetic acid and ABA and enhanced levels of organic acids and sugars in the fruits suggested the beneficial impact of SeNPs on the nutritional quality of strawberry plants cultivated under salinity stress (Zahedi et al. 2019).

In strawberry explants cv. Queen Elisa cultured in vitro and in the presence of 100 mM NaCl at drought conditions (10% PEG) the negative impact of both abiotic stresses was pronouncedly mitigated by the application of 0.8 ppm FeNPs, whereby the FeNPs were more efficient than Fe-EDTA (Mozafari et al. 2019). Priming of *Sorghum bicolor* seeds with 500 mg/L Fe_2O_3 NPs enhanced the germination and growth of plants under salt stress (150 mmol NaCl) due to improved PSII efficiency, Chl index, photosynthetic rate, and RWC as well as decreased lipid peroxidation (Maswada et al. 2018). Treatment with iron NPs (0.08 and 0.8 ppm) and K_2SiO_3 (1 and 2 mM), alone or in combination pronouncedly alleviated the adverse impact of salinity on morphological traits of grape cuttings cultivated in vitro and it could be assumed that moderate concentrations of iron NPs could act favorably in increasing the salinity tolerance (Asl et al. 2019). In this field experiment the foliar application of $NaSiO_3$ NPs and SiO_2 at doses 400 and 1000 ppm, respectively, to potato plants exposed to irrigation salinity (5, 8, and 12 dS/m) improved quantum yield of PSII, carotenoids content, radical scavenging activity, and enhanced dry matter and yield of tubers, $NaSiO_3$ NPs being more effective (Kafi et al. 2019).

Strawberry plants treated with 25 or 50 mM NaCl and SiO_2 NPs at a dose of 50 and 100 m/L before or with 50 mg/L SiO_2 NPs after flowering showed improved contents of assimilation pigments and accumulated lower amounts of Pro compared to those without SiO_2 NPs application (Avestan et al. 2019). A dose of 50 mg/L of SiO_2 NPs was reported to ameliorate the growth of *Solanum tuberosum* plants and attenuated the adverse impact of salt stress (Salah et al. 2017). Attenuation of adverse effects of the high salinity by application of SiO_2 NPs reflected in the enhancement of K^+ concentration, antioxidant activities, nonenzymatic compounds, and lower concentrations of Na^+ ions as well as reduced lipid peroxidation and production of ROS was reported also for soybean plants (Farhangi-Abriz and Torabian 2018). Treatment with 200 mg/kg SiO_2 NPs alleviated water deficit and salinity stresses in cucumber plant, whereby high Si content in leaves regulated water losses via transpiration and high K content in roots contributed to higher tolerance of plants against abiotic stresses (Alsaeedi et al. 2019).

Treatment with 0.01% TiO_2 NPs considerably enhanced the activities of antioxidant enzymes and concentrations of soluble sugars, AAs, and Pro in legumes exposed to salt stress compared with plants exposed to salt without TiO_2 NPs due to reduced H_2O_2 and MDA levels and better osmoprotection (Latef et al. 2018). Priming of seeds of *Lupinus termis* with 60 mg/L ZnO NPs contributed to higher salt tolerance of plants, which was reflected in improved growth, increased levels of assimilation pigments, total phenols, AscA and Zn content; the enhanced activities of antioxidant enzymes and reduced content of MDA compared to salinized plants alone were observed as well (Latef et al. 2017).

Induction of salt tolerance due to priming with ZnO NPs was reflected in stimulated carbon assimilation in *T. aestivum* plants. Moreover, it activated the antioxidant system and improved the biosynthesis of sucrose in leaves in the presence of salt (Wang et al. 2019a). Treatment with 10 mg/L ZnO NPs showed a beneficial impact on *Brassica napus* plants grown under salinity stress (6000 mg/L) caused by the upregulating oxidative defense system, synthesis of osmolytes, and ionic regulation reflected in increased N, K, and P levels in the plant tissues with simultaneous decrease of Na^+ and Cl^- contents (Farouk and Al-Amri 2019).

Addition of CeO_2 NPs (200 mg/L) to the hydroponic solution, in which *O. sativa* L. plants were co-exposed to NaCl and Cd, mitigated the damages caused by these both stressors, reduced Pro level, induced the antioxidant defense systems, slightly decreased the Cd content in plants and was found to reduce the DNA damage in NaCl treated rice (Wang et al. 2019b). Mesophyll cells of *Arabidopsis* leaves treated with 50 mg/L of poly(acrylic acid) coated CeO_2 NPs, which were exposed to 100 mM NaCl for 3 days, showed considerably higher carbon assimilation rates and Chl contents and improved photosynthesis compared to those of control plants. Moreover, under salinity stress, K^+ efflux from mesophyll cells of CeO_2 NPs-treated leaves was reduced. The ROS-activated nonselective cation channels situated in the plasma membrane of leaf mesophyll cells were found to be the major $HO^•$-inducible K^+ efflux channels. Reduced $HO^•$ levels and ameliorated retention of K^+ in leaf mesophyll due to application of CeO_2 NPs improved photosynthesis and biomass of *Arabidopsis* seedlings under salinity stress (Wu et al. 2018).

Combined addition of Zn, B, Si, and zeolite NPs to soil mitigated the adverse effects of salt excess on growth and yield of *S. tuberosum* L. plants and enhanced the contents of some elements needed for plant growth in plant tissues as well as levels of Pro and gibberellic acid in leaves; higher contents of protein, carbohydrates, and antioxidant enzymes in tubers were estimated as well (Mahmoud et al. 2020).

Using wheat seeds pretreated with polyhydroxy fullerenes NPs resulted in improved growth of roots and shoots of *T. aestivum* seedlings cultivated in sand-filled pots under salt stress due to reduced oxidative stress levels and improved activities of antioxidant enzymes. In plants exposed to these NPs also enhanced levels of Chl, free AAs, AscA, and soluble sugars were found. Moreover, higher K^+ and P concentrations in the root and shoot P contents were observed as well (Shafiq et al. 2019).

4.4 Flood Stress

According to EU Directive (2007) related to the assessment and management of flood risks, "flood means the temporary covering by water of land not normally covered by water," while "flood risk means the combination of the probability of a flood event and of the potential adverse consequences of flood for the environment and human population and economic activity associated with a flood event." Flood frequencies, which will increase under changing climatic conditions, will be reflected in enormous losses in crop production. A EURO-CORDEX RCP8.5 scenario was used by Alfieri et al. (2015) to assess the projected changes in flood hazard in Europe through the twenty-first century considering global warming and found that changes in frequencies of extreme discharges will probably affect the flood hazard to a greater extent than changes of their extents and it could be assumed that within three decades the number of flood peaks corresponding to return periods > 100 years will be doubled. Moreover, degradation of land use can affect pronouncedly the infiltration and surface roughness resulting in higher flood discharges (Saghafian et al. 2008).

Flooding arose from an overflow of water from water bodies when rainwater accumulates on the saturated ground or when the capacity of the river channel is insufficient to retain the flow rate. It can be classified as (a) waterlogging when only roots are covered with water and (b) submergence, when the aerial plant parts are completely covered with water (Sasidharan et al. 2017). Under flooding stress, the supply of O_2 to roots needed for respiration is limited, which results in hypoxia (at $< 21\%$ O_2). However, plants could respond to these unfavorable conditions via initiating organogenesis and by the formation of adventitious roots (Sauter 2013). Responses of plants to submergence and waterlogging stress in order to achieve enhanced internal O_2 status were discussed by Voesenek et al. (2006) and Fukao et al. (2019). Some metal-based NPs were found to attenuate the negative effects of flooding on plants (e.g., Jampílek and Kráľová 2019c, 2021).

For example, plants grown from corms of saffron pretreated with 40 or 80 ppm AgNPs and then planted under flooding stress showed a higher number of roots and improved root length and dry biomass and it was assumed that AgNPs prevented the adverse impact of ethylene on root growth (Rezvani et al. 2012). The reduction of O_2-deprivation stress in *Glycine max* plants under flooding treated with 2 ppm AgNPs (15 nm) was observed (Mustafa et al. 2015a) and in AgNPs-treated soybean plants under flooding stress increased levels of proteins related to AA synthesis as well as the formation of waxes were observed, what was reflected in improved plant growth (Mustafa et al. 2016).

In Al_2O_3 NPs-treated flooding-stressed soybean plants the NPs targeted the mitochondrion and regulation of membrane permeability and tricarboxylic acid cycle activity by Al_2O_3 NPs were found to affect mitochondrial proteins. Al_2O_3 NPs with sizes ranging from 30 to 60 nm improved the length of the root (including hypocotyl) of stressed *Glycine max* plants (Mustafa and Komatsu 2016). Application of 50 ppm Al_2O_3 NPs to soybean plants enhanced survival percentage, seedling biomass, and biomass/length of root ratio during the recovery stage from flooding.

During recovery after flooding protein synthesis and levels of stress related proteins showed an increase; *S*-adenosyl-L-methionine dependent methyltransferases and enolase were found to play a role in mediating recovery responses to flooding at treatment with Al_2O_3 NPs (Yasmeen et al. 2016). Cell death in roots including hypocotyls in flooding-treated soybean plants was reduced at the application of Al_2O_3 NPs compared to control and based on the proteomic analysis it was found that Al_2O_3 NPs applied to *Glycine max* plants under flooding stress regulated energy metabolism and cell death what was reflected in improved plant growth (Mustafa et al. 2015b).

5 Conclusions

The negative impact on agricultural production as a result of climate change needs to be mitigated by appropriate management in order to secure sufficient food for rapid global human population growth. Based on predictions that due to global warming in the period 2030–2050, the temperature can increase by a further

1.5 °C, prolonged drought periods as well as a higher occurrence of pests, and the incidence of crop diseases can seriously threaten the agricultural production. On the other hand, floods in coastal regions as a result of sea-level rise caused by melting glaciers and ice sheets due to increased temperatures or the overflow of water from rivers and lakes when the flow rate exceeds the capacity of the river channel due to massive rainstorms, can also cause immense damage to agriculture. One of the effective solutions that can be used to attenuate these adverse impacts on agriculture is the application of nanoscale materials as fertilizers effectively ensuring plant nutrition and nanosized pesticides formulations enabling not only the controlled release of the active ingredient but also the achievement of the required effects using its lower amount compared to bulk counterparts. Moreover, nanoparticles can be successfully used to mitigate the adverse impact of abiotic stresses (drought, heat, UV irradiation, salinity, and flooding) on crops, which are expected to occur more frequently under changing climate conditions. Improved crop practices, food quality, and packaging methods can be also achieved by the application of nanosensors, and the integration of those nanosensors into current processes and emerging trends of precision agriculture can also contribute to sustainable agriculture production. However, it is important to emphasize that it is necessary to stop the massive use of high-grade fertile soil for nonagricultural purposes globally as well as planting plants for industrial purposes and not for food crop production on too large areas. One of such plants is rapeseed, which requires excess nitrogen fertilization due to its low nitrogen use efficiency, often not exceeding 60% of the ratio of plant nitrogen content to nitrogen supplied. Its widespread cultivation for the production of an additive to biofuel contributes to increased emissions of N_2O, a greenhouse gas, the global warming potential of which is assumed to be 298-fold greater than that of CO_2 in the 100-year time scale. It is also urgently needed to reduce significantly wasting food in developed countries as much as possible. Effective agricultural production and sufficient healthy food on our planet at changing climate conditions can be ensured only by appropriate management based on the latest scientific findings used on the global scale together with the responsible attitude of people. On the other hand, the current problems in the partly limited cross-border supply of food products during the ongoing COVID-19 pandemic caused by SARS-CoV-2 coronavirus have also shown the urgent need for measures taken by individual states to ensure self-sufficiency in the production of basic food crops for their own population using smart farming locally.

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Chapter 18
Silver Nanoparticles as a Fungicide against Soil-Borne *Sclerotium rolfsii:* A Case Study for Wheat Plants

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1 Introduction

Agricultural production has been continuously suffering from severe threats due to phytopathogen attack worldwide leading to huge economic losses of 20–40% every year (Flood 2010; Worrall et al. 2018). Fungal species have been found accountable for nearly 70% of altogether main crop diseases and notable crop damage has been witnessed in various crop species like groundnut, rice, barley, wheat, cotton, and grapevine (Agrios 2005; Patel et al. 2014). Annual expenditure on fungicides in the United States alone exceeds $600 million (Fernández et al. 2010). In spite of several benefits like easy availability, reliability, and speedy action associated with the chemical fungicide applications; they suffer from shortcomings like adverse effects to nontarget plants, disease resistance development, and a resurgence of pest population (Yadav et al. 2020). Owing to this, environmental hazards caused by excessive use of fungicides have been widely discussed and addressed in recent years. Additionally, a significant portion of these fungicides is lost after application creating a fungicidal load in the soil. Therefore, agriculture scientists are searching for alternative innovative measures that can reduce the unrestrained use of chemical fungicides and minimize economic losses as well.

Wheat (*Triticum aestivum* L.) is an annual monocotyledonous plant belonging to the grass family, *Poaceae*. It is the second most-produced cereal grain after maize, grown on more land area than any other commercial crop, and is the most important staple food for human consumption. The whole grain is a concentrated source of vitamins, minerals, and proteins, while the refined grain is mostly starch. World trade in wheat is greater than all other crops combined. Unfortunately, the production of wheat is severely hampered due to the pathogen attacks, especially fungi (Mishra et al. 2015; Mishra et al. 2017). Estimates of the amount of wheat production lost owing to plant diseases vary between 10 and 25%, to which fungal diseases contribute significantly. Wheat crop is susceptible to the attack of various fungal phytopathogens that cause southern blight (better known as *Sclerotium* wilt), rust (affecting leaves and stem), root rot (affecting root), smut (affecting kernels, leaves), powdery mildew, and blotch and blight majorly affecting leaves (Yadav et al. 2020; Mishra et al. 2015).

The soil-inhabiting plant pathogenic fungus, *Sclerotium rolfsii* commonly occurs in the tropics, subtropics, and other warm temperate regions of the world causing root rot, stem rot, wilt, and foot rot on more than 500 plant species including almost all the agricultural and horticultural crops (Mishra et al. 2017). Susceptible host plants include wheat (*Triticum vulgare*), sweet potato (*Ipomea batatas*), pumpkin (*Cucurbita pepo* L.), corn (*Zea mays*), and peanut (*Arachis hypogea*). To design proficient crop protection frameworks, understanding the infection cycle and virulence factors of the phytopathogen is obligatory. The pathogenesis and spread of *S. rolfsii* take place through asexual and sexual reproduction methods and sporadically leads to the formation of basidiospores (the sexual stage of reproduction) surrounding outer ends of lesions in moist environments. However, this type of reproduction is of uncommon occurrence. Asexual mode of reproduction by the production of sclerotia is quite common in this fungus. A *Sclerotium* (plural sclerotia) is a compact dark mass of hardened fungal mycelium containing food reserves and can cleverly survive environmental extremes remaining dormant or quiescent during the stressful period and then germinate when conditions are more favorable. Sclerotia may go through either eruptive or hyphal germination. Hyphal germination is identified through the growth of individual hyphae originating from the surface boundary of sclerotia whereas eruptive germination can be best described as mycelial aggregations bursting out from the sclerotial surface (Parikh and Jha 2012).

S. rolfsii predominantly damages host crop shoots, while it is capable of infecting any plant part during favorable environmental settings comprising fruits, roots, leaves, petioles, and flowers. The infection of host tissue is facilitated by the production of oxalic acid, which sequesters calcium to form calcium oxalate and also lowers the pH, and by the production of endopolygalacturonase (Punja 2007). The initial signs of infection are dark-brown lesions on the stem that commonly goes unnoticeable. The main detectable symptoms are the progression of yellowing and drooping of the leaves. Subsequently, *S. rolfsii* produces profuse white and fluffy mycelium on the infected plant parts along with the soil (Parikh and Jha 2012; Boyle 1961; Singh et al. 2016; Yaqub and Shahazad 2011).

Traditional plant breeding used to develop new disease-resistant varieties, and sound crop management practices are important for preventing disease, but commercial agriculture is heavily dependent on chemical fungicides. These fungicides have added a significant cost to wheat production on one hand and a threat to the environment on the other hand due to fungicide resistance and harmful effects on nontarget organisms (Zaki et al. 1998; Manczinger et al. 2002). In traditional plant breeding only closely related species of plants can be crossbreed. If no varieties are naturally resistant to a particular fungus or insect, traditional breeders have no way to create resistance to that fungus or insect. Physical method such as soil solarization is also an age-old practice to control soil pests by the high temperature produced from trapped solar energy. Unfortunately, this method suffers from limited adoption due to a reasonably lengthier period of the process, reliance on weather conditions, and survival of pathogens at deeper layers in the soil (Patel et al. 2014).

The prospective aimed at the use of fungal antagonists as biocontrol mediators of crop diseases were advocated by Weindling (1932), being the first to mention the inhibitory action of *Trichoderma* sp. against *S. rolfsii* and *Rhizoctonia solani*. Complementing studies carried out by Parikh and Jha (2012) revealed the biocontrol ability of bacterial strain LK11 against *S. rolfsii* during in planta applications. Controlling *S. rolfsii* disease by means of biological methods in the field is difficult because the pathogen has a wide host range and can survive in the soil for a long time. It takes more intensive management and planning such as proper education and training to achieve success through biological control. Technological innovations have been offered by researchers to overcome the problem and nanotechnology has gathered noteworthy attention due to its specificity, robustness, and efficiency and as a result, has opened up new possibilities for vast applications in agriculture. Yadav et al. (2020) reviewed various research works and concluded that silicon-based fertilizers used to increase plant resistance as silicon dioxide nanoparticles can improve seedling growth and root development.

Nanotechnology presents prospective ideas to research the biological characteristics of previously identified antimicrobial compounds by manipulating their size to change the effect. The word nanotechnology is commonly used while mentioning the materials falling in the size range of 0.1–100 nm (Patel et al. 2014; Morones et al. 2005). Nanobiotechnology is a newfangled division of biology which has originated owing to the attainability of nano-sized organic and inorganic particles with life functions. Certain nanoparticles that have occupied a central position in phytopathogen control are nano-sized silver, carbon, silica, and aluminosilicates. These nanoparticles have been popularly known as bionanofungicides (Patel et al. 2014; Lamsal et al. 2011a; Huang et al. 2020).

1.1 Scope, Approach, and Current Applications of Silver Nanoparticles as Fungicide

Diversified approaches have been attempted to alleviate the effect of fungal phytopathogens, promote crop productivity, and maintain soil health in totality. Methods like soil solarization, application of chemical pesticides, employing disease-resistant plant varieties, and application of biocontrol agents have been practiced for years (Patel et al. 2014). Although these methods have several desirable effects but suffer from some glitches as well. Silver nanoparticles being used as small probes do not interfere with the basic physiological processes of plants owing to their nano-size. Silver can be used as AgNPs, nanocapsules, and viral capsids for the detection and treatment of plant diseases. Surprisingly, understanding the mechanism behind fungal phytopathogen control at the nanoscale has given prime impetus to nanobiotechnology (Bhattacharyya et al. 2016; Ismail et al. 2017; Gupta et al. 2018). Targeted application of silver nanofungicide will condense the effect on nontarget tissues along with the alleviation of environmental hazards and cost burden of chemicals. Regardless of several advantages associated, the agriculture sector has yet to explore this technology to its fullest.

Several researchers have highlighted the potential of AgNP for effectively managing the plant diseases with special reference to fungal diseases. Mishra et al. (2015) reviewed several research works and mentioned the immense applicability potential of AgNPs in the agricultural sector. They analyzed the studies specifically in terms of field applications like overall interaction of AgNPs with plants, biotic and abiotic components of soil environment, and toxicity associated with its usage in agriculture (Prasad et al. 2014, 2017). Nano-Ag has been utilized as a colloidal silver solution, AgNP with fluconazole, circular AgNPs prepared using cow milk, bioactive bile salt sodium deoxycholate-capped AgNPs, and so on. In an interesting study, strong botryoidal activity was shown by a nanosized Ag–exposed fungal CS composite. Inhibition of mycelial growth, spore germination rate, and colony formation has been reviewed and reported by several researchers (Table 18.1).

Table 18.1 Summary of the studies utilizing Nano-Ag for fungicidal applications and crop protection

Disease	Target fungal phytopathogen	Crop	Concentration of AgNP	Effect	References
Rice blast, spot blotch of wheat	*Magnaporthe* grisea; *Bipolaris sorokiniana*	Rice, wheat	25–200 ppm	Significant suppression of *M. grisea* and *B. sorokiniana* both in in vitro and in planta experiments (with perennial ryegrass *Lolium perenne*), EC50 of *B. sorokiniana* found higher than *M. grisea*	Jo et al. (2009)
Spot blotch	*Bipolaris sorokiniana*	Wheat	2–10 ppm	Complete inhibition of conidial germination in contrast to 100% conidial germination in untreated control	Mishra et al. (2014)
Pepper anthracnose	*Colletotrichum*	Pepper	100 ppm	100 ppm exhibited maximum blockage of hyphal growth and conidial germination (in vitro and in vivo)	Lamsal et al. (2011a)
Sheath blight, collar rot, root rot, damping off, basal drop disease	*Rhizoctonia solani, Sclerotinia sclerotiorum*, and *Sclerotinia minor*	Rice, lettuce, sugar beet	10–100 ppm	Effect seen in dose dependent manner inhibited both conidial and hyphal germination in in vitro studies	Min et al. (2009)
Japanese oak wilt	*Raffaelea quercivora*	Oak	5–25 ppm	Fungal inhibition in dose dependent manner, detrimental effects on fungal hyphae and conidial germination observed	Kim et al. (2009)
Leaf spot, collar rot, root rot, damping off, charcoal rot, sheath blight, gray mould rot	*Alternaria alternata, Sclerotinia sclerotiorum, Macrophomina phaseolina, Rhizoctonia solani, Botrytis cinerea* and *Curvularia lunata*	Soybean, Rice, lettuce, sugar beet, sugarcane, horticultural fruits and vegetables	5–15 mg	Great inhibitory action against all the tested pathogens in in vitro experimentation at 15 mg concentration	Krishnaraj et al. (2012)

(continued)

Table 18.1 (continued)

Disease	Target fungal phytopathogen	Crop	Concentration of AgNP	Effect	References
Powdery mildew	*Podosphaera xanthii*	Cucumbers and pumpkins	10–100 ppm	Lowest disease occurrence of 20% recorded in 100 ppm silver nanoparticles demonstrating the highest fungal inhibition rate in in vivo tests	Lamsal et al. (2011b)
Tomato anthracnose, brown rot, blast	*Colletotrichum coccodes, Monilinia* sp.*, and Pyricularia* sp.	Tomato, apple, rice	2–4 mM	Strong antagonistic activity (87.1%, 86.5%, and 83.5%) at 2 mM of nano-Ag against phytopathogens	Lee et al. (2013)
Seedling blight, foot rot, stalk rot	*Fusarium culmarum*	Cereals, grasses	0.12–10 ppm	2.5 ppm concentration greatly inhibited the number of germinating fragments and sprout length compared to the control	Kasprowicz et al. (2010)
Rice blast	*Magnaporthe grisea*	Rice	100 ppm	Damaged leaf area percentage (DLA %) reduced to 20% compared untreated plants with 80%. No phytotoxicity reports on the rice grains	Elamawi and EL-Shafey (2013)
Early blight disease	*Alternaria solani*	Tomato and potato	250 ppm	AgNP proved more inhibitory (27 mm inhibition zone) against *Alternaria solani* compared to the antibiotic Nystatin (4 mm mm inhibition zone).	Abbas et al. (2015)

Disease	Target fungal phytopathogen	Crop	Concentration of AgNP	Effect	References
Early blight disease	*Alternaria solani*	Potato	150 ppm + K_2SO_4 (2%) as plant foliar spray	Disease severity significantly reduced to 8.39% in treated plants in contrast to untreated plants (86.17%), overall improvement in physiological parameters and growth of treated plants	El-Batal et al. (2016)
Black spot	*Alternaria brassicicola*	Cauliflower, radish, cabbage, kale	100 ppm	Growth of *A. brassicicola* was considerably reduced by 92.2% under in vitro conditions	Gupta and Chauhan (2015)
Wilt, root rot, black rot whisker mold, crown rot, and damping-off	*Penicillium* sp., *Aspergillus* sp. and *Fusarium* sp.	Brinjal, cabbage, potato, tomato, onions, peanut, and garlic	400 ppm	*Penicillium* sp. inhibited strongly (92%) followed by *Fusarium* sp. and *Aspergillus* sp. (89%, 69%) in in vitro studies.	Haroon et al. (2019)
Leaf blight, dieback	*Colletotrichum capsci*	Basil, chickpea, pigeon pea	100–200 ppm	Mycelial growth reduced to 70% at 200 ppm AgNP concentration in in vitro studies	Atiq et al. (2020)
Northern corn leaf blight	*Setosphaeria turcica*	Maize	AgNP (12.5–200 ppm) + Epoxyconazole	Acted as novel fungistat for comprehencive fungal control	Huang et al. (2020)

1.2 Mechanistic Understanding of Silver Nanoparticles as a Fungicide

A plethora of researches have turned their eyes to the synthesis and application of AgNP in controlling and treating fungal phytopathogens, but very few of them have unraveled the underlying mechanism behind these activities (Siddhanta et al. 2016; Tripathi et al. 2017; Sharma et al. 2018; Aziz et al. 2016). Mechanistic understanding of AgNPs' action is obligatory for constructing a robust solution toward pathogen management. This will also help to understand the functionality of plant, pathogen, and the plant–pathogen–soil system as a whole in presence of AgNPs. Pronounced antimicrobial activity of nanoparticles have been largely attributed to their unusual crystal morphologies with edges, corners, and reactive sites and the large surface area (Allaker 2010), but sometimes size may not be the sole reason behind such effects as per the recent finding (Yadav et al. 2020). The basic nature of silver in an atomic form is inert and stable, but its ionized form (oxidation state of +1) is highly reactive and unstable. Ag+ ions are released as a result of the AgNPs dissolution that accelerates its toxicity effects through nonselective reaction with e-donating groups namely thiols, imidazoles, hydroxyls, and phosphates (Franci et al. 2015; Osonga et al. 2020) (Fig. 18.1). Furthermore, such cationic Ag+ efficiently bind with the proteins present in plasma and nuclear membranes, thus forming a complex eventually causing remarkable structural changes in these membranes

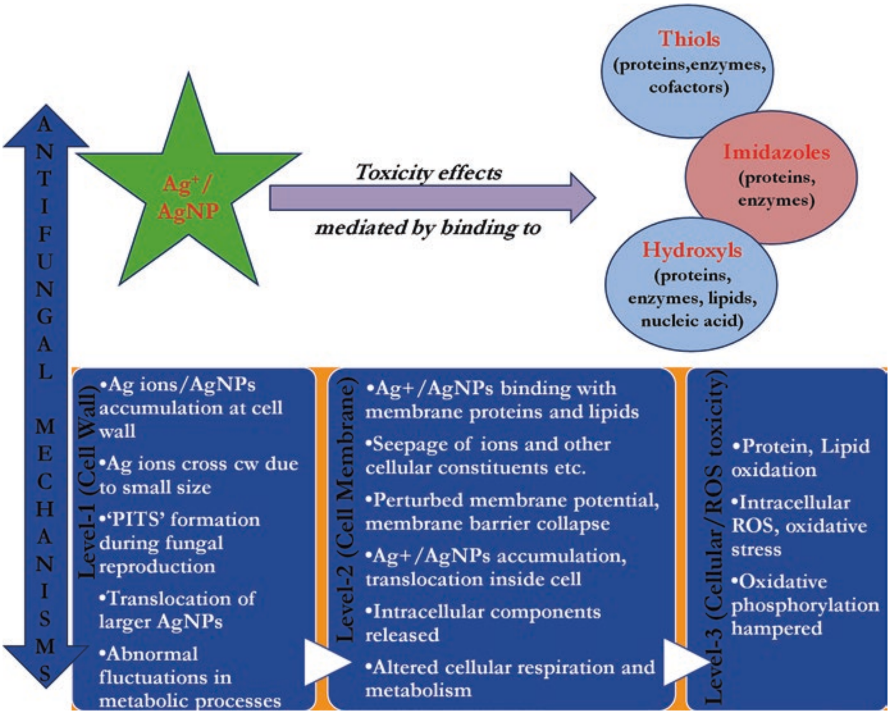

Fig. 18.1 General mechanism of antifungal activity of silver nanoparticles

(Reidy et al. 2013; Le Ouay and Stellacci 2015; Aziz et al. 2019). After reviewing and gathering insight from the work of some potential researchers, the antifungal mechanisms exhibited by nano-Ag can be subdivided into three broad categories:

1.2.1 Adhesion to Cell Wall

The fungal cell wall and cell membrane satisfy a number of vital functions that obstruct the transition of AgNP inside the cells. Chitinous cell wall is the key component of fungal cells forming a potential barrier that prevents protoplast disruption and thus maintaining cellular integrity in totality. It is comprised of certain important components like carbohydrates forming a rigid and elusive configuration (Navarro et al. 2008). The cell wall being semipermeable in nature acts as a filter allowing the movement of small particles whereas preventing the larger ones. Conversely, an increase in pore size has been observed all through the reproduction period owing to the presence of AgNPs, then eventually these pores allow transition of the larger silver nanoparticles (Ovecka et al. 2005; Navarro et al. 2008). Similar findings have been reported by Navarro et al. (2008). They found considerable alteration like "pits" formed on the cell wall surface when subjected to AgNPs exposure, which led to considerable abnormal fluctuations in cell metabolism (Fig. 18.1). Strong interactions of AgNPs with the cell wall layer stimulate greater surface energy and thus the easy movement of nanoparticles (Dakal et al. 2016; Haroon et al. 2019). Wang et al. (2002) confirmed that nanofertilizer encapsulated nanosilica can form a binary film on the fungal cell wall; hence, restraining infections, helping plants in combating disease, and promoting overall plant growth especially in high temperature and humidity conditions.

1.2.2 Interaction with Cell Membrane

Mechanistically, next to the cell wall AgNPs likewise hamper the membrane transport systems (including ion efflux) which form the second level structural barrier after the cell wall. Any kind of damage and distortion in the cell membrane weakens this barrier to translocate and accumulate Ag+ ions (released from AgNPs supplemented in the nutrient media) inside the cells (Fig. 18.1). This induces a shock state in the cell finally obstructing cellular respiration and metabolic activities (Dakal et al. 2016; Haroon et al. 2019). The investigation carried out by Siddhanta et al. (2016) centered upon the fact that membrane barriers may collapse in later stages owing to AgNPs accumulation by seepage of ions and other cellular constituents leading to perturbation in membrane electrical potential. Such perturbations cause the release of glucose and trehalose externally indicating that these are the intracellular constituents of the cell membrane (Siddhanta et al. 2016; Tripathi et al. 2017).

1.2.3 Cellular Toxicity and ROS Toxicity

Oxidation of lipids and proteins and generation of intracellular ROS is nevertheless an additional mechanism via which the biomolecules like proteins, lipids, and nucleic acids get severely affected (Ahmed et al. 2018). Another hypothesis focuses on the possible mechanism that the thiol groups found in proteins might also be targeted with the interaction of silver ions (Lok et al. 2006; Tripathi et al. 2017; Prasad 2019). An interesting study conducted by Feng et al. (2000) established that the application of nano silver even at the micromolar level can obstruct the pathways of microbial respiration via uncoupling the electrons involved in phosphorylation event and thus disturb the membrane permeability (Fig. 18.1).

Nevertheless, the researchers have been able to unravel some of the important aspects regarding defense mechanisms underlying AgNPs interaction with the bacterial cells, such investigations concerning fungal systems are still insufficient and an immense work dealing with the AgNPs–fungal cell interaction at a cellular and molecular level yet needs to be done. Some investigations have established the fungicidal impact of AgNPs against numerous fungal phytopathogens (Yadav et al. 2020; Kim et al. 2012; Prasad 2016, 2017, 2018), but most of them have established only in vitro effects. Since Ag exhibits several means of inhibitory function against microbes in general; hence, it may be applied with relative safety in controlling many phytopathogens in contrast to synthetic fungicides. There is a possibility to use silver nanoparticles (AgNPs) as an alternative to fungicides for *Sclerotium*-forming phytopathogenic fungi, surprisingly only a handful of information is available on the plant application of silver nanoemulsion as antifungal agents and promoting plant growth in totality. Application of silver nanoparticles in soil and as seed/seedling treatment might not only control the plant pathogen but also augment crop growth and yield via some unknown and known mechanisms.

In the present chapter, we report our investigatory efforts as a case study that encompass the synthesis of highly stable silver nanoparticles endowed with significant antifungal properties that can be proposed as an effective control measure for the wheat plants against devastating phytopathogen *S. rolfsii*.

2 Case Study: Silver Nanoparticles against *Sclerotium rolfsii*

2.1 Synthesis and Characterization of Silver Nanoparticles (AgNPs)

2.1.1 Synthesis of Silver Nanoparticles

AgNPs were synthesized as described by Pal et al. (2008) using two neck flask (Fig. 18.2). The reaction mixture contained 1% SDS, 2.5 ml of sodium citrate, and heated till temperature was attained 90 °C. This was followed by the addition of 1 mM silver nitrate; the neck was sealed by cotton plug and maintained at 50 rpm shaking for 1 h.

Fig. 18.2 Nanoemulsion preparation assembly

2.1.2 Characterization of Silver Nanoparticles

U.V. visible spectroscopy: Preliminary characterization of silver nanoparticles was achieved by U.V visible spectroscopy. The synthesized sample of silver nanoparticle solution was scanned for absorbance in the range of 400–430 nm for the actual synthesis of silver nanoparticles.

Dynamic light scattering (DLS) for measurement of particle size: Dynamic light-scattering machine measures the particle size dimension of nanoparticles in the aqueous solution. Thus, 1 ml emulsion suspension was of AgNPs was placed into polystyrene micro cuvette and placed in the DLS machine, and the program was run to measure the size of Ag nanoparticles. The measurement was performed with three replications at temperature 25°C for 50s to observe the stability of the nanoemulsion.

2.2 *In Vitro Antifungal Activity*

2.2.1 Purification and Maintenance of Fungal Culture

The fungal stock of *Sclerotium rolfsii* used in this study was obtained as agar slants maintained in the departmental microbial stock. Mature brown-colored sclerotia were carefully removed with a pair of sterile fine forceps from the host plant and placed in distilled water to wash off any adhering soil particles. They were then surface-sterilized by immersing them in 1.0% sodium hypochlorite for 3 min, rinsed after that in three changes of sterile distilled water, and inoculated onto sterile potato dextrose agar (PDA) plates and incubated at 28°C. The growing mycelium was subcultured after 4 days. A second subculturing was again done to ensure a completely pure culture. The pure cultures were maintained on PDA slants and kept at 4°C till further use.

2.2.2 Plate Assay

Antifungal activity of AgNP was checked against phytopathogen *S. rolfsii* by testing variable prepared concentrations of silver nanoemulsion (15–100 ppm) by directly adding into the PDA media. Ampicillin added in PDA acted as an antibacterial agent. A block of 0.5cm^2 was cut from the periphery of the actively growing fungal mycelia of the test fungi and was placed in the center of PDA plates containing different concentrations of AgNP and then incubated at 28°C. A control plate was also prepared which contained the test pathogen only.

2.2.3 Broth Assay and Microscopy

Variable concentrations of silver nanoemulsion (2–100 ppm) were prepared and directly added in potato dextrose broth (PDB) containing Ampicilin antibiotic for inhibiting bacterial growth. A block of 0.5cm^2 was cut from the periphery of the actively growing fungal mycelia of *S. rolfsii* and was added in PDB media. A flask containing only mycelial block in the medium served as control. The flasks were then incubated on an orbital shaker at 27°C for 15 days. After incubation, the fresh mycelial mat was harvested and dried at 60°C for 24 h to constant weight for obtaining fungal dry weight. Microscopic analysis of cultures after 15 days was also performed to observe the effect of different concentrations of silver nanoemulsion on the growth and morphology of fungal mycelia.

2.2.4 In Vitro Sclerotia Germination

A drop of silver nanoemulsion from variable concentrations was placed on separate glass slides. Fungal spores were picked from 7 to 10 days old culture with sterilized inoculation needle and mixed with nanoemulsion. The slides were placed in a moist chamber made by placing two sterile filter papers each on the lid and base of Petri plates. The slides with spores were then incubated at room temperature and spore germination was observed at different time intervals under a light compound microscope. Spores mixed with sterile distilled water served as a control. All experiments were conducted in triplicates (Shrivastava and Shalini 2008).

2.3 **In Planta** ***Studies: Impact of AgNP Treatment on Growth Profile of*** **Sclerotium** ***Challenged Wheat Plants***

Wheat grains were surface sterilized by immersing the seeds in 0.1% $HgCl_2$ for 2 min ($HgCl_2$ was prepared in sterile distilled water) followed by sterile distilled water rinsing several times and drying. Seeds were then dipped in different concentrations of silver nanoemulsion for 5 min. and kept for drying at room temperature. Treatments were managed as per the following sets:

1. Control (C_1): Seeds treated with distilled water.
2. Control (C_2): Seeds coated with fungal mycelium.
3. Control (C_3): Seeds treated with Silver nanoemulsion (C3: Seed+50 ppm AgNE; C4: Seed+100 ppm AgNE).
4. Experimental (E): Seeds treated with Silver nanoemulsion and coated with fungal mycelia (E1: Seed+50 ppm AgNE+ fungi; E2: Seed+100 ppm AgNE+ fungi).

These seeds were placed on 3% sterilized water agar tubes at room temperature for 7 days. To observe the effect of AgNPs on growth and morphology of fungal mycelia and the overall growth of wheat plants following agronomic traits were scored after 7 days:

Percent germination, root length, shoot length, plant dry weight, and vigor index All experiments were conducted in triplicates. All these steps were carried out taking all possible aseptic measures in the laminar airflow unit. Seedling vigor index was calculated following the method given by Maisuria and Patel (2009) as given below:

$$\text{Vigour Index} = \left(\text{Root length} + \text{Shoot length}\right) \times \%\text{Seed germination.}$$

2.3.1 Microscopy

The sections of roots, leaves, and stem regions were observed under a compound microscope after staining with safranine.

3 Results and Discussion

Effects of silver nanoparticles on the fungal phytopathogens, especially Sclerotium-forming species have been investigated owing to their significant functions in survival and disease cycle. There is a possibility to use silver nanoparticles as an alternative to fungicides for Sclerotium-forming phytopathogenic fungi, surprisingly meager information is available on the field application of silver nanoemulsion as antifungal agents and promoting overall plant growth. Principal requirements for the prospective use of silver for controlling plant diseases encompass the need for additional information on the antifungal action of several silver compounds against plant pathogens and formulation of improved application schemes to enhance the effectiveness of disease suppression. The present investigation gave an insight into the role of silver nanoparticles in combating the severe *Sclerotium* infection in wheat, and thus, the experiments were based on in vitro and in vivo studies.

3.1 Synthesis and Characterization of Silver Nanoparticles (AgNPs)

3.1.1 U.V Visible Spectroscopy

To reveal the spectral characteristics of synthesized silver nanoemulsion following standard procedures, the samples were scanned in the range of 200–700 nm in a spectrophotometer. Sample showed a peak in the range 380–420 nm. Hence the synthesis of nano-Ag was ascertained based on this observation. This gave the confirmation that the synthesized silver nanoparticles were perfect for carrying out further investigations through the dynamic light scattering method.

3.1.2 Dynamic Light Scattering (DLS)

Nanoemulsion prepared from SDS, sodium citrate, and silver nitrate blends successfully formed AgNP of the size 106.6 nm as exhibited by the size distribution spectra of the emulsion system determined by dynamic light scattering. The visual appearance of the nanoemulsion was bright (Fig. 18.3). The nanoemulsion enhanced the dispersion of formulation so that a larger specific area was available that

Fig. 18.3 Visual appearance of prepared silver nanoemulsion

eventually led to bright color formation (Çinar 2017). A study conducted by Silva et al. (2011) inferred that the most significant factors affecting the particle size reduction were the speed and time of homogenization.

3.2 Role of AgNE in Suppression of S. rolfsii Growth under in Vitro Conditions

In order to elucidate the antifungal activity of silver nanoemulsion (AgNE) against *S. rolfsii*, the behavior and growth of mycelia, as well as spores in semisolid and liquid culture media, were investigated. Promising results were obtained in these studies and the mode of fungal growth inhibition could also be partially deciphered.

3.2.1 Plate Assay

During in vitro plate studies, the effect of varying AgNE concentrations on fungal mycelial growth was evaluated.

As the concentration of AgNPs increased, the mycelial growth inhibition percentage also increased linearly and sporulation was totally restrained when compared with the untreated control (Fig. 18.4). Fungal sporulation and mycelial inhibition were visible even at 15 ppm, the lowest dose of AgNE. At 40 ppm AgNE concentration, the fungal growth was suppressed by ~60%. Surprisingly, the fungi could not grow at all when subjected to 100 ppm AgNE concentration (Table 18.2). This means that 100 ppm AgNE can effectively control the growth of *S. rolfsii* under in vitro laboratory conditions. Nevertheless, 75 ppm concentration could also inhibit the fungal growth commendably to ~93%.

Mishra et al. (2017) observed the antifungal efficacy of biosynthesized AgNPs against foliar and soil-borne phytopathogens during their investigation. The

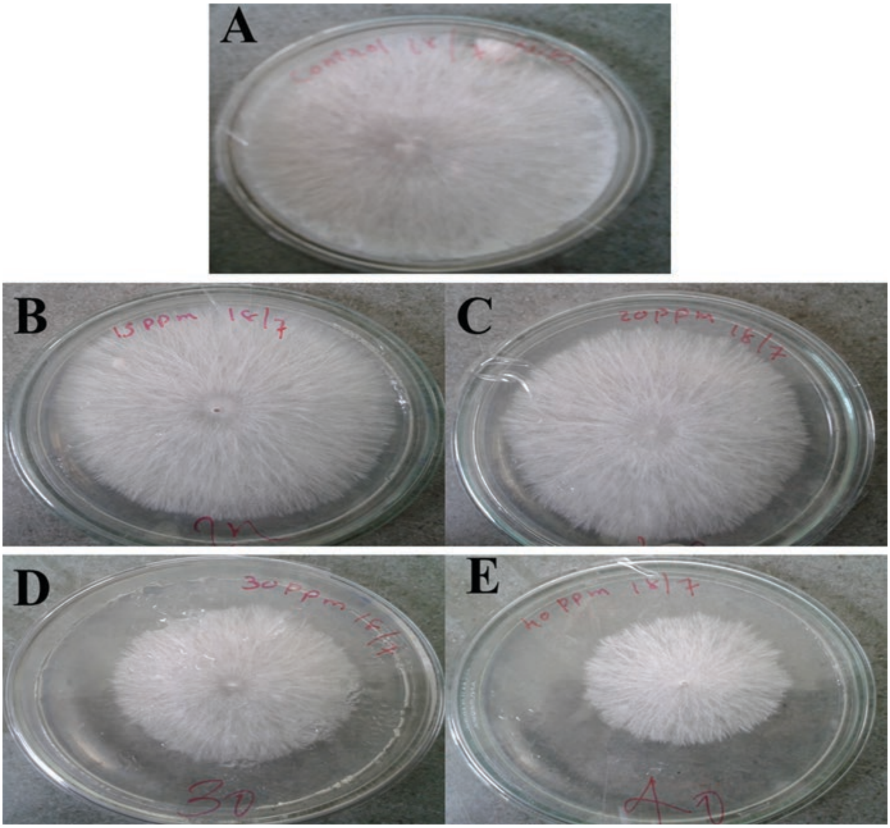

Fig. 18.4 Fungal growth inhibition exhibited by varying concentrations of AgNE (**a**) Untreated Control, (**b**) 15 ppm AgNE, (**c**) 20 ppm AgNE, (**d**) 30 ppm AgNE, (**e**) 40 ppm AgNE

Table 18.2 Mycelial growth of *S. rolfsii* (in PDA plate) in presence of different concentrations of AgNE

AgNE concentration (in ppm)	Growth diameter (in cm)				
	Day1	Day3	Day5	Day 6	% Inhibition on day 6
Untreated control	1.5 ± 0.1	5 ± 0.3	7 ± 0.3	Sporulation	0
15	0.5 ± 0.1	3 ± 0.2	6 ± 0.4	7 ± 0.3	0
20	No growth	2 ± 0.1	4 ± 0.2	5 ± 0.2	28.6
30	No growth	0.5 ± 0.1	3.5 ± 0.1	4 ± 0.3	42.8
40	No growth	0.5 ± 0.1	2 ± 0.1	3 ± 0.2	57.1
50	No growth	No growth	0.5 ± 0.1	2 ± 0.2	71.4
75	No growth	No growth	No growth	0.5 ± 0.1	92.8
100	No growth	No growth	No growth	No growth	100

inhibitory effects of AgNPs (2, 4, and 10 ppm) on conidial germination were documented in in vitro conditions. Interestingly, sclerotia of *S. rolfsii* treated with AgNPs failed to germinate on the PDA medium as well as in the soil system. Likewise, AgNPs application also controlled collar rot of chickpea (caused by *S. rolfsii*) effectively in greenhouse settings. Reduced sclerotia germination, phenolic acid induction, altered lignification, and H_2O_2 production were observed to be the probable mechanisms protecting chickpea from adversities of *S. rolfsii* infection. Their data indicated that AgNPs treated plants are superiorly equipped to manage with pathogen challenge directing toward their robust applications in plant disease management (Mishra et al. 2017).

3.2.2 Broth Assay and Microscopy

It is a common observation that microorganisms flourish in a better way when they are cultivated in a liquid culture medium compared to a semisolid medium. This happens due to the fact that nutrition and aeration both are properly accessible to them in a liquid medium. With this background, the growth behavior of *S. rolfsii* was investigated in PDB liquid culture media supplemented with variable concentrations of AgNE.

Silver nanoemulsion considerably inhibited the growth of *S. rolfsii* as compared to control. As it is apparent from Fig. 18.5 that a heavy mycelial mat is formed in a control flask while negligible fungal growth can be seen in 25 ppm and onward AgNE inoculated flasks. The pattern of fungal growth inhibition in liquid culture conditions corroborated with the pattern followed in the agar medium as indicated

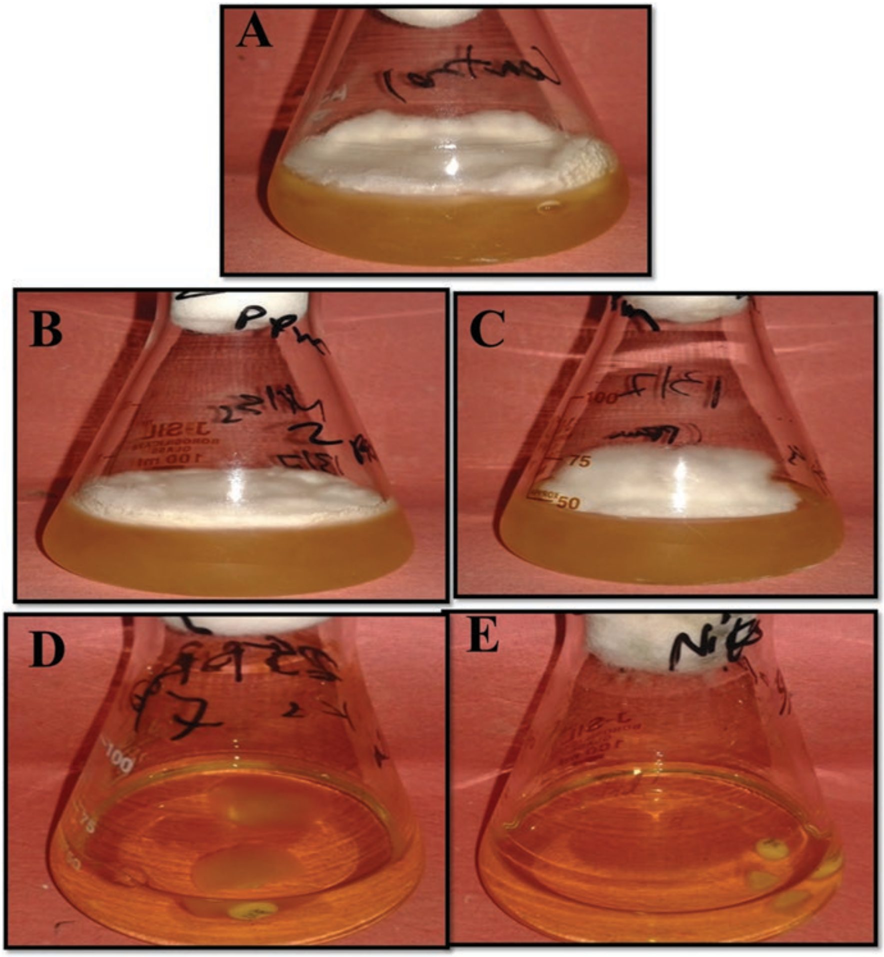

Fig. 18.5 Antifungal activity of Ag Nanoemulsion (AgNE) in PDB medium (**a**) Untreated control (no AgNE) (**b**) 2 ppm AgNE, (**c**) 15 ppm AgNE (**d**) 25 ppm AgNE (**e**) 50 ppm AgNE

in Table 18.3. In broth assay too, as the concentration of AgNP increased the fungal growth decreased, but a plateau could be observed at higher concentrations that is, from 50 to 100 ppm (96.4–97.6% fungal growth inhibition). It was indicative of the saturating concentration of AgNE. The observation clearly displayed that 50 ppm concentration was the most effective concentration in terms of pathogen control. AgNPs have been previously used against several phytopathogens like *Sclerotinia sclerotiorum, Alternaria alternata, Rhizoctonia solani, Macrophomina phaseolina, Botrytis cinerea*, and *Curvularia lunata* by well diffusion test. Only a 50% reduction was observed in the growth of fungal colonies that cause disease in *Lolium perenne* when treated with 200 ppm AgNPs (Jo et al. 2009) in contrast to 97% reduction observed at 50 ppm in our study. Some in vitro investigations have

Table 18.3 Mycelial growth of *S. rolfsii* (in PDB Broth)[a] in presence of different concentrations of silver nanoemulsion (AgNE)

S.N.	AgNE concentration (ppm)	Mycelial dry weight (mg)	% inhibition
1	Untreated control	768 ± 4.2	0.00
2	2	682 ± 3.5	11.2
3	15	620 ± 3.6	19.28
4	25	144 ± 2.8	81.25
5	50	28 ± 2.2	96.4
6	75	22 ± 1.4	97.2
7	100	19 ± 2.5	97.6

[a]Values are average of three replications

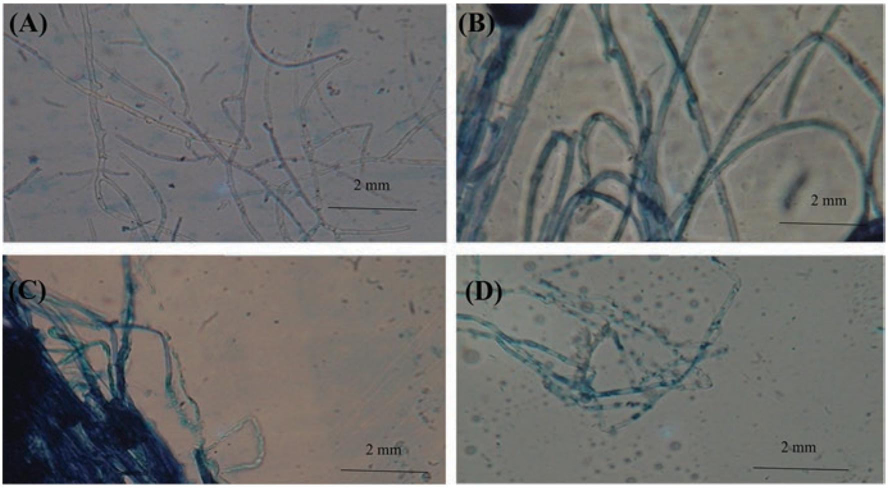

Fig. 18.6 Microscopic analysis of slide culture of *S. rolfsii* cultivated in presence of a variable concentration of AgNE. (**a**): Control (Untreated), intact septate hyphae; (**b**): 2 ppm, spindle-shaped cytoplasm, swelled mycelia; (**c**): 25 ppm, hyphal constriction, breakage; (**d**): 50 ppm, cytoplasm aggregation, hyphal degradation

revealed that 100 ppm concentration of AgNPs inhibited the activity of *Colletotrichum* spp. by controlling conidial germination as well as fungal hyphae compared to control (anthracnose pathogen) (Yadav et al. 2020; Lamsal et al. 2011a).

3.2.3 Microscopic Studies Demonstrating the Effect of AgNE on Fungal Growth

To understand the mechanism of growth inhibition displayed by various concentrations of silver nanoparticles, the fungal samples taken from broth were stained with cotton blue and observed in a compound microscope. The normal growth of fungal septate mycelia with branching is apparent in a control set (Fig. 18.6a) without

AgNE, whereas spindle-shaped cytoplasm and swelled mycelia (Fig. 18.6b) in the experimental set (fungi treated with 2 ppm AgNE) can be seen. Cytoplasmic aggregation, hyphal constriction, and breakage were some of the characteristic patterns at higher AgNE concentrations (Fig. 18.6c, d) to stop the aggravation of pathogenic fungi. Thus, AgNE demonstrated intense antifungal potential against phytopathogenic fungi, *S. rolfsii*. Silver ions are very reactive, leading to inhibition of microbial respiration and metabolism as well as physical damage (Thurman et al. 1989). Silver ions intercalate into fungal DNA once entering the cell, which prevents the further proliferation of the pathogen (Feng et al. 2000).

3.2.4 In Vitro Sclerotia Germination

S. rolfsii is well known for its propagation via robust and resistant spores that have the capability to survive in extremes of weather and can germinate through hyphal and eruptive germination under favorable moisture containing environment (Parikh and Jha 2012). In this view, the effect of variable AgNE concentrations on spore germination of *S. rolfsii* was checked and observed under a compound microscope. Highly promising results were apparent at 100 ppm AgNE concentration that didn't allow any spore to germinate compared with the control where 100% spore germination displaying both hyphal and eruptive modes, was seen (Table 18.4; Fig. 18.7). As expected, the spores exhibited both hyphal and eruptive germination in distilled water control that provided an ambient moisture environment (Table 18.4), but the presence of nano-Ag hampered the spore germination process (only 20% at 50 ppm) and also restricted its mode to eruptive type only. Majority of the studies have been centering on sclerotia germination in PDA media and soil at various time intervals (Mishra et al. 2017) but not focused on the type of sclerotia germination. Processes such as permeation into the microbial cell, disruption of the transport system, accretion of Ag^+ ions, and production of ROS are the definite modes of actions of AgNPs accountable for its cidal effect on microorganisms (Morones et al. 2005; Hwang et al. 2008; Abd-Elsalam and Prasad 2018, 2019). Hence, it can be postulated that the inhibitory action of biosynthesized AgNPs on these plant pathogens is primarily credited to one of such mechanisms. Nonetheless, for verifying the precise mechanism a detailed investigation is required.

Table 18.4 *S. rolfsii* percent sclerotia germination and its type in presence of two different AgNE concentrations

Treatments	Hyphal germination				Eruptive germination				Percent spore germination
	2 h	4 h	22 h	24 h	2 h	4 h	22 h	24 h	
Water	1	1	7	7	3	3	3	3	100
AgNE (50 ppm)	0	0	0	0	2	2	2	2	20
AgNE (100 ppm)	0	0	0	0	0	0	0	0	0

Note: Total number of spores taken for the study = 10

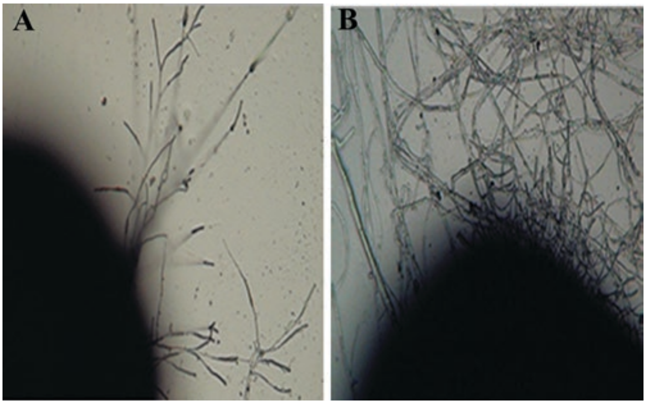

Fig. 18.7 Microscopic images of (**a**) hyphal germination; (**b**) eruptive germination

3.3 In Planta *Studies on Tripartite Interaction Concerning AgNP, S. rolfsii and Wheat and its Overall Impact on Growth Profile of Wheat Plants*

On several occasions, it has been observed that in vitro findings are not in coherence with the in planta studies due to drastic differences in the prevailing microenvironment of pathogen and plant (presence of plant root exudates); therefore, it was quite relevant to carry out in planta studies in the present investigation. The antifungal potential of Silver nanoemulsion was tested against *Sclerotium rolfsii* infection in wheat plants grown on water agar and the following parameters were tested after 7 days of growth.

3.3.1 Percent Seed Germination

The percent germination was compared after 2 days of setting the experiment and it was found that all seeds got germinated in the AgNE-treated experimental sets and untreated control sets, whereas the control seeds challenged with the pathogen showed 90% germination initially but the fungal infestation converted it into a dead mass within few days. It proves that AgNE did not interfere with the seed germination process instead it controlled the fungal invasion and enhanced the seed germination efficiency.

3.3.2 Plant Height (Shoot+Root Length)

Plant height is indicative of its growth and eventually determines the crop yield. Increase in shoot length values was most striking in the case of wheat plants treated with 50 ppm AgNE, where an 8% increase was seen in comparison to the control plants (Table 18.5). The control plants subjected to pathogen stopped growing after 2 days and 100% mortality occurred after 7 days of the experiment due to heavy fungal mycelial infestation (Fig. 18.8). On contrary, the experimental sets (seed+fungus+silver nanoemulsion) treated with two different concentrations of AgNE, looked as green and healthy similar to control (without pathogen challenge). Some significant results were produced in terms of plant protection as well as plant growth suppression. The emulsion was effective in controlling the infection at lower concentrations (50 ppm AgNE) in comparison to higher concentrations (100 ppm AgNE). At higher concentrations the growth of the plant was suppressed, indicating it as the toxic concentration. Thus, AgNE can be recommended safely up to 50 ppm concentration as its maximum concentration.

3.3.3 Vigor Index

It can be easily inferred from Table 18.5 that the highest value of vigor index was found in 50 ppm AgNE treated wheat plants (i.e., 1600) compared to the control untreated seeds (i.e., 1450), whereas the fungi treated plants were affected maximally reducing the plant vigor to minimal values of 150 among all control and experimental sets. According to a study conducted by Maisuria and Patel (2009) the influence of various fungi in seed germination, shoot and root length of seedlings can be predicted from the vigor index. It was observed in their study that six fungi used in the study caused a reduction in plant vigor index in the range of 23.24–30.45% over control.

Table 18.5 Growth parameters of wheat plants recorded 7 DAS[a] treated with AgNE and challenged with *S. rolfsii*

	Treatments					
Growth parameters	C_1	C_2	C_3	C_4	E_1	E_2
Shoot length (cm)	12 ± 0.9	1 ± 0.1	13 ± 1.1	7 ± 0.6	10.1 ± 0.8	5.5 ± 0.7
Root length (cm)	3 ± 0.2	0.5 ± 0.1	2.5 ± 0.3	2.1 ± 0.2	2.4 ± 0.3	1.9 ± 0.1
Plant weight (g)	0.20 ± 0.02	0.06 ± 0.00	0.31 ± 0.01	0.14 ± 0.01	0.18 ± 0.01	0.14 ± 0.01
Vigor index	1450 ± 11	150 ± 2.5	1600 ± 15	910 ± 8	1250 ± 7.6	74 ± 4.2

Note: Control (C_1): Seeds treated with distilled water; Control (C_2): Seeds coated with fungal mycelium; Control (C_3): Seeds treated with 50 ppm AgNE; Control (C_4): Seeds treated with 100 ppm AgNE; E1: Seed+50 ppm AgNE+ fungi; E2: Seed+100 ppm AgNE+ fungi

[a] Days after sowing

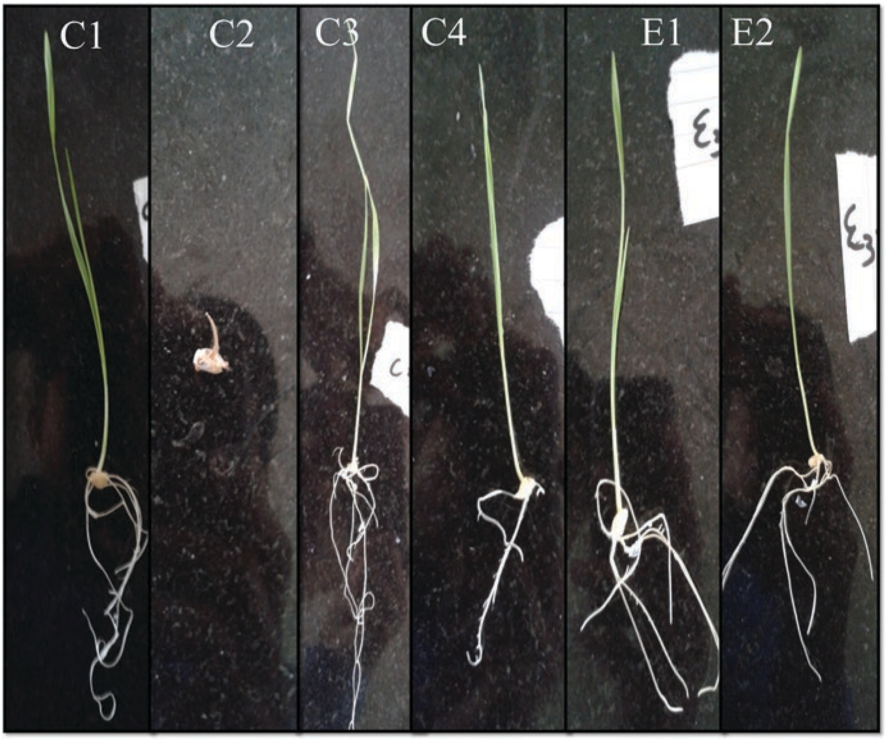

Fig. 18.8 Depicting wheat plant (treated with AgNE and challenged with *S. rolfsii*) after 7 days of growth. C1(untreated), C2 (seed+fungus), C3 (seed+50 ppm silver nanoemulsion), C4 (seed+100 ppm silver nanoemulsion), E1 (seed+fungus+50 ppm silver nanoemulsion), E2 (seed+fungus+100 ppm silver nanoemulsion)

3.3.4 Plant Weight (Shoot+Root)

As shown in Table 18.5 there is a remarkable increase in dry weight of 50 ppm AgNE treated plants over uninoculated control.

Significant results were obtained in the experimental sets (seed+fungus+silver nanoemulsion) treated with two different concentrations of nanoemulsion and the emulsion was effective in controlling the infection at a lower concentration in comparison to a higher concentration (100 ppm). Such an increase in dry weight may confer advantages to the host system with respect to its health and growth. At 100 ppm nano-Ag concentration, plant weight remained the same in fungi challenged plants (E2) as well as in plants that were not challenged by the pathogen (C4). It indicates that the presence of AgNp protected the plants from the phytopathogen attack. In general, 50 ppm AgNE concentration (E1) resulted in plant weight comparable to the untreated control (C1), as it prevented the *S. rolfsii* invasion in plants and also improved plant growth at the same time. On the contrary, 100 ppm AgNE concentration (C4) reduced plant growth compared to untreated control (C1). Thus, this concentration can be considered unsafe for wheat plants in absence of any pathogen but can be applied in phytopathogen's presence. Several studies have revealed (Ma et al. 2013; Anjum and Pradhan 2018; Pallavi et al. 2016) that the effect of nanoparticles is variable from one plant species to another; in wheat, no significant effect of AgNPs was observed on growth parameters, with the exception of root fresh weight and root length, which showed a negative response at 75 ppm treatment, while in cowpea and *Brassica*, a positive response was observed toward AgNPs. The exact reasons behind the differential sensitivity of different plants toward NPs remain unknown to this date (Ma et al. 2013; Anjum and Pradhan 2018; Pallavi et al. 2016). Thus, it can be concluded that the response level of different crop species for nano-Ag is variable toward its different concentrations.

An investigation conducted by Mishra et al. (2017) showed a marked difference in phenolics content among the treatments when challenged with *S. rolfsii*. The chickpea plants felt stressed and exhibited accelerated stimulation of phenolic compounds due to the plant's innate immunity response in order to combat the biotic stress. The maximally induced phenolic acids are known to display antioxidant and antimicrobial properties (Shetty et al. 2011; Jain et al. 2015).

3.3.5 Microscopic Observations

Microscopic analysis (400× magnifications in a compound binocular microscope) of the shoot, root, and leaf sections of wheat plants revealed that the disease progression happened in pathogen challenged plants over the period of 7 days of growth. This was confirmed by the presence of disorganized, ruptured, and damaged groups of cortical and endodermal cells along with changes in cell morphology in these sections which were not treated with AgNE. In general, Silver accumulation was highest in leaves compared to shoot and root. Blackening of the shoot, root, and leaves in the treatment C2 (seed+pathogen) started on the second day of *S. rolfsii* infection and advanced till seventh day making the seed as a dead mass. Due to this glitch, the microscopy could not be performed for C2 plants.

Leaf section: As apparent from Fig. 18.9a the untreated control plants that were not challenged by the pathogen showed normal anatomy of the leaf. Microscopy of leaf samples revealed that the internalization of nano-Ag occurred more in the samples treated with 100 ppm AgNE (C4) (Fig. 18.9c) compared to the plants challenged with the pathogen and treated with 100 ppm AgNE (Fig. 18.9c). On one hand presence of pathogen reduced the toxicity levels of AgNE at 100 ppm concentration, on other hand, the AgNP reduced the impact of *Sclerotium rolfsii* attack observed as the presence of nano-Ag mostly on the surface and less in the cortical regions. A similar pattern was recorded for 50 ppm AgNE concentration (Fig. 18.9b, d) as well, but less internalization of nano-Ag happened at this concentration, eventually helping the plant to overcome the pathogenic impact and grow healthy comparable to the normal untreated plants (C1).

Silver ions target several biological structures and processes like cell membrane, cytosolic functions, and various ATP associated proteins also, although the exact

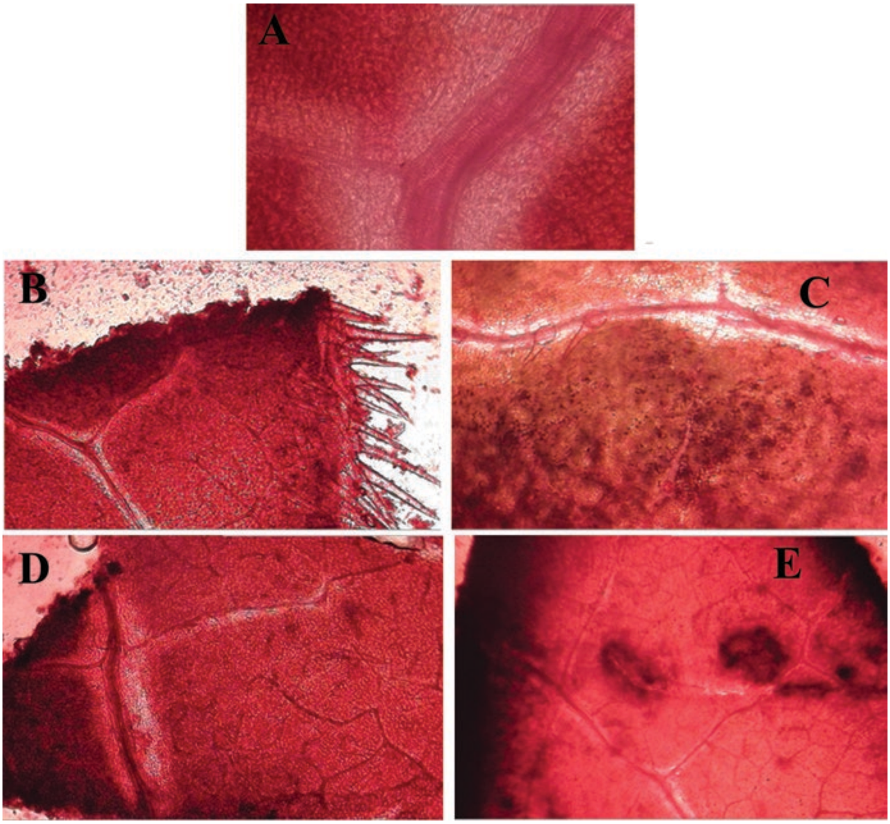

Fig. 18.9 (**a**–**e**) Microscopic images depicting the role of AgNE in reducing the damage caused by *S. rolfsii* infection in wheat leaves. (**a**) Untreated control (**b**) 50 ppm AgNE (**c**) 100 ppm AgNE (**d**) 50 ppm AgNE+ *S. rolfsii* (**e**) 100 ppm AgNE + *S. rolfsii*

mechanism has still been partially deciphered (Lamsal et al. 2011a). Among prime mechanisms, the reduced sclerotia germination, phenolic acid induction, altered lignification, and H_2O_2 production were observed to be the probable mechanisms providing protection to chickpea against *S. rolfsii* (Dixon 2001; Treutter 2005; Mandal et al. 2010). Data outcome in a study carried out by Mishra et al. (2017) revealed that AgNPs treated plants are better equipped to cope with pathogen challenge management. Morones et al. (2005) suggested that silver nanoparticles disrupt transport systems including ion efflux. Silver ions are known to produce reactive oxygen species (ROS) via their reaction with oxygen, which is detrimental to cells, causing damage to proteins, lipids, and nucleic acids (Storz and Imlay 1999; Prasad and Swamy 2013; Prasad 2014; Aziz et al. 2014, 2015). These results confirmed the antifungal potential of AgNP and suggested that nano-Ag can be a potent compound in combating *S. rolfsii* instigated plant diseases with special reference to wheat plants.

4 Conclusions and Future Prospects

Critical analysis of the present case study centered on the possible use of AgNE as a bionanofungicide which confirmed its ability in improving wheat plant growth by protecting it from the attack of a devastating phytopathogen *S. rolfsii* in a superior manner during in vitro and in vivo studies. None of the studies to date have focused on the type of sclerotial germination taking place in presence of nano-Ag. Owing to the importance of knowing such a mechanism, the present work revealed a very low sclerotial germination at 50 ppm AgNE concentration and was restricted to eruptive type only. Amazingly, the sclerotial germination and mycelial growth were completely inhibited at 100 ppm AgNE concentration in in vitro as well as in vivo conditions, but the wheat plants showed certain toxic effects in roots at this concentration. Largely, 50 ppm was the optimum concentration in controlling the disease progression to a minimum and helping plant growth without triggering any phytotoxicity. Thus, the undertaken hypothesis has been successfully proven, though has left some unanswered questions leading scope for further investigation. The toxicity studies on higher Ag concentrations and its possible mechanisms are in offing.

The prime requirements for possible applications of nano-Ag lie in the fact that exhaustive investigations on impact of various silver compounds in disease suppression and also, improved application technologies to enhance the efficacy of these applications should be pursued. Nanofungicides in combination with reduced quantities of chemical fungicides can be optimally used to augment the effectiveness of nanofungicides. Concept of "nanofertilizers" encompassing the crop productivity enhancement via direct and indirect mechanisms is new and has opened up new avenues for researchers as well as farmers. Further detailed research should be focused on the mechanistic elucidation of pathways involved in disease suppression by nano-Ag to enhance its efficacy in disease control. To date no standard regulatory authority at any national or international level has been set up who can define, provide license, or declare the requirements/guidelines associated with the nanotechnology applications. The understanding concerning plant applications of nano-Ag and its eventual influence on human health and the ecosystem should be expanded for their better use as bionanofungicides.

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Chapter 19
Novel Strategies for Environmental Remediation of Pesticides Using Nanocatalysts

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1 Introduction

In the modern system of agriculture, pesticide use has become an important part. For pest control, annually four million tons (approximate) of pesticides are spread over the world crops (Pimentel 1983). Since these pesticides get accumulated in supplies of water or food products, therefore, there is a necessity to establish safe, economical, novel and convenient feasible methods for the detoxification of pesticides (Singh et al. 2019; Zhang and Qiao 2002). There are several strategies available to remove the pesticides such as leaching, volatilisation, incineration and chemical treatment (Sahin and Karpuzcu 2020). The pesticides leaching into the surrounding supplies of groundwater and soil are one of the causes of environmental concern. In volatilisation and chemical treatment, alkalis and acids are produced in large amount, which becomes problematic (Richins et al. 1997). The nanocatalysis has the fundamental concept of the catalysis, which includes the volume and surface area ratio. This is an important step for the chemical reactions as smaller molecules have a larger surface area compared to their volume (Chaturvedi et al. 2012). Due to the effectiveness and versatility of the nanocatalyst, they are more productive than the conventional one. Therefore, novel strategies involving nanocatalysts are required for the removal of pesticides.

The material catalytic activity gets affected by the nanoscale size, shape and structure of the material (Nehra et al. 2020; Yan et al. 2013a, b). They are known for their best catalytic activity for use in industries as a nanocatalyst. There are various benefits (Singh and Tandon 2014) of using the nanocatalyst such as:

1. Helps in the remediation of water.
2. Reduce global warming.
3. Improve the economy.
4. Super catalysts and reagents.
5. Highly energy efficient.
6. Minimum chemical waste.
7. Helps in the removal or degradation of pesticides.

There are various techniques reported for the eradication of pesticide, namely, adsorption, membrane filtration, oxidation and treatment with a biological way (Sidhu et al. 2019; Li et al. 2010; Zinovyev et al. 2005; Smith et al. 2004). As the nanomaterials have a higher capacity of adsorption and a lower rate of diffusion resistance, they have come to the consideration for the remediation of contaminants or helps in the environmental remediation (Shanker et al. 2016; Ma et al. 2011; Jassal et al. 2016). It is in demand to discover the unique nanocatalyst for the efficient removal or degradation of pesticides (Bhadouria et al. 2020). Their cost should be less as well as ecofriendly. The toxaphene, pentachlorophenol and quintozene pesticides are perilous to the atmosphere because of their noxious nature. Therefore, nanocatalyst should be developed to degrade those (Rani et al. 2017).

2 Types of Nanocatalysts

There are various types of nanocatalysts reported such as gold nanocatalyst, which deoxygenates the epoxides (Amin et al. 2020; Noujima et al. 2011); calcium oxide nanocatalyst involved in the trinitrophenol photodegradation (Imtiaz et al. 2013); copper nanocatalyst which catalysis the phenols, anilines and thiophenols synthesis (Xu et al. 2011).

Metal-based or metal oxide-based nanocatalysts have a porous structure, stability and selective activity, which makes them perform to the specific reactions. They exhibit good dispersibility, shape-controlled and good stability (Que et al. 2014). The metal-based nanocatalysts include core-shell nanocatalyst, nanosilica catalyst, double-layered hydroxides nanocatalysts, nano-carbon catalyst (Bhadouria et al. 2020). To facilitate the pendimethalin catalytic degradation, a recyclable multipurpose catalyst has made comprising silver/polydopamine/polystyrene films (Xu et al. 2019). For the removal of chlorpyrifos, the nanoparticle (NP) catalyst composed of bimetallic copper or silver were synthesised using the herbal extract (Rosbero and Camacho 2017). The iron, cobalt, nickel and palladium-based catalyst are cheaper and easily available which are used for the catalytic reactions. For constructing the nanocatalyst, manganese oxides, cerium oxides, aluminium oxides, titanium oxides, iron oxide have been used (Manoharan and Sankaran 2018). The nanocatalyst of tungsten doping into titanium oxides degrades the paraquat at a faster rate (Kaur et al. 2019). Another type of catalyst is core-shell nanocatalyst. It consists of two metals which are designed in such a way that these metals are arranged in a core-shell manner. It has magnetic and synergistic properties (Trujillo-Reyes et al. 2014). The mesoporous and nanosilica materials are the multipurpose catalytic agent (Rastogi et al. 2019). The nanocarbon catalysts have unique electronic, chemical and physical properties (Mohamed et al. 2018).

The reaction between the metallic NPs and light energy is known as photocatalytic reactions. The nano-photocatalyst plays a vital role in the remediation of numerous pollutants from the environment (Akhavan 2009). They usually degrade the different class of pollutants that are present in the effluent streams namely pesticides, dyes and organic compounds (volatile) as these catalysts are composed of the metals, which are semiconductors in nature (Lin et al. 2014). With the help of the bio-mineralisation process, magnetic NPs were obtained via magnetotactic bacteria. These magnetic NPs have the ability to breakdown ethyl-paraoxon pesticides. The NPs of copper, zinc and nickel were produced by *S. mukorossi* with the help of crystalline metal. This nanocatalyst has the potential to reduce hazardous pesticides such as tebuconazole, chlorpyrifos and thiamethoxam (Gautam et al. 2020). The gold nanocatalyst was produced from the yeast strain, namely *S. cerevisiae* for the degradation of quinclorac herbicide. The complete quinclorac removal was achieved in 24 h of time (Shi et al. 2017). The titanium dioxide nanocatalysts modified with gold were produced, which effectively degrades the phenoxyacetic acid pesticide. The acetochlor pesticide was degraded up to 91% by photocatalytic degradation using the NP of iron (III) oxide (Fu et al. 2019).

The graphene nanocatalyst or nanomaterials are involved in the purification of water and the eradication of pesticides (Maliyekkal et al. 2013). Along with this, metal oxides of nanocrystalline are also acted as pesticide absorbents. The aluminium oxide, manganese oxide, cerium oxide and ferric oxide are the metal oxides that are low cost (Armaghan and Amini 2012; Lan et al. 2014; Bardajee and Hooshyar 2013). Different types of nanocatalysts are depicted in Fig. 19.1.

3 Applications of Nanocatalysts for the Pesticide Removal

The multipurpose catalyst has various applications in the area of sewage treatment, contamination removal from soil and environmental protection (Handojo et al. 2020; Xu et al. 2019). The various scientists have explained the significance of bimetallic nanocatalyst for the degradation of pesticides and removal such as organochlorine and organophosphorus (Lu and Astruc 2020; Ortíz and Velasco 2019; Nguyen et al. 2018; Marcelo et al. 2016). In the environment, the nanosilica catalyst showed the multifaceted applications due to their porous structure and high surface area. They play an imperative role in catalytic degradation of pollutants, adsorption and wetting (Gao et al. 2019). The nanocarbon catalysts show the resonance stability C–C bonds and quantum effects that were utilised for contaminants degradation and adsorption, which are present in the matrices of the environment

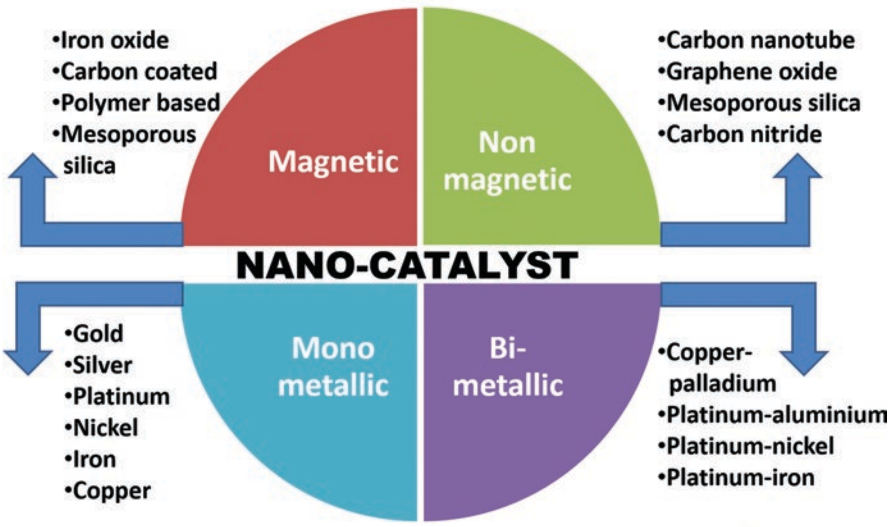

Fig. 19.1 Different type of nanocatalysts

(Singh et al. 2018). To enhance the food characteristics and productivity and in identifying the disease in the plants (Servin et al. 2017).

The carbon nanocatalyst (carbon nanotubes) has unique properties of mechanical and physical (Ruoff and Lorents 1995; Saito et al. 1992). In various fields, carbon nanotubes have been used as molecular sieves (Wang et al. 1999), electric capacitors of a double layer (Frackowiak et al. 2000). The carbon nanotubes are quite potent for the degradation of the diverse class of pesticides.

The graphene nanocatalyst helps in the removal of the pesticide as they are the good absorbents. Due to their polar structure, it helps in forming the effective bonding between pesticides and graphene. It has a high capacity of adsorption of pesticides which ranges from 600 to 2000 mg/g approximately (Sen Gupta et al. 2015; Pei et al. 2013). To improve their adsorption capacity, it can associate with other materials (Liu et al. 2013; Mahpishanian et al. 2015). It has been observed that silica coating on graphene acts as a valuable sorbent for removing organophosphorus pesticide from water (Zhang et al. 2015). The nanometal oxides catalyst also abolishes the chemical threats by converting into the non-hazardous products (Fryxell and Cao 2012). The nanometal oxides are also involved in pesticide removal, mainly organophosphorus (Hinklin et al. 2004; Carnes et al. 2002).

The nanocatalyst of titanium dioxide has the capability of increasing the stress resistance in the plant seed as well as intake of the oxygen and water in the plants which mainly requires for the plant growth (Zheng et al. 2005; Yang et al. 2007; Raliya et al. 2015; Suman et al. 2010). This nanocatalyst also helps in controlling the disease in the crops (Yao et al. 2007a, b). It has shown a bactericidal effect on cucumbers (Cui et al. 2013). The sensors which are made up of nanomaterials, that is, nanosensors are competent to detect the residues of pesticides at a faster rate (Hu et al. 2010; Bao et al. 2016; Liu et al. 2015). The nanocatalyst is quite efficient in recognising phosphorylation moiety, which is favourable for pesticide detection (Kumar and Devi 2011; Awazu et al. 2008; Li et al. 2013).

4 Mechanism of Nanocatalyst Action on Pesticides

4.1 Nanocomposites: Graphene Oxide

Graphene is a type of carbon-based nanomaterial, its composites and modified forms are attracting the tremendous consideration of several researchers owing to its unique physio-chemical properties and novel structure in environmental remediation (Gulati and Kakkar 2020). Graphene oxide or graphene-based nanomaterial hold vast potential in the removal of one of the organic pollutant classes such as pesticides from effluents as an adsorbent (Lu and Astruc 2020; Lazarević-Pašti et al. 2018). Few researchers have stated that the polar structure of water plays an incredibly imperative role in the effective interactions between pesticide and graphene particles (Maliyekkal et al. 2013; Paramasivan et al. 2019). Graphene has great adsorption capacities for different classes of pesticides (ranging from 600 to

2000 mg/g). Among the literature available, researchers have reported halogenation and dehalogenation for the amputation of pesticides from effluents using graphene oxide as nanocatalyst (Zhang et al. 2015; Koushik et al. 2016).

They have demonstrated that π–π interactions between aromatic rings are accountable for the adsorption of pesticides through carbon-based and graphene-based nanomaterials. Graphene, in combination with other nanomaterials, is well known to adsorb pesticide (Zhang et al. 2015).

Graphene-coated silica (GCS) as a highly efficient sorbent was used for the elimination of residual organophosphorus pesticides from effluents. This study revealed the mechanism behind the adsorption of OPPs on GCS is based on the electron-donating abilities of phosphorous, sulphur and nitrogen atoms and the very strong π-bonding arrangement of the benzene ring (Koushik et al. 2016). Action mechanism of nanocatalyst is represented in Fig. 19.2.

4.2 Carbon-Based Nanocatalysts: Carbon Nanotubes (CNTs)

The role of carbon nanotubes for the remediation of pesticide has been shown in the previous studies (Lu and Astruc 2020; Jakubus et al. 2017). CNTs present a novel

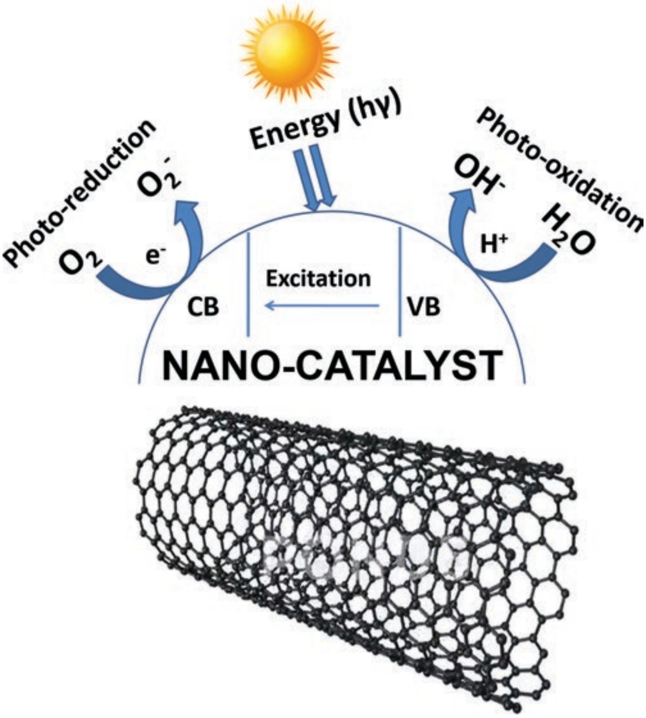

Fig. 19.2 Action mechanism of nanocatalyst

class of nonmaterial and are made up of sp^2-hybridised graphitic carbons with one or many concentric tubules with the mutual longitudinal axis (Jampílek and Kralova 2020). CNTs exit as single-walled nanotubes (SWNTs) with diameter up to 2 nm and multiwalled nanotubes (MWNTs) with diameter ranges from two to a few hundred nanometers, are unique macromolecules that have a 1-D structure, large surface area, enormous chemical and thermal stability and special optical and mechanical properties. These nanomaterials are known to possess diverse applications to eliminate a range of organic pollutants. The adsorption capability of pesticides by carbon nanotubes is mostly influenced by the porous structure and the presence of a wide range of functional groups on the surface that can be exhibited by thermo-chemical modifications to progress the remediation. In general, the adsorption of pesticides on carbon nanotubes may involve one or more mechanisms, such as an electrostatic bond, hydrogen bond, hydrophobic interactions, covalent bond, Van der Waal's forces and π–π interactions (Ahmad et al. 2019). The existence of a wide range of functional moieties on the surface can modify the properties making them more hydrophilic for the adsorption of comparatively low molecular mass and less polar pollutants. The electrostatic bonds are more responsible for the sorption of pharmaceutics, textile dyes and pesticides at optimum pH. At the same time, polar aromatic compounds and polycyclic aromatic hydrocarbons are adsorbed on carbon nanotubes through π–π interactions. Adsorption is the main mechanism that can occur with the formation of a hydrogen bond between functional groups such as –carboxyl, −hydroxyl, −amino and organic molecules (Liu et al. 2018).

4.3 Nanoparticles: Metal-Based Oxides

Nanocrystalline metal oxides NPs have been well known as effective adsorbents for an extensive variety of pesticides owing to their superconducting properties. The superconducting properties of nanocrystalline metal oxides making them a great adsorbent and their specific photocatalytic activity, which has been studied by many researchers for pesticide removal (Lu and Astruc 2020; Nagpal and Kakkar 2019; Gusain et al. 2019).

Different types of metal oxides, for instance, zinc oxide, aluminium oxides, titanium oxides, ferric oxides, magnesium oxides, manganese oxides and cerium oxides are very efficient and less expensive adsorbents. All the aforesaid metal oxides have gained the attraction among the scientists due to their superior adsorption ability, quick kinetics as they possess larger surface area, short intra-particle diffusion distance followed by the maximum number of surface reaction sites and cost-effective as well (Khan and Pathak 2020; Nagpal and Kakkar 2019). Metal oxides have enabled their usage not only by the destruction of organic pesticides but also by altering them to safer by-products under a wide range of temperature and pH. Size quantisation effect is the main reason behind their higher surface area and high photocatalytic activities. Nanocrystalline alumina NPs have been utilised for the degradation of organophosphate pesticides in a shorter time period because of the large surface area and the presence of –OH group on the surface (Gusain et al. 2019). The impact of particle size on the adsorptive capacity showed that if particle size decreases from 300 to 12 nm, the adsorptive capacity elevates approximately 200 folds. Although if the particle size decreases from millimetres to nanometres, the improved surface area certainly leads to their reduced stability of metal oxide particles.

5 Significance of Nanocatalysts in Pesticide Remediation

Different types of pesticides are being used broadly for agricultural purposes all over the globe. Mitigation strategies to reduce pesticides inputs into groundwater and surface water has become a matter of major concern as many incidents of pollution have been documented in developed and developing countries. Even if the pesticides are present in small quantities then also their type, toxic nature, and persistence for longer time period have an undesirable impact on ecological systems such as birds, fishes, and plants for the sustainability of the environment. Nowadays, nanotechnology has emerged as the superior technology which gives tool in the hands of scientists to prepare such sorbents that are quite efficient in the amputation of pollutants such as pesticides from water (Taghizade Firozjaee et al. 2018). Nano means decreasing the size of any material at nanoscale, and by doing so, the characteristics of that material change enormously. Nanomaterials are gaining momentous progress as adsorbents owing their perfect particle size, porosity and large surface area followed by enormous adsorption capacity to bind pesticides. Besides this, they also show electromagnetic properties, which improve their applications in different branches of science, including material science, chemistry and physics (Rawtani et al. 2018). For the treatment of wastewater polluted with pesticides, heavy metals, dyes and pathogenic microbes, the efficiency of graphene composites and carbon nanotubes has been reported by Power et al. (2018). A study conducted by Wang et al. (2018) showed complete removal of pesticides chlorantraniliprole and acetochlor by the application of magnetic NPs attached fluoro graphene-based sorbent material. Earlier studies displayed the remediation of pesticides by employing the use of magnetic/iron NPs (Sajjadi et al. 2019; Chahkandi et al. 2019). The most commonly used NP (Fe_3O_4) fabricated with C-18 has been used for the removal of organophosphorus pesticides due to their easy separation capability, easy operation and high stability (Chahkandi et al. 2019).

6 Challenges in the Use of Nanocatalyst for Environmental Remediation

Environmental pollution is elevating gradually due to various human activities on a global scale. Emerging pollutants are a plethora of contaminants such as organic textile dyes, pesticides, pharmaceutics and toxic metal ions possessing potential hazards on all living beings. All these pollutants have been released into the environment since their use has commenced, but they might be beyond their detection limits of analytical methods. All the enlisted pollutants are highly toxic in nature and may cause various detrimental diseases and even death if they enter the body. Nanotechnology by using nanomaterials (nanocatalysts) has been proven as a sustainable solution to global challenges related to the remediation of the environment. The techniques based on nanotechnology are very promising and can contribute to novel and cheap methods for the remediation of organic/inorganic pollutants, namely, organic dyes, pesticides and heavy metals.

Although potential beneficial effects on the sensing, degradation and removal of pesticides have been suggested for nanocatalysts, there is still a dearth of literature regarding their regenerative properties, re-usability on wide scale applicability and their efficiencies in environmental remediation. Moreover, very little literature is available about the life cycle of nanocatalysts, that is, from their uptake into the environment, through their "active working phase," up to the removal of pollutant loaded nanocatalyst with the possible release of metallic ions and nanocatalyst impact on the ecosystems. All these challenges must be addressed by research scientists to carry out in vitro and in vivo studies. Attention should be given to identify those factors that influence the ability of nanocatalysts for decontamination and to define the possible physical and chemical reactions to verify the fate of these nanomaterials in the environment. In addition to this, it is of serious concern to interpret and validate some toxicological models which can extend the scope of nanocatalysts and can cover more global significance. It is essential to build up and corroborate toxicological models capable to envisage nano-remediation in the fields at a pilot scale as well as probable environmental toxicity level derived from the introduction of nanomaterials into groundwater and soil. Overall, proper evaluation of these aspects may lead to the development of broad policies and effective sensing mechanisms to remediate and accurately detect such obnoxious pollutants in the environment. These issues, if solved, can be a step towards the successful implementation of nanotechnology in terms of environmental remediation and safety management, in order to attain long-lasting sustainability of this novel and promising technology in the quick, sensitive, and reliable determination of organic pollutants in water (Prasad and Thirugnanasanbandham 2019; Shah et al. 2019).

7 Conclusion

The advent of nanotechnology has served effectively in improving the different aspects of agriculture systems. The new technologies like nano-carriers, nano-fertilisers, nano-herbicides, nano-pesticide and nanosensors have emerged and have shown effective results in delivering of nutrients, protecting from weeds and pests, and developing sensing system for plants. However, these NPs have unforeseen risks and literature has reported about the toxicity of NPs on the plant as well as microbiota. But it has also been found that NPs have a varied impact depending upon environment and species. Now, researchers are focusing on the positive effects of NPs and investigating their action mechanism to understand their interaction with biomolecules as well as genes to improve the crop yield as well as remediation process in agricultural soil. Furthermore, researchers are focusing on enhancing the biocompatibility of these NPs, so that the catalytic activity of the NPs works for effective remediation.

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Chapter 20
Synthesis of Novel Metal/Metal Oxide-Based Nanomaterials Using Plant Derivatives and Their Potential Environmental Applications

Chinmoy Kalita, Bijoy Tudu, and Pranjal Saikia

Contents

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1 Introduction

The word “Nano” refers to one billionth of a meter. It is taken from the word “nanus” which means dwarf in the classical Greek language. Nanotechnology is one of the growing interests since the last decade in all fields of sciences (Zare et al. 2017). The nanoparticles (NPs) have exclusive physicochemical properties like optical, electronic, catalytic, and so on, which makes them different from bulk particles. Their high surface to volume ratio actually confers their high reactivity (Gomaa 2017). There are many examples where people have used nanoparticles for thousands of years unknowingly. One of them was the use of gold nanoparticles which were used to strain drinking glasses as it has the capacity to cure certain diseases (Singh et al. 2016). Moreover, nanotechnology has a broad variety of applications in medical sciences, pharmaceutical, food, environment, materials, energy, defense, transportation, and many more (Prasad et al. 2017a, b, 2019; Thangadurai et al. 2020a, b; Maddela et al. 2021). In the last few years, systematic development in the arena of nanotechnology has opened an expansive array of applications in agriculture and plant sciences, biomedical applications like cell treatment, tissue fixing, drug delivery, and so on (Kuppusamy et al. 2016; Mahnaz et al. 2013; Prasad et al. 2014, 2017c). Researchers have used different routes for the synthesis of nanoparticles, namely, sol-gel, hydrothermal, electrochemical, coprecipitation method, and many more. Although conventional methods take comparatively less time for synthesizing nanoparticles in large amount, use of toxic and harmful chemicals make the process hazardous. These processes require a lot of chemicals like reducing agent, capping cum stabilizing agents such as hydrazine, sodium borohydride, and dimethylformamide and also require the tedious procedure, sophisticated instruments for the purification process (Abdul Salam et al. 2014; Tamboli and Lee 2013; Karnan and Selvakumar 2016). In the worldwide efforts to decrease produced hazardous wastes, “green” chemistry and chemical processes are progressively incorporating with present-day improvements in technology and research (Sharma et al. 2009; Abdel-Aziz et al. 2018). Hence, to overcome the difficulties in the synthetic process of nanoparticles, people usually demand a new route which is a less expensive, clean, and environment-friendly approach (Herlekar et al. 2014; Ismail et al. 2017). Biosynthesis of nanoparticles is not just a great approach to synthesize nanostructured materials, yet likewise to decrease the utilization of hazardous chemicals to human health and nature (Jacob et al. 2012; Srivastava et al. 2021). Biosynthetic strategies have more advantages over other conventional techniques because of the following reasons;

(a) Clean and green approach, as no toxic chemicals are used (Senapati et al. 2005);
(b) The active biomolecules, enzymes, and polyphenols can simultaneously have a reducing and stabilizing property making the overall process cost-effective (Senapati et al. 2005);
(c) Tiny nanoparticles can also be prepared during bulk production (Klaus et al. 1999);
(d) The whole process is energy saving as no harsh condition is maintained during synthesis (Shankar et al. 2004).

The rich biodiversity and simple accessibility of plant substances have been remarkably utilized for nanomaterials synthesis. To date different organisms like, bacteria, fungi, yeast, seaweeds, and plant derivatives have been well investigated for metallic and metal oxide nanoparticle fabrication (Singh et al. 2015; Mishra et al. 2011; Arun et al. 2014; Momeni and Nabipour 2015; El-Kassas and El-Sheekh 2014; Shameli et al. 2012; Narayan and Saktivel 2008; Prasad 2014; Prasad et al. 2016, 2018). The utilization of bacteria for the nanoparticle synthesis is developing these days because of the simplicity of the activity, flourishing advances, and the chance of genetic modification (Priyadarshini et al. 2013). Among bacteria, Bacillus strains were used more habitually for the synthesis of nanoparticles (Vaseghi et al. 2018). The rate of formation and stability of the resulting NPs with less accumulation up to a few months was one of the main advantages of this production method. Proteins discharged by bacteria likely to cap the nanoparticles which are the most plausible cause for the stability of the nanoparticles (Saifuddin et al. 2009). Additionally, there are lots of microorganisms like *Bacillus*, *Klebsiella*, *Pseudomonas*, *Escherichia*, *Aeromonas*, *Lactobacillus*, *Rhodococcus*, *Streptomyces*, *Trichoderma, Weissella oryzae,* and so on, which have been used already for nanoparticles synthesis (Li et al. 2016). Among various methodologies, extracellular synthesis has gained more interest as the said procedure eliminates several steps like purification, recovery of the nanoparticles, and many more. Moreover, proteins, enzymes, peptides, organic substances, and metal-resistant genes have noteworthy roles as they can act as reducing agents (Vaseghi et al. 2018). In addition to that, they can act as natural capping agents which can prevent the agglomeration of the synthesized nanoparticles and providing them more stability (Kuppusamy et al. 2016). Few groups have reported the synthesis of NPs using both living and dead fungus have low toxicity and doesn't require culture medium and nutrients (Bhainsa et al. 2006; Senapati et al. 2005; Mukherjee et al. 2008). Yeasts are also a good alternative for the production of various nanoparticles. Although the bio-reduction mechanism is unrecognized, some biogenic reducing agents are accountable for nanoparticle fabrication. *Saccharomyces cerevisiae* is a notable strain broadly investigated for its ability in green synthesis of nanoparticles by means of a bio-reduction procedure (Vaseghi et al. 2018; Seshadri et al. 2011; Sen et al. 2011; Salunke et al. 2015; Kumar et al. 2011; Eugenio et al. 2016; Agnihotri et al. 2009).

Plants have been widely used for the biological fabrication of nanoparticles. Since hundreds of years to date, plants having medicinal properties have been widely used in Ayurveda. Presently, numerous such plants have been picking up significance because of their interesting constituents and their flexible applicability in different fields of science, technology, and research. Plants comprise plentiful natural substances like alkaloids, steroids, flavonoids, and so on. These are extracted from different segments of plants like roots, stems, seeds, leaves, flowers, and barks (Kuppusamy et al. 2016). Bio-fabrication of metal and metal oxide nanoparticles is a sustainable approach in which no toxic chemicals as well as harsh conditions are used. Nanoparticle synthesizing using plant materials is relatively a simple and straight process (Iravani 2011; Thakkar et al. 2010; Prasad 2014). Moreover, the biosynthesis process of nanoparticle using plant materials is cost-effective and relatively easier for a large amount of nanoparticle synthesis. Although the exact mechanism and the components which are responsible for the synthesis process is yet unknown, it is believed that the presence of amino acids, proteins, vitamins, organic acid, as well as secondary metabolites, namely, alkaloids, flavonoids, polyphenols, polysaccharides, and heterocyclic compounds are crucial in reducing the metal salt (Prasad 2014; Joshi et al. 2018). Furthermore, these constituents stabilize and cap the synthesized nanoparticles. Biogenic nanoparticles have found utilization in numerous biomedical purposes, involving antimicrobial and anticancer applications as they have higher efficacy compared to physiochemical nanoparticles (Bar et al. 2009; Bansal et al. 2004; Duan et al. 2015; Aziz et al. 2016, 2019). For example, Mukherjee et al. demonstrated the efficiency of silver nanoparticles (Ag NPs) obtained from *Olax scandens* leaf in anticancer activity, showing its biocompatibility for delivering drugs in comparison to chemically synthesized silver nanoparticles. Moreover, there is also the provision of using these nanoparticles as drug delivery carriers in the future (Mukherjee et al. 2014). Besides antimicrobial and anticancer activities, biological nanoparticles have additionally been found actively participating in sensor design (Tagada et al. 2013).

2 Advantages of Biosynthetic Method in Nanoparticle Synthesis

For biomedical applications, low metal cytotoxicity is required in the synthesized nanomaterials. In comparison to physicochemically derived nanoparticles, nanoparticles acquired from biogenic sources are free of toxic impurities and other byproducts. The biosynthesis process of nanoparticle formation has many favorable advantages over conventional methods including rapid, cost-effective, and eco-friendly methodologies having biogenic properties. This process doesn’t need any stabilizing and capping agents as they can itself act so (Baker et al. 2013). Moreover, the synthesis of nanoparticles using chemical methods may lead to absorb some chemical substances on the surface of the nanoparticle which can make various contrary effects in its applications (Gomathi et al. 2017). Biogenic nanoparticles are progressively efficient for the connection of biologically functional components from microorganisms and plants on the surface of the nanoparticles. These components are likely to make the nanoparticle biologically more active. The extra bit of scope of this process is that it can decrease multiple steps like microbial isolation, culturing, refining, and maintenance, and so on. The requirement of trained and skilled professionals and maintenance of low preparation cost are the major drawbacks of microbe-mediated nanoparticle synthesis (Baker et al. 2013; Sathishkumar et al. 2010). On this ground, plants-based materials are more ideal natural resources than microbes. But unfortunately, their potential is not broadly utilized till now in the synthesis of metallic nanoparticles. The utilization of improved tissue culture methods could be viable for the production of metal nanoparticles at a large scale for industrial purpose (Jha et al. 2009; Makarov et al. 2014; Mukherjee et al. 2012). Reduction of metal ions during the synthesis depends on the type of plant and the concentration of phytochemicals present there. Generally, plant-based methods of nanoparticle synthesis require lesser time than microorganism-based methods (Rai et al. 2008).

3 Biosynthesis of Metal and Metal Oxide Nanoparticles

There exists an expanding demand for nontoxic and earth benevolent methods with elevated yield and minimal effort for synthesizing metallic nanoparticles. In this manner, the biological methodology for the synthesis of nanoparticles gets significance. In the biosynthesis of nanomaterials, proteins, peptides, enzymes, reducing cofactors, and biomaterials have played a critical role by acting as reducing agents (Singh et al. 2016). Efforts have been devoted in this regard utilizing microscopic organisms like yeast (Seshadri et al. 2011; Sen et al. 2011; Salunke et al. 2015; Kumar et al. 2011; Eugenio et al. 2016; Agnihotri et al. 2009), bacteria (Wang et al. 2015; Bharde et al. 2005; Shamsuzamman et al. 2014; Kuppusamy et al. 2016; Singha et al. 2011; Shende et al. 2015), viruses (Lee et al. 2002), fungi (Castro-Longoriaa et al. 2011; Rai et al. 2008; Tarafdar et al. 2013; Mukherjee et al. 2001; Honary et al. 2012; Salvadori et al. 2014; Prasad 2016, 2017; Prasad et al. 2018; Aziz et al. 2016, 2019), actinomycetes (Karthik et al. 2014), algae (Singaravelu et al. 2007; Lee et al. 2002; Lengke et al. 2007; Dhas et al. 2014; Azizi et al. 2014; Aziz et al. 2014, 2015), and many more (Table 20.1).

In contrast to microbes, plant-mediated synthesis strategy (phytosynthesis) is a favorable and beneficial methodology for nanomaterial synthesis as it is free from multiple steps like microbial isolation, culture preparation, and so on, and financially savvy approach with scale-up possibilities (Shankar et al. 2004; Shankar et al. 2003a, b). Different groups have demonstrated the synthesis of various nanoparticle like gold (Au NPs), silver (Ag NPs), palladium (Pd NPs), platinum (Pt NPs), zinc oxide (ZnO NPs), nickel (Ni NPs), and many more, using the extract of several naturally available plant parts and reported about their various applications. Nanoparticles synthesized from different biological sources and their various important applications are shown in Fig. 20.1.

3.1 Plant-Mediated Synthesis of Silver Nanoparticle (Ag NPs)

Silver is well known for its defending impact for different microorganisms normally present in clinical and manufacturing procedures. Among different procedures, phytosynthesis of Ag NPs has appeared as a simpler and faster strategy than the repetitive and tedious microbial synthesis procedures (Sastry et al. 2003; Prasad 2014, Prasad and Swamy 2013; Swamy and Prasad 2012; Prasad et al. 2012; Joshi et al. 2018). The rate of synthesis using plants was compared to that of the nanoparticle synthesized by microorganisms. It was found that the rate of the reaction was high when the nanoparticle was synthesized by using plants. Later, the synthesis of Ag

Table 20.1 Microorganisms used for the biosynthesis of different nanoparticles, together with their shape, size, and applications

Microorganism	Type of nanoparticle	Shapes	Size (nm)	Application	References
Yeast					
Rhodosporidim diobovatum	PbS	Spherical	2–5	–	Seshadri et al. (2011)
Saccharomyces cerevisiae	Au	Cap shaped	15–20	–	Sen et al. (2011)
Saccharomyces cerevisiae	MnO_2	Hexagonal and spherical	35	–	Salunke et al. (2015)
Candida sp.	Ag	–	87	Antimicrobial activity	Kumar et al. (2011)
Cornitermes cumulans	Ag/AgCl	Spherical	35	Antibacterial activity	Eugenio et al. (2016)
Yarrowia lipolytica	Au	Hexagonal and triangular	15	–	Agnihotri et al. (2009)
Bacteria					
Bhargavaea indica	Ag	Nanobar	30–100	Antimicrobial	Singh et al. (2015)
Actinobacter spp.	Magnetite	Spherical	10–40	–	Bharde et al. (2005)
Bacillus subtilis	ZnO; Cr	Cr = spherical	Cr = 50–78	ZnO in the synthesis of steroidal thiophenes	Shamsuzamman et al. (2014), Annamalai et al. (2014)
Bacillus amyloliquifaciens	CdS	Spherical	3–4	–	Khursheed et al. (2016)
Fusarium acuminatum	Ag	Spherical	5–40	Antibacterial activity against some human pathogens	Rai et al. (2008)
Fungus					
Neurospora crassa	Au; Ag; bimetallic Au and Ag	Quasi-spherical	3–100;3–50; Au/Ag 70/30 = 3–90, Au/Ag 50/50 = 3–110	–	Castro-Longoriaa et al. (2011)
Aspergillus niger	Ag	Spherical	20	Antibacterial activity	Rai et al. (2008)
Aspergillus tubingensis	TiO_2	Downy outer surface D	<100	Enhancement in the leaf chlorophyllcontent of arid crops	Tarafdar et al. (2013)

Verticillium sp.	Au	Mostly spherical.	20	Catalysis and as a coating for electronic applications	Mukherjee et al. (2001)
Penicillium aurantiogriseum, Penicillium citrinum, and *Penicillium waksmanii*	CuO	Spherical	–	–	Honary et al. (2012)
Aspergillus aculeatus	NiO	Film	5.89	–	Salvadori et al. (2014)
Actinomycetes					
Streptomycessp. LK3	Silver	Spherical	5	Acaricidal	Karthik et al. (2014)
Algae					
Sargassum wightii	Au	Spherical	8–12	–	Singaravelu et al. (2007)
Chlorella vulgaris	Au	Triangular, hexagonal	9–20	–	Xie et al. (2007)
Plectonema boryanum	Pd	Spherical and elongated	1–20	–	Lengke et al. (2007)
Sargassum plagiophyllum	AgCl	Spherical	18–42	Antibacterial activity	Dhas et al. (2014)
Sargassum muticum	ZnO	Hexagonal wurtzite	30–57	–	Azizi et al. (2014)

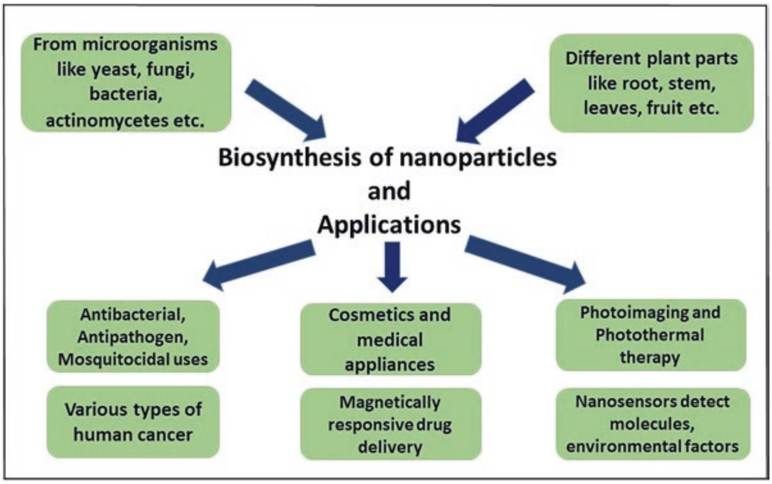

Fig. 20.1 Biological synthesis and applications of metal nanoparticles in biomedical and environmental fields.

NPs from the fruit extract of *Embalica officinalis* was reported (Sastry et al. 2005). *Aloe vera* extract was used for the synthesis of Ag NPs by Chandran et al. (Sastry et al. 2006). An interesting experiment for Ag NPs synthesis was performed by Leela et al. They used leaf extracts of different plants, namely, *Basella alba*, *Helianthus annus*, *Saccharum officinarum*, *Oryza sativa*, *Zea mays*, and *Sorghum bicolar*, and found *H. annus* plant extract with the maximum capacity for quick reduction of Ag ions (Leela and Vivekanandan 2008). Silver nanoparticles prepared by Jain et al. using *Carica papaya* fruit extract are toxic against various human pathogens (Jain et al. 2009). Latex and seed extract of *Jatropha curcas* was also used for the synthesis of Ag NPs (Bar et al. 2009). *Curcuma longa* was employed by Sathiskumar et al. for the formation of silver nanoparticles and obtained a high yield while bark extract was used. The obtained nanoparticles were of different sizes and shapes and had significant antibacterial activity versus *Escherichia coli* (Mukherjee et al. 2012). Similarly, reports are there for the use of extracts of *Argemone maxicana*, *Euphorbia hirta* (Elumalai et al. 2010), *Z. mays* (Rajkumar et al. 2019), purple heart (Hasnaina et al. 2019), *Theobroma cacao* (Thatikayala et al. 2019), and so on. Balachandar et al. 2019 reported the use of stem extract of *Phyllanthus pinnatus* for Ag NPs synthesis and showed their wonderful antibacterial activity against pathogens (Balachandar et al. 2019). Some reports are cited in Table 20.2 (Aygün et al. 2020; Banerjee and Narendhirakannan 2011; Song et al. 2009; Singha et al. 2013; Sougata et al. 2012).

Table 20.2 Plants and their parts used for green synthesis of Au and Ag nanoparticles, together with their shape, size, and applications

Plant	Part used (Extract)	Nanoparticle type	Size (nm)	Shapes	Application	References
Coriandum sativum	Leaves	Au, Ag	6.7–57.9	Spherical, triangular truncated, triangulate, decahedral	–	Narayanan and Sakthivel (2008)
Azadirachta indica	Leaves	Au, Ag and bimetallic Au core–Ag shell	Silver 5–35, bimetallic 50–100	Gold–triangular, silver–spherical, bimetallic–spherical	–	Shankar et al. (2004)
Aloe vera	Leaves	Au	15.2, 8–18, 20–30	Spherical; spherical, oval and hexagonal; spherical	–	Chandran et al. (2006)
Rheum ribes	Leaves	Ag	18.2 ± 3.6	Spherical	Anticarcinogenic and antimicrobial	Aygün et al. (2020)
Syzygium cumuni	Seed	Ag	93	–	Antioxidant activity	Banerjee and Narendhirakannan et al. (2011)
Coriandrum sativum	Leaves	Au	6.7–58	Spherical, triangle, decahedral	–	Song et al. (2009)
Ginko biloba	Leaves	Ag	15–500	Cubic	–	Song et al. (2009)
Dillenia indica	Fruit	Ag	11–24	Spherical	Antibacterial activity	Singha et al. (2013)
Dioscorea bulbifera	Tuber	Ag	8–20	Rod, triangular	Antimicrobial	Sougata et al. (2012)
Convolvulus fruitcosus	Flower extract	Au	35	Spherical	Photocatalytic and antibacterial	Ebrahimzadeh et al. (2020)
Diopyrus kaki	Leaves	Au	5–500	Spherical, triangle, Pentagonal, Hexagonal	–	Song et al. (2009)
Beta vulgaris	Sugar beet pulp	Au	10–25	Spherical, rod shaped, nanowires	–	Castro et al. (2011)
Nyctanthes arbortristis	Flower extract	Au	19.8	Spherical, triangular, hexagonal	–	Das et al. (2011)
Psidium guajava	Leaves	Au	25–30	Spherical	–	Raghunandan et al. (2009)
Cassia fistula	Stem	Au	55–98	Spherical	Antihyperglycemic	Daisy and Saipriya (2012)

3.2 Plant-Mediated Synthesis of Gold Nanoparticles (Au NPs)

Gold nanoparticles are ideally the most interesting noble metal nanoparticles in view of their prospective applications in catalysis, nonlinear optics, nanoelectronics, quality articulation, and infection determination (Aromal and Philip et al. 2012). Expanded ecological worries for chemical synthesis have pinched extensive enthusiasm regarding the phytosynthesis of Au NPs. Researchers have reported the synthesis of Au NPs using extracts of various plant parts like *Emblica officinale* (Ankamwar et al. 2005), Aloe vera (Chandran et al. 2006), and many more. Polyshaped gold nanoparticles were obtained by Raghunandan et al. by using microwave-exposed aqueous extracellular guava leaf extract (Raghunandan et al. 2009). More recently, Saravanan et al. synthesized potentially active Au NPs using *Pongamia pinnata* leave extract which has prominent antifungal activity (Khatua et al. 2020). Some representative TEM images of coriander leaf-mediated gold nanoparticles having different morphologies are shown in Fig. 20.2 (Narayanan and Sakthivel et al. 2008).

Additionally, numerous studies have stated Au NPs synthesis by aqueous gold precursor solution reduction using different plant materials. Ramezani et al. have used leaf extract of *Eucalyptus camaldulensis*, *Pelargonium roseum*, and *A. indica* to produce Au NPs and found a significant increase in rate when they used menthol extracts of *E. camaldulensis* and *P. roseum* (Ramezani et al. 2008). Few of reported synthesis of Au NPs is listed in Table 20.2 (Ebrahimzadeh et al. 2020; Song et al. 2009; Castro et al. 2011; Das et al. 2011; Daisy and Saipriya 2012).

3.3 Plant-Mediated Synthesis of Platinum (Pt NPs) and Palladium Nanoparticles (Pd NPs)

Phytosynthesis of Pd NPs has been satisfactorily reported in the last few years (Table 20.3). Jia et al. reported the synthesis of Pd NPs by using aqueous extract of *Gardenia jasminoides* which contains different antioxidants, namely, chlorogenic

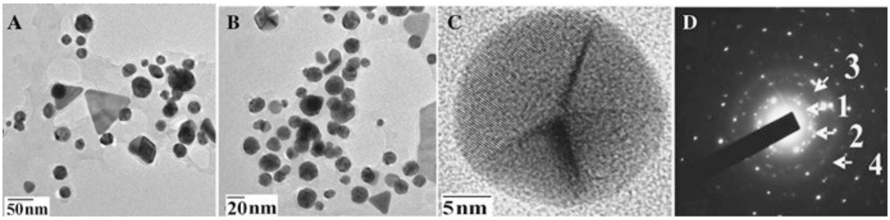

Fig. 20.2 TEM images of gold nanoparticles synthesized by coriander leaf extract with different magnifications (**a**–**c**). Selected area of electron diffraction pattern (SAED) of the nanoparticles (**d**) shows the rings designated as 1, 2, 3, and 4 due to the refle41ctions from (111), (200), (220), and (311) planes. (Reproduced with permission from Narayanan and Sakthivel 2008, Copyright 2008, Elsevier Ltd.)

Table 20.3 Plants and their parts used for green synthesis of Pd and Pt nanoparticles, together with their shape, size, and applications

Plant	Part used (extract)	Nano particle type	Size (nm)	Shapes	Application	References
Gardenia jasminoides	Leaves	Pd	3–5	Spherical	p-nitrotoluene hydrogenation	Jia et al. (2009)
Musa paradisica	Banana peel	Pd	50	Crystalline irregular	–	Bankar et al. (2010)
Doipyros kaki	Leaves	Pt	2–12	Crystalline	–	Song and Kim et al. (2009)
Wood nano materials	Wood	Pt	16–20	Spherical	Reduction of 4-nitrophenol	Lin et al. (2011)
Lignin obtained from red pine	Lignin	Pt, Pd	Pt ~ 100, Pd = 16–20	Spherical	Reduction of 4-nitrophenol and aerobic oxidation of alcohols.	Coccia et al. (2012)
Ocimun sanctum	Leaves	Pt	23	Irregular	Water electrolysis	Soundarrajan et al. (2012)

acid, geniposide, crocetin, and crocins. These antioxidants act both as reducer and stabilizer (Jia et al. 2009). Satishkumar et al. have prepared uniform-sized Pd NPs having a particle size of 50 nm by using the bark extract of *Cinnamom zeylanicum* (Sathishkumar et al. 2009). Again, Petla et al. prepared Pd NPs of ~15 nm by using leaf extract of protein-rich soybean (Petla et al. 2012). Synthesis of Pd NPs using banana peel extract was reported by Bankar et al. (2010). Platinum nanoparticles (Pt NPs) were obtained by Song et al. using *Diopyros kaki* leaf extract. They stated that more than 90% of platinum ions reduction was possible using only 10% leaf concentration at 95 °C (Song and Kim 2009). Phytosynthesis of well-ordered Pt NPs was reported by the use of plant wood nanomaterials (Lin et al. 2011). Successful synthesis of Pd and Pt NPs was reported by Coccia et al. who used isolated lignin from Red pine (Coccia et al. 2012). Swift synthesis of Pt NPs was also narrated by (Soundarrajan et al. 2012).

3.4 *Plant-Mediated Synthesis of Zinc Oxide Nanoparticles*

A variety of plant extracts and microorganisms have been reported for the production of metal/metal oxide NPs. The production of NPs is completely dependent on biomolecules exist in the precursor, for example, alkaloids, terpenoids, and so on. Dobrucka et al. used flower extract of *Trifolium pretense*, which contains various phenolic acids, anthocyanins, and minor quantities of carotene, tannins, vitamins C, and essential oils for ZnO NPs synthesis. These nanoparticles showed efficient antibacterial activity against *Pseudomonas aeruginosa*, *Staphylococcus aureus,* and

E. coli (Dobrucka and Dugaszewska 2016). Variable-shaped ZnO NPs (with 8–18 nm size range) was formed using *Aloe barbadensis* leaf extract. These NPs were tested against *S. aureus* and *E. coli* bacteria. These biosynthesized NPs caused cell and tissue damage in the bacterial strains (Khursheed et al. 2016). *C. papaya* milk latex was used to obtain ZnO nanoflower by Sharma et al. These biomaterials contain some promising properties like the ability for lessening the electron-hole pair recombination, crystallite size, surface defect, texture, and large energy band-gap. These properties are important for the superb photocatalytic activity and notable antimicrobial activity against *S. aureus* and *P. aeruginosa* (Sharma 2016). Similarly, the synthesis of ZnO nanoparticles by using various plant and plant derivatives is reported for their applications including antibacterial, anti-inflammatory, anti-biofilm, antioxidant properties, urinary tract infection pathogen, and photocatalytic activity (Elumalai and Velmurugan 2015; Nagajyothi et al. 2015; Bhuyan et al. 2015). ZnO NPs synthesized by the biological method showed their catalytic activity in the Claisen–Schmidt reaction. It was reported that ZnO NPs with particle size ranging from 8.48 to 32.51 nm could be used in condensation of 3, 4-dimethyl benzaldehyde, and acetophenone (Li et al. 2017). Few researchers have reported ZnO synthesis using different plant parts like a flower, peel, and so on. (Yuvakkumar et al. 2014a, b; Mohamed et al. 2020; Rajan et al. 2020); a few of them are listed in Table 20.4.

3.5 *Plant-Mediated Synthesis of Nickel and Nickel Oxide Nanoparticle*

Very few researchers have reported about the biosynthesis of Ni and NiO NPs in comparison to the chemical synthesis. Chen et al. informed the use of the *Medicago sativa* (alfalfa) extract for the synthesis of Ni NPs which involves robust stirring of precursor solution with *M. sativa* solution (Chen et al. 2014). Leaf extract of *Ocimum sanctum* was utilized to prepare Ni NP by Pandian et al. The synthesized Ni NP had efficient photocatalytic activity by adsorbing various dyes like eosin Y (EY), crystal violet (CV), Orange II (OR), and anionic contaminants nitrate (NO_3^-) and sulfate (SO_4^{2-}) from aqueous solution (Pandian et al. 2015). Kar and Ray developed Ni NPs with the help of petals of *Hibiscus rosa-sinensis*. They stated that the nanoparticles were stable for 20 days (Kar and Ray 2014). Glucose was used for the production of glucose-capped nickel nanoparticles by Vaseem et al. Because of their superior biocompatibility nature, these nanomaterials found use as biosensors and heat non-mediator for cancer hyperthermia (Vaseem et al. 2013). Moreover, a few groups have reported the phytosynthesis of Ni NPs with different morphologies in recent years having some important applications (Mamuru and Jaji 2015; Bibi et al. 2017; Rahman et al. 2020). Metal components are capable of forming a large variety of compounds with oxygen. They may be semiconductors, conductors, or insulators, relying upon their structure arrangements which offer ascent to specific electronic structure.

Table 20.4 Plants and their parts used for green synthesis of few metallic nanoparticles, together with their shape, size, and applications

Plant	Part used (extract)	Nanoparticle type	Size (nm)	Shapes	Application	Reference
Azadirachta indica	Leaves	ZnO	40	Spherical	Cytotoxic effect against the HT29 cell line	Elumalai and Velmurugan 2015
Camellia sinensis	Leaves	ZnO	16	–	Antibacterial and antifungal activity	Nagajyothi et al. (2015)
Nephelium lappaceum	Peel	ZnO	50	Needle like	Antibacterial activity	Yuvakkumar et al. (2014a, b)
Hyphaene thebaica (L.) Mart.	Fruit	ZnO	8–23	Spherical	Antibacterial and antioxidant	Mohamed et al. (2020)
Phoenix loureiroi	Fruit	ZnO	81–187	Spherical	Comparison with chemically synthesized ZnO and antioxidant	Rajan et al. (2020)
Ocimum sanctum	Leaves	Ni	30	Spherical	Dye and pollutant absorption	Pandian et al. (2015)
Glucose	Solution	Ni	3–5	Spherical	Biosensor	Vaseem et al. (2013)
Rambutan	Peel	NiO	50	Nanocrystal	Antibacterial	Yuvakkumar et al. (2014a, b)
Aegle marmelos	Leaves	NiO	8–10	Spherical	Antibacterial and photocatalytic	Ezhilarasi et al. (2018)
Moringa Oleifera	Leaves	NiO	9–10	Spherical	Antibacterial and anticancer	Ezhilarasi et al. (2016)
Camellia sinensis	Leaves	Fe	5–15	Spherical	Bromothymol degradation	Hoag et al. (2009)
Amaranthus spinosus	Leaves	FeO	91–125	Spherical	Antioxidant and photocatalytic	Muthukumar and Matheswaran (2015)
Eucalyptus	Leaves	Fe/Ni	20–50	Spherical and irregular	Photocatalytic degradation	Weng et al. (2017)
Psidium guajava	Leaves	TiO_2	32	Spherical	Antibacterial and antioxidant	Santhoshkumar et al. (2014)
Myrtus communis L.	Leaves	Pd/TiO_2	17–25	Spherical	Suzuki–Miyaura coupling reaction	Nasrollahzadeh and Sajadi (2016)
Citrus medica Linn.	Fruit	Cu	20	–	Antimicrobial activity	Shende et al. (2015)
Euphorbia esula L	Leaves	Cu	20–110	Spherical	Ullmann coupling and 4-nitrophenol reduction	Nasrollahzadeh et al. (2014)
Tinospora cordifolia	Leaves	CuO	6–8	Sponge like	Photocatalytic, antioxidant, and antibacterial properties	Udayabhanu et al. (2015)

Recently, the ecological benevolent green chemistry approach has been successful to integrate NiO NPs. NiO is an extensive p-type semiconductor material. It shows weak absorption in the visible region with electrical resistivity due to cation vacancies (Helan et al. 2016). Some reports are there on the synthesis of plant-mediated NiO NPs. Yuvakkumar et al. prepared NiO nanocrystals by the reaction of nickel nitrate with rambutan peel waste. They checked the antibacterial activity of the synthesized NiO NPs against *E. coli* (Gram-negative bacteria) and *S. aureus* (Gram-positive bacteria) (Yuvakkumar et al. 2014a, b). Tema et. al have reported the formation of single-phase Bunsenite NiO NPs by using leaves extract of *Agathosma betulina*. Various analytical techniques were used by them to characterized the NiO nanoparticles. The average diameter of NiO NPs was found to be in the range of 15.23–23.15 nm (Thema et al. 2016). Antimicrobial activities against *E. coli* and *Staphylococcus* bacteria were checked by NiO NPs synthesized using neem leaves (Helan et al. 2016). Similarly, *Aegle marmelos* leaf extra was used by A. Angel Ezhilarasi et al. for the synthesis of NiO NPs and studied their photocatalytic and antimicrobial activity. As *A. marmelos* contains essential bioactive compounds, they induce antibacterial effects on different pathogens as well as act as an adsorbent by removing toxic metals from the environment (Ezhilarasi et al. 2018). A. A. Ezhilarasi et al. again reported the use of *Moringa oleifera* in the production of NiO NPs. These nanoparticles showed effective result in treating HT-29 cancer cells and antimicrobial activity against both various Gram-positive and negative bacteria (Ezhilarasi et al. 2016). Some representative images of NiO nanoparticles prepared using *M. oleifera* plant extract are shown in Fig. 20.3.

3.6 Plant-Mediated Synthesis of Iron Nanoparticle

To date, the iron nanoparticle has (Fe NPs) been mostly synthesized using extracts of different plants (Table 20.4). As the polyphenols present in plants acts as reducing and stabilizing agents, it has been used by researchers for the synthesis of magnetic nanoparticle at ambient temperature or by the hydrothermal process maintaining a fixed ratio of metal precursor solution to plant extract (Herlekar et al. 2014). Tea plant extract has been used commonly for Fe NPs synthesis which showed degradation efficiency toward degradation of dyes like bromothymol blue (Kar and Ray 2014). In another study, Fe NPs was synthesized using different amount of tea extract concentration. It was reported that particle size was inversely proportional to extract concentration (Nadagouda et al. 2010; Shahwana et al. 2011; Chen et al. 2014). In addition to that extracts of eucalyptus leaf and grape seed *Proantho cyanidin* were also used for the synthesis process (Kuang et al. 2013; Narayanan et al. 2012). Machado has screened extracts of 26 plants to prepare iron nanoparticle and studied the different reaction parameters and calculated the total polyphenol content (TPC). On the basis of those results, they had used mulberry, pomegranate, and cherry extract in their synthesis (Machado et al. 2013). Leaf extract of three plants namely *Melaleuca nesophila*, *Eucalyptus tereticornis,* and *Rosmarinus ofcinalis* which are found near to Australia was used by Wang et al. to synthesize Fe NPs. The efficacy

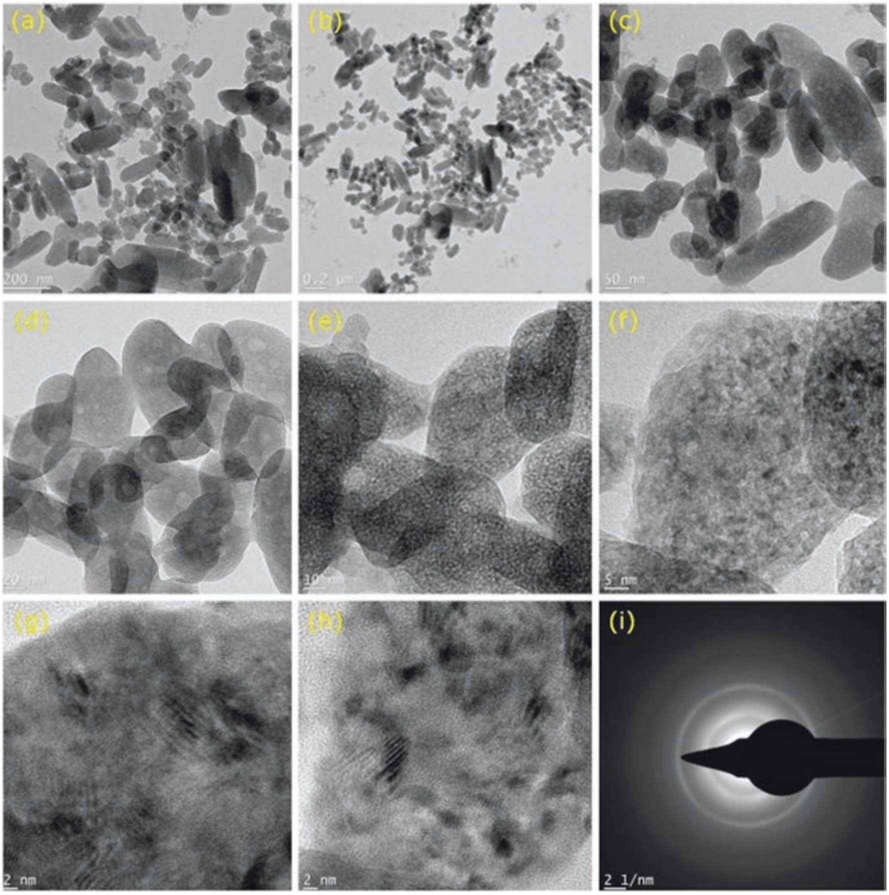

Fig. 20.3 HRTEM images of NiO nanoparticles prepared using *Moringa oleifera* plant extract. (Reproduced with permission from Ezhilarasi et al. (2016). Copyright 2016, Elsevier Ltd.)

of the nanoparticles was checked for the decolorization of azo dyes (Wang et al. 2014). Recently, Manickam reported the synthesis of FeO nanoparticle using *Amaranthus spinosus* leaf extract and its photocatalytic and antioxidant activity (Muthukumar and Matheswaran 2015). Moreover, eucalyptus leaf was used for bimetallic Fe/Ni nanoparticle synthesis in a single step. The catalyst was tested for the degradation of methyl orange in an aqueous solution (Weng et al. 2017).

3.7 Plant-Mediated Synthesis of Titanium Dioxide (TiO_2 NPs)

There are a number of reports on the phytosynthesis of important metal oxides nanoparticles, one of them is titanium oxide nanoparticles (Table 20.3). Leaf extracts of *Nyctanthes arbor-tristis* and *Eclipta prostrata* were utilized to produce spherical TiO_2 nanoparticles particles of size 100–150 and 36–68 nm, respectively (Sundrarajan and Gowri 2011; Rajakumar et al. 2012). Leaf extract of *Catharanthus roseus* could synthesize irregular shaped TiO_2 NP as stated by Velayutham et al. (2012). TiO_2 NP resulted after reaction with *Psidium guajava* extract was examined for antimicrobial activity versus *Proteus mirabilis*, *S. aureus*, *Aeromonas hydrophila*, *P. aeruginosa,* and *E. coli* bacteria. But effective results were obtained against *S. aureus* and *E. coli* only (Santhoshkumar et al. 2014). There was also a report on the green synthesis of spherical Pd/TiO_2 nanoparticles active for Suzuki–Miyaura reaction.

3.8 Plant-Mediated Synthesis of Copper (Cu NPs) and Copper Oxide Nanoparticle (CuO NPs)

Cu NPs have lately got particular attention owing to their cost-effectiveness and novel properties different from their bulk forms. Because of their various important functions, the focus has grown on Cu NPs synthesis (Lee et al. 2009). Copper oxide is a p-type semiconductor material having a bandgap of 1.2 eV. Recently, CuO has received great attention because of flexible properties and their prospective use in solar cells, sensors, heterogeneous catalysis, and antimicrobial activity, and so on (Yadav et al. 2017). Moreover, CuO NPs are more stable having a lengthier shelf life. Rai et al. reported the green synthesis of Cu NPs by *Citrus medica Linn.* (Idilimbu) juice and showed noteworthy activity against *E. coli* followed by *K. pneumoniae*, *P. aeruginosa*, *P. acnes*, and *S. typhi* (Shende et al. 2015). Nasrollahzadeh performed a very important application of Cu NP synthesized by using *Euphorbia esula L* leaf extract. The catalyst was used for the Ullmann-coupling reaction and 4-nitrophenol reduction (Nasrollahzadeh et al. 2014).

Very few groups have reported about the phytosynthesis of CuO NPs (Table 20.3). Pammi et al. prepared CuO NPs using *Aloe vera* extract and showed their action for fish bacterial pathogens (Kumar et al. 2015). They also reported the use of *Asparagus racemosus* roots' extract to synthesize CuO nanorod and tested their activity against various bacterial pathogens (Kumar et al. 2019). Again, Udayabhanu et al. reported the preparation of highly efficient CuO NPs by *Tinospora cordifolia* extract which was used in photocatalytic degradation of methylene blue as well as an antioxidizing and antibacterial agent (Udayabhanu et al. 2015).

4 Factors Influencing the Synthesis of Nanoparticles

The characteristic hydrogen ion concentration is responsible for the distinctive size and morphology of nanoparticle formation. As reported by Shankar et al., Au–Ag NPs synthesized using Aloe vera having different sizes and shapes is highly influenced by the pH of the solvent (Ahmad et al. 2003). Temperature is also playing an important role in nanoparticle synthesis by varying the sizes and shapes. The concentration of salt is also an important parameter for various morphologies of nanoparticles. In addition to that, the reduction reaction time is also crucial for nanoparticles synthesis. It decides the growth condition of the nanoparticles resulting in different morphologies (Kuppusamy et al. 2016).

5 Catalytic Applications of Nanoparticles

Since the last few decades, lots of modification is going on to develop the quality of nanomaterials for industrially produced items like cosmetics, electronics, and so on. They have also been attempted for molecular imaging to attain high resolution images for the diagnosis, which could be applied for cardiovascular and oncology treatment (Medina et al. 2007). Other than this, nanotherapeutic has been promoted throughout the world after 1990, to build up different nano-based prescriptions (Ahmed et al. 2017). Different nanostructured metal and metal oxides of gold, silver, nickel, zinc, and so on have been used worldwide for their antibacterial and antimicrobial properties as they have the potential of inducing oxygen reactive species and the tendency to release their ions to break the bacterial cell wall (Ingle et al. 2008; Khatua et al. 2020; Ezhilarasi et al. 2016). Nanoparticles have been used as anticancer agents for its cytotoxic activity against different cancer cell lines (Elumalai and Velmurugan 2015; Ezhilarasi et al. 2016; Aziz et al. 2019). A schematic mechanism of the toxicity effect of NiO nanoparticles against bacteria is shown below (Fig. 20.4).

Besides these, there are diverse applications of nanomaterials in solar cells, biosensors, and photocatalyst, and so on (Lin et al. 2011; Vaseem et al. 2013). Nanoparticles have numerous active sites that allow them to generate hydrogen peroxide and superoxide radicals. These radicals make them very much suitable for photocatalytic degradation of organic pollutants from wastewater (Sastry and Kumar et al. 2001; Vijaya and Kaviyarasu et al. 2018; Aziz et al. 2015). The effluents delivered by textile, cosmetics, paper, plastic, and pharmaceutical enterprises ordinarily contain dyes and their metabolites, which are poisonous, carcinogenic, stable to oxidizing agents, and nonbiodegradable. The wastewaters formed by dyeing factories have the most significant level of poisonousness, with genotoxic, cytotoxic, and mutagenic impacts. Consequently, it is essential to expel dye pollutants from industrial waste before they reach common water bodies. In addition, biotoxicity assessments have shown a significant reduction in the harmfulness of the reaction products and metabolites produced after the photodegradation of dyes (Iqbal and Nisar 2015). A general mechanism of photocatalytic degradation of dye using TiO_2 nanoparticle is shown below (Khataee and Kasiri 2010) (Fig. 20.5).

6 Conclusion and Future Aspect of Plant-Derived Nanoparticles

This chapter highlights the recent works on the biogenic synthesis of metallic nanoparticles using microorganisms and plants. Among different biological strategies for nanoparticle synthesis, microorganism-based synthesis isn’t of industrially

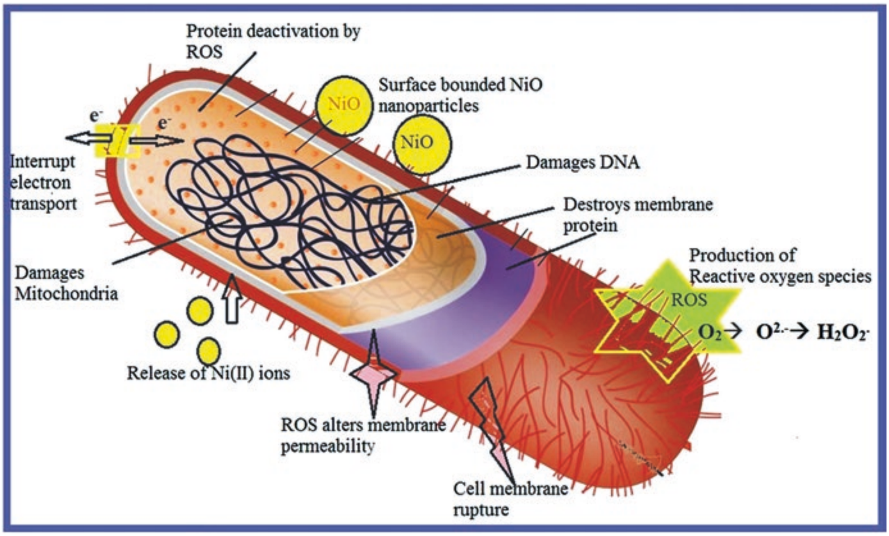

Fig. 20.4 Schematic mechanism of toxicity effect of NiO nanoparticles against bacteria. NiO nanoparticles and their ions generate ROS and induce oxidative stress resulting in the damage of mitochondria, DNA, proteins, and cell membrane with consequent cell death. (Reproduced with permission from Ezhilarasi et al. (2018), Copyright 2018, Elsevier Ltd.)

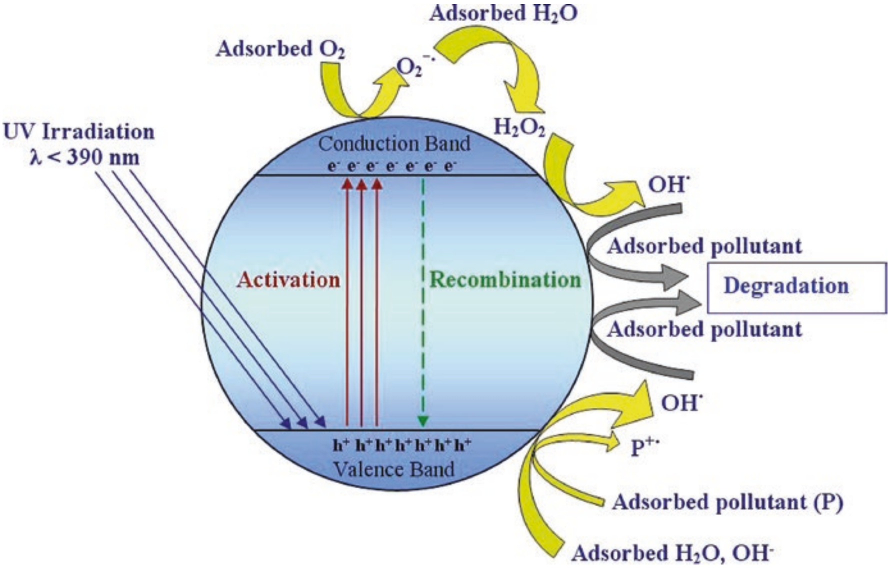

Fig. 20.5 General mechanism of the photocatalysis on TiO_2 nanomaterials. (Reproduced with permission from Khataee and Kasiri 2010. Copyright 2010, Elsevier Ltd.)

feasible because of the necessities of exceptionally hygienic conditions, care, and upholding. In this manner, the utilization of plant extracts is possibly favorable in comparison to microorganisms because of the simplicity of progress, less hazard, and the expanded procedure of keeping up cell cultures. While the chemical and physical synthesis methods are common, a few eco-accommodating and financially feasible synthesis procedures are known; in few cases even by utilizing unexploited plant parts like peels, seeds, and so on. These plant-based nanoparticles can possibly be utilized in different fields, for example, therapeutics, pharmaceuticals, energy storage, and other industrial products. The plant-mediated metallic nanoparticles have been successfully applied in the diagnosis and treatment of diverse diseases with the minimum side effects. Moreover, this biosynthesis process can be used to synthesize nanoparticles in a bulk manner. In the future, there is a wide range of scope to utilize this process to synthesize nanoparticle for healthcare as well as commercial purposes.

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Chapter 21
Dry Deposition of Atmospheric Nanoparticles

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Abbreviations

EC	Elemental carbon
OC	Organic carbon
PAHs	Polycyclic aromatic hydrocarbons
PM	Particulate matter
PM_1	Particulate matter with aerodynamic diameter < 1 μm
PM_{10}	Particulate matter with aerodynamic diameter < 10 μm
$PM_{2.5}$	Particulate matter with aerodynamic diameter < 2.5 μm
U.S. EPA	United States Environmental Protection Agency

1 Introduction

The anthropogenic actions are one of the main precursors of the modifications that are happening in the ecosystem. The intensification of the changes in the ecosystem occurred mainly as a consequence of the episodes of detriment and neglect in relation to the environment during the Industrial Revolutions (Pott and Estrela 2017). The high concentrations of emitted pollutants and the lack of bodies that make the rules of the limits of pollutant concentrations sharply contributed to the intensifications of the changes in the ecosystems.

Besides causing environmental modifications, the ambiental pollution caused harm to the population's health. These harms became more visible in the regions where the industrialization happened more intensely and consequently had more intense pollutant emissions (Dapper et al. 2016).

Among the pollutants, there are some that are considered more harmful to human health and because of that must receive more attention. The U.S. EPA (2017) established national standards to the air quality for the six main atmospheric pollutants: nitrogen dioxide (NO_2), ozone (O_3), sulfur dioxide (SO_2), particulate material (PM), carbon monoxide (CO), and lead (Pb).

In addition to being one of the main atmospheric pollutants, the particulate matter mainly absorbs the compounds: organic carbon, elemental carbon, sulfate, nitrate, ammonium, the metals, and the cyclic aromatic hydrocarbons (Han et al. 2020).

The particulate matter is one of the air pollutants that has been being studied due to the health problems caused by the exposition to high concentrations of it and for the possibility of causing big environmental issues. Thus, it is necessary to comprehend the possible sources, environmental impacts, the impacts on human health, the characterization of the emission, the composition of the soluble ions, and the ways of removal of the particulate matter (Behera and Prasad 2020).

The pollutants' dry deposition is one of the most common ways of removal of these components from the atmosphere and the deposition mechanism can be compared with a resistances association and it depends on the shape, size, and the surface where the particle will be deposited. As the deposition mechanism is related to the size of the particles, those with larger size tends to deposit close to the emission source. And those particles with smaller sizes, known as fine and ultrafine particles, are transported by the air mass and will deposit far from the emission source, changing the atmosphere chemical composition from other regions and having harmful effects on its population health.

In Brazil, the use of biomass as fuel to produce energy has grown in the last decade, but on the other hand, its impact on the atmosphere chemical composition, population health, and pollutant emission still developing. In other countries, the fast economic development and population growth in the last decades have brought the researchers attention to the effects of it on the environment. So the study of the dry deposition flux and the development of new parametrization of dry deposition mechanisms has shown to be a valued effort to determine pollutant emissions impacts on the local area and other areas, and can bring more knowledge to prevent harmful anthropogenic effects.

2 Fundamentals of Particulate Matter

Particulate matter (PM) is the term used to characterize the mixture of solid particles and water droplets present in the air (U.S. EPA 2016b). The emitting sources of particulate matter can be classified into two groups: natural and anthropogenic. It is understood as natural sources the volcanoes emissions, pollen, particles originated from the decomposition of plants and the sea spray aerosol, and by anthropogenic sources, the emission from vehicle combustion processes and the burning of biomass in the industries.

Another way of classification of the emissions is by the way of emission of the particulate matter, the emission is classified as primary when the particles are emitted directly into the atmosphere, while secondary emissions are the result of chemical reactions that occur in the atmosphere (Ali et al. 2019).

The PM can be classified according to the size of the particles that form it. It is called coarse PM the inhalable particles that have diameters bigger than 2.5 μm and smaller or equal to 10 μm (PM_{10}), the fine PM the inhalable particles with a diameter smaller or equal to 2.5 μm ($PM_{2.5}$) (U.S. EPA 2016a, b).

The characteristic properties of the PM as the diameter of the particles, chemical composition, concentration, and aerodynamic properties are related to the emitter source of this PM and the harmful effects on human health (Souza et al. 2017). The PM stands out among the main atmospheric pollutants established by the U.S. EPA due to its presence in the atmosphere and because it is identified as one of the most harmful to health (Balakrishnan et al. 2019).

The concentration is a very important parameter for the characterization, control of PM emission, and the evaluation of the harmful effects on human health. The responsible agencies for air quality control use the data of concentration obtained during the sampling period to evaluate the quality of the air in the sampled region and if it is under the current regulations.

The definition of mass concentration of particulate matter the mass of PM present in a unit volume of air (Vincent 2007) and can be expressed in units of ng m^{-3}, μg m^{-3}, or mg m^{-3}. The number of particles by unit volume of aerosol can be defined as numerical concentration and is generally expressed in units of the number of particles per cubic meter or the number of particles per cubic centimeter (Kulkarni et al. 2011).

Several studies have been carried out in different regions through the concepts of number concentration and mass concentration with the purpose of characterizing and evaluating the emissions of PM.

In the Monitoring Station of Crete Island, a suburban and rural region, studies carried out during 6 years, sampled medium concentrations for PM_{10} and $PM_{2,5}$ of 36.1 ± 9.5 and 23.6 ± 5.8 μg m^{-3}, respectively (Kopanakis et al. 2012).

In Venice, Italy, for example, Valotto et al. (2014) showed the PM_{10} and PM_1 during the four seasons of the year. During spring, the concentrations of PM_{10} and PM_1 were of 27.8 ± 1.2 and 9.1 ± 1.3 μg m^{-3}, respectively. During summer, the concentrations of PM_{10} and PM_1 were of 19.3 ± 1.1 and 5.8 ± 1.2 μg m^{-3}, respectively. During fall, the concentrations of PM_{10} and PM_1 were of 29.6±1.2 and 13.3±1.2 μg m^{-3}, respectively. And during winter, the concentrations of PM_{10} and PM_1 were of 45.2±1.2 and 26.2±1.3 μg m^{-3}, respectively.

Taiwo et al. (2014) used the MOUDI to make the samples and compare the composition of the particulate matter both in an industrial area of Port Talbot and in an urban area of Birmingham. The researchers analyzed the presence of anions and cations soluble in water and the samples of the industrial area had predominantly coarse particulate matter, while the samples from the urban area had a predominantly fine particulate matter. The sampled concentrations were approximately 100 particles per cubic centimeter for the particulate matter with a diameter between 300 and 400 nm.

In rural areas in eastern Central India, Nirmalkar and Deb (2016) sampled medium concentrations of 329 ± 25.6 μg m^{-3} for PM_{10}; 108 ± 5.02 μg m^{-3} for $PM_{2.5–10}$; 221 ± 25.1 μg m^{-3} for $PM_{2,5}$ and 90.4 ± 18.2 μg m^{-3} for PM_1. On the other hand, in India, during a campaign between January 2013 and May 2014 samples were collected with a medium concentration of $PM_{2,5}$ of 125.5 ± 77.2 μg m^{-3}, with minimum and maximum concentrations of 31.1 and 429.5 μg m^{-3}, respectively (Sharma and Mandal 2017).

Kantová et al. (2017) observed in his research the existence of relations between the concentration and distribution of the size of the PM with chemical composition and the conditions of the combustion process. The researchers made analyses of samples of particulate matter originated from the combustion of wood chips from spruce wood in a boiler with a moving grate about rated heat power 5 MW. The authors obtained a level of sulfur of 0.398% in the particulate matter of the coal and most of the particles had diameters between 20–100 μm.

3 Size distribution of Particulate Matter (PM)

The particulate matter has a large range of sizes, going from small particles that need electronic microscopes to be observed to particle big enough to be observed with the naked eye (U.S. EPA 2016a, b). Due to the big range of sizes of the particulate matter, the samples are a big challenge, including the samples of particulate matter originated from the burning of biomass (Obaidullah et al. 2012).

The distribution of size is a property that relates to the harm to human health caused by the high concentrations of PM, choice of equipment to the control of industrial emissions, to the behavior of the particles, and the possible emitter sources of PM.

According to Kantová et al. (2017), the distribution of the size of the PM is one of the properties with the highest influence on the behavior of the particles when they are spread on the gas. This difference in the behavior of the particles is related to the different laws of physics that may influence the behavior of the particles (Kulkarni et al. 2011).

The particles present in the atmosphere are not completely spherical, which makes it difficult to determine their diameter and, consequently, to determine the size of the particle. Thus, different metrics were created in order to calculate with more coherence with the reality of the diameter of the particles. According to Vincent (2007), the equivalent volume diameter, equivalent projected area diameter, equivalent superficial area diameter, and the aerodynamical diameter are the main metrics used.

The concepts of the equivalent size of particles are important to some aspects as diffusion and interaction with the electromagnetic radiation, but they do not describe the behavior of the particles (Vincent 2007). Thus, the concept of aerodynamical diameter has great relevance in the determination of the particle behavior because it can represent the geometrical size, density, and shapes of the particles (Vincent 2007). The aerodynamical diameter is defined as the diameter of a sphere that has 1 g cm^{-3} of density (Finlayson-Pitts and Pitts Jr. 2000).

The size distribution of the particulate matter in three main modes was introduced by Whitby et al. in a series of works. The three modes are Aitken or nuclei mode (10 – 80 nm), accumulation mode (80 nm and 1–2 μm), and the coarse particles mode (>2.5 μm) (Finlayson-Pitts and Pitts Jr. 2000). With the technological advancements, new PM sampling equipment was created, these advancements enabled to create the mode of ultrafine particles and develop studies about these particles. The ultrafine particles are usually defined as particles with a lower diameter to 10 nm, including nucleation and Aitken mode particles (Finlayson-Pitts and Pitts Jr. 2000).

The modes of size distribution are related not only to the range of PM size because the particles of different modes also present distinct mechanisms of formation and behavior. In the case of the ultrafine PM, the mechanism of formations of the PM may occur by homogenous or heterogeneous nucleation.

The homogenous nucleation occurs when molecules with a low vapor pressure of the gaseous form condensate and form very small particles (Souza et al. 2017). Differently, the heterogeneous nucleation occurs with the condensation of molecules in the already existent particles (Souza et al. 2017). The particles belonging to the Aitken mode are formed by the process of homogenous nucleation, the particles belonging to the accumulation mode are formed by the process of heterogeneous nucleation and the particles belonging to the coarse particle mode are formed by mechanical processes (Alves 2005).

4 Ionic Composition of the Particulate Matter

The ionic composition of the particulate matter present in a region is directly related to the anthropogenic activities and to the natural processes that occur in the region. The anthropogenic activities have more influence over the changes in the inorganic composition of the local atmosphere, mainly if these activities alter the use of the soil or if they are emitter sources of PM (Souza et al. 2017).

The atmospheric acidity of certain regions is influenced by the presence of organic and inorganic acids in higher concentrations. Samplings of the particulate matter collected in the southeast region of Brazil showed that during the period of burning the sugarcane straw, the smaller particles presented higher concentrations of sulfate (SO_4^{2-}), oxalate ($C_2O_4^{2-}$), nitrate (NO_3^-), formate ($HCOO^-$), acetate (CH_3COO^-) and chloride (Cl^-), while the smaller particles presented a deficit of anions (Rocha et al. 2005).

The acetic and formic acids are more significant gaseous organic acids to the atmospheric acidity (Cruz et al. 2019). The formic acid is resultant from the photochemical reactions that occur in the atmosphere and the acetate is originated from the direct emissions (Rocha 2005).

The potassium, calcium, and magnesium ions, when found in the coarse PM, are originated from the resuspension of soil dust, however, when the potassium and the calcium are present in the fine PM fraction they are originated from the processes of biomass burning (Souza et al. 2017). The potassium ion is used as a biomass burning tracker, thus when this ion has correlations with the sulfate and nitrate ions, it indicates that these ions are also originated from the biomass burning (Allen et al. 2004).

Studies carried out in Beijing by Cheng et al. (2013) showed that the concentration of potassium ion (K^+) was 5.81 ± 2.75 μg m^{-3} in the days when the biomass burning occurred, in contrast to the days when it did not occur and the concentration of the potassium ion (K^+) was 1.74 ± 2.29 μg m^{-3}.

According to Jung et al. (2019), the concentration results in the samples collected from ammonium, nitrate, and water-soluble organic nitrogen were 0.768–25.3, 0.195–5.94, and 0.116–14.7 nmol m^{-3}, respectively. From the analysis of the ions carried out by Costa et al. (2017), higher concentrations of acetate, formate, and ammonium for the bigger particles (9–10 μm) were found; and nitrate, sulfate, and potassium in stages with particles with lower diameter to 1 μm.

Valotto et al. (2014) studied the characterization of the PM_1 in the region near Venice, analyzed the elemental concentration of the PM_1 during the four seasons of the year. For potassium, the highest concentration (528.5 ± 1.4 ng m^{-3}) was sampled during winter, for sulfur, the highest concentration (586.6 ± 1.3 ng m^{-3}) was sampled during winter, for magnesium, the highest concentration (37.5 ± 1.5 ng m^{-3}) was sampled during summer and for sodium, the highest concentration (646.3 ± 1.2 ng m^{-3}) was sampled during spring.

Sharma and Mandal (2017), in their work, registered the concentrations for the ions ammonium (NH_4^+), sulfate (SO_4^{2-}), and nitrate (NO_3^-) present in the $PM_{2,5}$ of 10.9±8.4, 13.1±5.9, and 10.8±8.2 μg.m^{-3}. In addition to correlating the presence of sulfate (SO_4^{2-}), nitrate (NO_3^-), and chloride ($C1^-$) with the presence of ammonium (NH_4^+), suggesting a possible formation of secondary pollutants. Nevertheless, nitrogen is an essential nutrient for the ecosystems, this way the atmospheric deposition becomes one of the main sources of nitrogen (Jung et al. 2019). The reactive species of nitrogen, among them, NO, NO_2, and NH_3 are the most abundant and are increasingly interfering in the relations among the biogeochemical cycles over the years, a consequence of the increase of emission of NO_x originated from the vehicle emission, industrial activities, and the burning of biomass (Follett et al. 2010).

Studies carried out in the city of Araraquara, Brazil, analyzed the size distribution and the ionic concentrations of the species: sodium, (Na^+), ammonium (NH_4^+), potassium (K^+), magnesium (Mg^{2+}), calcium (Ca^{2+}), fluoride (F^-), acetate (H_3CCOO), formate ($HCOO^-$), chloride (Cl^-), nitrite (NO_2^-), nitrate (NO_3^-), phosphate (PO_4^{2-}), sulfate (SO_4^{2-}), and oxalate ($C_2O_4^{2-}$) (Costa et al. 2017). The authors obtained, through the samplings, concentrations near 90 μg m^{-3} for particles with a diameter of 85 nm. Higher concentrations of PM_1 associated with higher concentrations of potassium indicate biomass burning. Beyond that, in this study, the authors conclude that potassium, nitrate, and sulfate were related to the burning of biomass from sugarcane. Indicting that the use of biomass to generate energy through burning is affecting the ecosystem of the studied region.

Samplings of $PM_{2.5}$ collected in Huaniao Island, China, analyzed the particulate matter in relation to the concentrations of organic carbon and elemental carbon. The average of coal concentration in the $PM_{2.5}$ and the total of suspended particles varied from 0.13 to 1.01 and 0.31 to 1.44 μg.m^{-3}; in the case of the soot, they were 0.03–0.21 and 0.16–0.56 μg m^{-3} (Wang et al. 2019). The sample concentrations of coal were bigger in winter and smaller in summer, while for soot the biggest concentrations were sampled in fall and the smallest in summer (Wang et al. 2019). The researchers concluded that the increase in the winter is possibly related to biomass burning and coal burning, which are used as indoor heating, and the higher concentration in fall also are related to biomass burning from anthropogenic activity. These results demonstrate the impact of biomass burning and anthropogenic pollutant emission on the atmosphere chemical composition over the coastal region.

In studies carried out in Mumbai, India, most particles of PAHs in the coarse fractions were found using a cascade impactor of eight stages (Dotel et al. 2020). The samplings were carried out in the cities of Kathmandu and Pokhara, which are two major cities in Nepal, between the years of 2015 and 2016, the levels of cyclic aromatic hydrocarbons were higher for the city of Kathmandu and the samplings showed that the winter and the post-monsoon seasons have higher concentrations of the cyclic aromatic hydrocarbon (Dotel et al. 2020). The authors found that those higher levels of PAHs were probably correlated with the burning fuel to generate heat because they were sampled in the residential area. The PAHs are toxic organic pollutants, and some are related to cancer, thus the determination of higher levels of PAHs in residential areas shows the importance of the analysis and calculation of the pollutants' concentration to evaluate the impact on the community.

In a study carried out between the period of July 18th and August 1st in the year 2018 in the city of Lahore, Pakistan, a medium concentration of $PM_{2.5}$ of 170.0 ± 54.9 $\mu g\ m^{-3}$ was obtained, and the most abundant species were: the carbon compounds, sulfate, nitrate, chloride, and ammonium (Ahmad et al. 2020). The carbon compounds were related to the emissions from vehicular fuels, while sulfate, nitrate, and ammonium originated from mixed source burning in industries, and chloride was present in the dust source from multiple sources. The results from this research showed that the predominant emission sources are from the local area and it shows that is important to identify the emission sources, so the government and companies can create action plans to improve pollutant emission prevention and to understand how the natural and anthropogenic emission effects the environment.

5 Dry Deposition Mechanism

The particles, present in the atmosphere, pass through different processes as atmospheric dispersion, chemical reactions, deposition in dry via, and wet deposition. The two most common mechanisms of particulate matter removal are the dry and wet deposition. These mechanisms of atmospheric particulate matter removal are related to the size and the behavior of the particulate matter.

Particles with bigger diameters are subjected to a bigger action of the gravity and, therefore, are deposited faster, while the fine and ultrafine particles are influenced by the Brownian movement, they can be transported through long distances and remain longer in the atmosphere. Thus, the evaluation of the deposition speed of the particulate matter, mostly in the fine and ultrafine fractions is important.

The dry deposition is the process of removal through which the aerosol particles are absorbed by the Earth's surface. In a wet deposition, particles are incorporated into water droplets and then reach the surface through precipitation (Pellerina et al. 2017).

Dry deposition acts efficiently and continuously in cleaning the atmosphere (Wu et al. 2018). This process acts in the absence of precipitation; however, it transports gaseous and particulate species from the atmosphere to different surfaces. This mechanism can cause severe impacts, even in biogeochemical cycles.

Studies relate the dry deposition through the speed of deposition, and it is a challenge to be overcome to quantify the impact of the pollutants on the populations and the environment (Pellerina et al. 2017). The process of dry deposition is associated with meteorological phenomena and chemical and biological nature. These interactions that influence the flux of gas and particulate pollutants, reaching with the soil surface without involving water in the atmosphere (Giardina and Buffa 2018).

Forest areas and areas with green spaces help in the mitigation and the deposition of the atmospheric particulate, due to their superficial microstructures the leaves may intercept the big particles (Yin et al. 2019).

The dry deposition has awakened the interest of the scientific community due to the effects caused to the environment by the dry deposition of the adsorbed compounds to the PM, consequently, the efforts to measure or estimate the dry deposition increased significantly (Mohan 2016).

In this field, the understanding of the dry deposition of the particles is far from being completed due to the dependence of the deposition in relation to the particle size, density, terrain, vegetations, characteristics of the place of deposition, and chemical compounds. The complex interaction between the turbulent transport process and the deposition elements, such as Brownian sedimentation, governs the dry deposition mechanism (Huang et al. 2014).

This dependence of the deposition with the diameter of the particles makes the particles from the coarse fraction of the PM to sediment faster, while the particles from the fine and ultrafine fraction may be transported by the air masses to other regions and remain in the atmosphere for some days.

The process of dry deposition of particles usually consists of three steps: aerodynamical transport from the atmosphere layer to the quasi-laminar sublayer; Brownian transport through the quasi-laminar sublayer; adsorption to the surface (Seinfeld and Pandis 2006).

The transport from the atmospheric layer until reaching the quasi-laminar sublayer happens through turbulent diffusion, the transport through the quasi-laminar sublayer happens through diffusion or sedimentation and the last step is the adherence of the particles to the surface (Seinfeld and Pandis 2006).

The primary phenomena that are considered to affect the process can be described as follows: when the transport is due to atmospheric turbulence in the low layer of the Planetary Boundary Layer (PBL), in this condition the dry deposition is independent of the physical and chemical nature of the pollutant and depends only on the atmospheric turbulence level.

When the transport is due to the turbulence present in the low atmospheric layer, only the level of atmospheric turbulence influences the dry deposition and does not depend on the physical and chemical nature of the pollutant. If the diffusion occurs at the air–soil interface (called Sublayer Quasi-Laminar, QLS), molecular diffusion for gas, Brownian motion, turbulent diffusion for particles, and gravity for heavier particles becomes dominant; the transfer to the ground by different mechanisms shows a pronounced dependence on the type of surface with which the pollutant interacts (Giardina and Buffa 2018). The ultrafine particles similarly to gaseous molecules so that deposition occurs by diffusion processes. Deposition of coarse particles occurs due to sedimentation, as they are more susceptible to gravitational action (Janhäl 2015).

According to Giardina and Buffa (2018), the total dry deposition rate for particles with sizes ranging from 0.01 μm to approximately a few micrometers is affected by the contribution of Brownian diffusion and turbulent swirl effects. For particles of intermediate size, in the range of approximately 10 nm–1 μm, the process strongly depends on the atmospheric conditions, characteristics of the surface, and the particle size. Deposition is dominated by turbulent and inertial impaction for particles with diameters above this size range.

In the inertial impaction mechanism, the particle has high inertia due to its size, so the particle is transported by the flow toward an obstacle, the particles are not able to follow the gas flow due to inertia and, consequently, collide with an obstacle and remain on the surface. In the turbulent impaction, the particle has a high velocity, creating turbulent and present enough momentum to reach the surface (Giardina and Buffa 2018). However, it is important to balance all the strengths, because not all the particles that reach the surface will adhere to it.

The dry deposition can be calculated through the flux of deposition of a species, the flux of deposition (F) is a function to the velocity of deposition (V_d) and the concentration (C) of the species in question (Seinfeld and Pandis 2006). The concentration and the velocity of deposition depend on the height of the sampling place in relation to the ground (z), it is adopted that the flux downward is negative for the velocity of deposition to be positive. The process of deposition can be interpreted analogously to an association in series of three resistances: the aerodynamical resistance (r_a), the quasi-laminar sublayer resistance (r_h), and the surface resistance (r_c) (Seinfeld and Pandis 2006). The sum of these three ways of resistance is equal to the inverse of the deposition velocity.

Several studies have evaluated the deposition flow composed on different surfaces using mathematical models, which predict the phenomenon of dry depositions from the determination of the deposition speed. The dry deposition of particles in vegetal surfaces has been theoretically studied by Slinn (1982); Zhang et al. (2001, 2003); and empirically by Pryor et al. (2007, 2009) and Wasiuta et al. (2015).

The first study on dry deposition in a wind tunnel was carried out in the 1970s by Möller and Schumann (1970), followed by Schumann (1975), specifically for particle sizes ranging from 10 nm to 1 μm. The results showed that the dry deposition on the water surface depends a lot on the particle size (Calec et al. 2017). According to Sehmel and Sutter (1974) which measured the velocity of the dry deposition of particles with many micrometers of diameter in a wind tunnel over a water surface. The contribution of the effects of eddy diffusion was comparable to the ones of the Brownian and turbulent diffusion.

Liu et al. (2016) calculated the deposition of particulate matter in forests, lakes, and fields of the Beijing Olympic Park, obtaining a medium daily flux of 0.08±0.09 $\mu g\ m^{-2}\ s^{-1}$ for fine particles in the region of the forest, where the depositions were bigger, according to the authors. The deposition of fine particles was predominantly in winter, while in spring the deposition of coarse particles was bigger.

Based on the observations from September 2015 to March 2015 in the Daya Bay, China, researchers could analyze the different concentrations of ions in the aerosol and could also calculate the flux of deposition of these nutrients in each studied month. The obtained results demonstrated that the nutrients as the nitrogenated ions presented seasonal behavior, having their biggest presence in spring and winter. Besides that, they could also prove that the dry deposition in a place can cause a bad distribution of nutrients in the atmosphere of other places remote from the place where the deposition occurred, because of the action of the air masses (Wu et al. 2018).

Several studies have recognized the complexity and limited theoretical understanding of its mechanism for 100 nm size particles, considering the importance and the high deposition rate on plant surfaces. Due to this complexity, models have been proposed to predict the deposition of particles in different locations with speeds and deposition flows for particles from 100 nm to 2.5 μm (Wasiuta et al. 2015). The dry velocity deposition speeds of this study were evaluated in the range of 0.04–0.14 cm.s^{-1} for particles of 100–500 nm in diameter, according to the measured values of 0.01 ± 0.03 cm s^{-1}. A minimum value was obtained for the deposition speed for particles between 500 nm and 1 μm in diameter. The average values obtained for particles of 10 nm, 1 μm, and 500 nm were, respectively, 0.09, 0.03, and 0.52 cm s^{-1}. In the work of sampling and chemical composition by Rocha et al. (2005), the influence of burning sugarcane biomass on the granulometric distribution was evaluated, using the dry velocity deposition according to the Zhang model and determining the flows in the city of Araraquara during a period of open sugarcane burning. The results induced that although the highest deposition rates were obtained for calcium, sulfate, and nitrate, these were only partially affected by burning and related activities. The addition to the annual nitrogen deposition flow was approximately 9% directly due to the burning of sugarcane (Rocha et al. 2005).

The parametrization of the dry deposition of particles was developed for the Canadian Aerosol Model (CAM) and in the model by Slinn (1982) (Mammarella et al. 2011). Zhang et al. (2001) developed a parametrization capable of calculating the velocity of dry deposition of a particle as a function of the particle size, density, and meteorological variations. The model by Zhang et al. (2001) allows obtaining a more realistic determination of the velocity of deposition for particles with a diameter in the submicron fraction. These values of the velocity of depositions are important to the samplings collected in the field. Another parametrization used to determine the velocity of dry deposition is the model by Nho-Kim et al. (2004). This parametrization calculates the velocity of deposition with a function of the particle size, density, properties of the surface, and meteorological conditions near the surface. The parametrization by Nho-Kim et al. (2004) obtained satisfying results, they obtained velocities of deposition over land surfaces with a magnitude order bigger than over oceans. However, this parametrization has its bigger uncertainty for particles in the size range of 100 nm to 1 μm with deposition over very rough surfaces.

The widely used parametrization to determine the velocity of deposition of particles over aqueous surfaces is the parametrization created by Slinn and Slinn (1980), this parametrization was obtained by modifying the theory developed in the previous years for the deposition over solid and soft surfaces.

Budhavant et al. (2012) collected samples of the dry deposition between the years of 2006 and 2009 in four different places near the city of Pune in India, the researchers used a high-volume sampler to make the collections. The collections of the samples of dry deposition were made weekly and were analyzed the presence of chloride (Cl^-), nitrate (NO_3^-), sulfate (SO_4^{2-}), sodium (Na^+), potassium (K^+), ammonium (NH_4^+), calcium (Ca^{2+}), and magnesium (Mg^{2+}). The researchers also determined the velocity of dry deposition for these ions from the definition that the velocity of deposition is equal to the reason between the flux and the concentration of the ion in the atmosphere.

Liu et al. (2016) calculated the PM deposition for forests, swamp zones, and lake surfaces in the Olympic Park of Beijing. The researchers obtained a daily medium flux of 0.08 ± 0.09 μg m^{-2} s^{-1} for fine particles in the forest region. According to the authors, the velocity of deposition was bigger for the forest, the fine particles deposed predominantly during winter, while the coarse particles deposed predominantly in spring.

In studies carried out in the cities of Kathmandu and Pokhara in Nepal determined the flux of deposition PAHs between the years of 2015 and 2016, the flux of annual dry deposition was of 281±145 ng m^{-2} day^{-1}, for each of the cities was of 66 and 5 kg $year^{-1}$, respectively (Dotel et al. 2020). The biggest values of the flux of dry deposition calculated by the authors were for the residential areas during winter.

Jung et al. (2019) estimated the medium flux of deposition for the ions of ammonium, nitrate, and organic nitrogen soluble in water in 3.4 ± 4.6, 2.2 ± 3.3, 3 0.69 ± 2.0 μmol m^{-2} day^{-1}, respectively. The authors used Equation (21.1) to determine the flux of dry deposition.

$$F_d = C_a^c V_d^c + C_a^f V_d^f \tag{21.1}$$

Where C_a is the concentration for coarse particles (c) and fine (f), V_d is the velocity of dry deposition for the two ranges of particle sizes.

Wang et al. (2019) observed three episodes with high concentrations of coal and soot, during the winter, it became evident the increase of the rate of deposition for OC and EC in relation to the days without burning. The flux of deposition found for OC was of 269.8 and 151.7 μg m^{-2} day^{-1}, for EC 109.3 and 37.6 μg m^{-2} day^{-1} for the days with episodes of burnings and days without burnings, respectively. The authors concluded that the biggest relation between coal/soot in winter suggests a dominance of the biomass burning and coal combustion; while lesser relations between coal/soot in fall and summer indicate the influence of the burning originate from vehicles.

6 Effects of PM on Environment and Human Health

The presence of particulate material in high concentrations can impact the environment and human health. The fact that particulate material is transported by air masses increases the area that can be affected by these impacts, moving from local impacts to regional impacts.

Several studies presented by the World Health Organization (WHO) relate the increase in cases of respiratory diseases, cardiovascular diseases, hospital admissions, and even in some cases the increase in deaths with exposure to particulate material (WHO 2003).

The harmful impacts of exposure to particulate matter are related to the size of the particles, their penetrating power, concentration, and chemical composition. Regarding the size of the particles, the coarse particulate material (PM_{10}) is more likely to accumulate in the nose and pharynx due to the impaction process, when the particles collide with the mucosa of the upper airways because they are not able to follow the flow of inhaled air when there is a sudden change of direction (Areskoug et al. 2000). In the case of fine particulate material ($PM_{2.5}$), these particles have greater penetrating power, that is, they reach the lungs and bronchi (Riva et al. 2011). The particles that have greater penetrating power are particles of particulate material with diameters less than 1 μm, these particles are deposited in the alveoli, and can cross into the bloodstream (Liu et al. 2020).

The particulate matter for having a large surface area can adsorb pollutants, toxic compounds, carcinogens, organic molecules, and heavy metals, so when inhaled the PM can transport these harmful substances to the health through the airways (Kwon et al. 2020).

Non-ecological impacts are related to visibility. Fine particulate material ($PM_{2.5}$) is the main cause of reduced visibility, this is because part of the sunlight is absorbed by these particles, and the higher the concentration of PM the more sunlight will be absorbed (U.S. EPA 2016a, b).

The ecological impacts depend on the chemical composition of the PM, the effects include changes in the acidity of lakes, changes in the balance of nutrients, depleting soil nutrients, damaging forests and plantations, affecting the diversity of ecosystems, and contributing to acid rain (U.S. EPA 2016a, b). The presence of high concentrations of ions contained in the sea salt, sulfates, nitrates, and some organic compounds causes an increase in the number of cloud condensation nuclei (Souza et al. 2017). The vegetation is highly affected by the deposition of particle matter including nitrates, sulfates, and the acid forms of the respective compounds, trace elements, and heavy metals (Mohapatra and Biswal 2014). For example, the deposition of nitrogen compounds on the soil interferes with biogeochemical cycles, high concentrations of nitrogen deposited on the soil alters the nitrogen content available in the soil, and nitrogen leaching will occur if the absorption of this compound exceeds the soil's retention capacity (Liu et al. 2011).

Because of the negative impacts on the environment, human health, and the increase in emissions of particulate matter mainly after the Second World War, laws,

Table 21.1 WHO air quality guidelines and interim targets for particulate matter: annual mean concentrations.

	PM_{10} (µg/m^3)	$PM_{2.5}$ (µg/m^3)	Basis for the selected level
Interim target-1 (IT-1)	70	35	These levels are associated with about a 15% higher long-term mortality risk relative to the AQG level
Interim target-2 (IT-2)	50	25	In addition to other health benefits, these levels lower the risk of premature mortality by approximately 6% (2–11%) relative to the IT-1 level
Interim target-3 (IT-3)	30	15	In addition to other health benefits, these levels reduce the mortality risk by approximately 6% (2–11%) relative to the –IT-2 level
Air quality guideline (AQG)	20	10	These are the lowest levels at which total, cardiopulmonary and lung cancer mortality have been shown to increase with more than 95% confidence in response to long-term exposure to $PM_{2.5}$

WHO (2006)

and agencies responsible for controlling concentrations of air pollutants were created. In 2005, the World Health Organization (WHO) updated the guideline values for air pollutants to protect the health of the population (Table 21.1). WHO believes that to adopt air quality policies, local factors, technical limitations, and public health must be considered (WHO 2006).

7 Case Study: Dry Deposition in Araraquara city

7.1 Methodology

This research was developed in the city of Araraquara, located in the central region of the state of São Paulo – Brazil, in the core of the cultivation of sugarcane and near industries that uses the bagasse as fuel, with the geographic coordinates 21°47´37" (south latitude) and 48°10´52" (west longitude). The samples were collected using an optical monitor DataRAM 4 (DR4, collect particles with diameters ranging from 0.0 to 4 µm) and the sampler Cascade Impactor de Andersen with nine stages (stage 1 (10–9 µm), stage 2 (9–5.8 µm), stage 3 (5.8–4.7 µm), stage 4 (4.7–3.3 µm) stage 5 (3.3–2.1 µm), stage 6 (2.1–1.1 µm), stage 7 (1.1 µm–700 nm), stage 8 (700–400 nm), and stage 9 (<400 nm). The samples were collected every 15 days, except on rainy days, between November 2016 and 2017. At the calibration, the sampling flow was fixed in 28.3 L min^{-1}. In both samplers, suitable glass fiber filters were used. The collected material in the filters was conditioned and stored for later chemical analysis. For the chemical analysis, the glass fiber filters used in the DR4 monitor were totally used and each of the stages of impactor filters was cut into 8 cm^2 dimensions. These areas of the filters were inserted into a falcon tube and were solubilized in Milli-Q Millipore deionized water (18 MΩ resistivity). Isopropanol + deionized water (0.5 and 9.5 mL, respectively) was added to minimize the hydrophobic character of the filters. These tubes were mechanically shaken for 40 min. The resulting solutions were filtrated in a porosity membrane (Millipore Millex-HV 450 nm). Approximately 1.5 mL of the filtrate was analyzed for ion-exchange chromatography using an Ion Chromatograph (Thermo Scientific), model ICS 5000 analytical. The species analyzed were the anions: fluoride (F^-), acetate (HCH_3COO^-), formate ($HCOO^-$), chloride (Cl^-), nitrite (NO_2^-), nitrate (NO_3^-), sulfate (SO_4^{2-}), oxalate ($C_2O_4^{2-}$), phosphate (PO_4^{3-}) and the cations: sodium (Na^+), ammonium (NH_4^+), potassium (K^+), magnesium (Mg^{2+}), and calcium (Ca^{2+}).

7.2 Air Mass Trajectories and Number of Fires

It was utilized by the National Oceanic and Atmospheric Administration (NOAA) HYSPLIT 4 (Hybrid Single Particle Lagrangian Integrated Trajectory Model) to calculate the trajectories of air masses (NOAA 2018). The air mass trajectories were tracked for 4 days before the sampling and the sampling day during a period of 24 h. It was fixed as the starting time of the calculations of the air mass trajectories at the same time as the sampling beginning. The arrival points of the air mass trajectories were fixed at 300 and 500 m above ground level. The total number of burning zones present in Araraquara, in the cities of the region, and all the State of São Paulo were obtained through consulting the data of the National Institute for Space Research Burn Database (Instituto Nacional de Pesquisas Espaciais, 2018).

In this research, two parametrizations were used, Zhang et al. (2001) and Nho-Kim et al. (2004), to determine the velocities of dry deposition. The parametrization of Zhang et al. (2001) was based on the Slinn model (1982); the latter is a model that includes processes of Brownian diffusion, impaction, interception, gravitational sedimentation, and particle bounce. While the parametrization of Nho-Kim et al. (2004) was based on the models of Slinn and Slinn (1980) and Slinn (1982). It is possible to find in many works the application of parameterization of the deposition of dry particles was developed for the Canadian Aerosols Module (CAM) and the model of Slinn (1982) and several authors use this model to predict the velocity and deposition flows (Mammarella et al. 2011). The particle density of 2000 kg m^{-3}, and wind speeds ranged from 0.8 to 5.0 m s^{-1} were used.

It was used the categories LUC 6, LUC 7, and LUC 15, for the stations' SC 1, SC 2, SC 3, and SC 5 because of the geographic and economic characteristics of Araraquara and the cities in the region. However, as the parameter of SC 1 and 2 for all the used LUCs are equal, the values of velocities of dry deposition will be equal.

The flux of deposition can be calculated according to Equation (21.2) described by Seinfeld and Pandis (2006):

$$F = V_d . C \tag{21.2}$$

Where F is the flux of deposition, V_d is the velocity of deposition, and C is the concentration of the compound.

7.3 Evaluation of the Concentration and the Distribution of the Particulate Matter Diameter

From the data that was sampled by the DataRAM (DR4), it was constituted the graphics of concentration of particulate matter and mass mean diameter of the particles in function of time for each one of the samplings collected since November 26th, 2016 until October 27th, 2017. The mean results of concentration and diameter for all the sampled days are shown in Table 21.2.

The samplings from August 14, 2017 had a higher result of concentration with the smaller diameter of particles. Figure 21.1 presents the concentrations of the particulate matter from August 11, 2017 to August 14, 2017. Figure 21.2 presents the mass mean diameter of the particulate matter between August 11, 2017 and August 14, 2017. Analyzing the data of concentration and mass mean diameter of the particulate matter obtained by the DR4, it was possible to determine some patterns among all the samplings. In most of the sample days, the mean concentration of particulate matter was approximately 35 μg m^{-3}, and the mass mean diameter was approximately 300 nm.

There were samplings that obtained mean concentrations smaller than 20 μg m^{-3}, it occurred on March 09, 2017, March 16, 2017, June 22, 2017, and July 03, 2017. In these days, the mass mean diameter during all the sampling time remained between 200 and 500 nm. It was also possible to notice an increase in the PM

Table 21.2 Mean values of concentration and diameter of the particulate matter sampled on the period of the collection (November 26th, 2016 until October 27th, 2017).

Date	Average concentration (μg/m^3)	Average diameter (nm)
11/25/2016	16.07	220
02/24/2017	44.34	120
03/09/2017	2.44	290
03/16/2017	0.99	330
04/20/2017	15.32	180
05/09/2017	70.98	200
06/22/2017	8.75	250
07/03/2017	2.48	320
08/11/2017	49.46	150
08/14/2017	97.79	140
09/04/2017	11.00	240
09/14/2017	30.32	160
10/27/2017	33.49	170

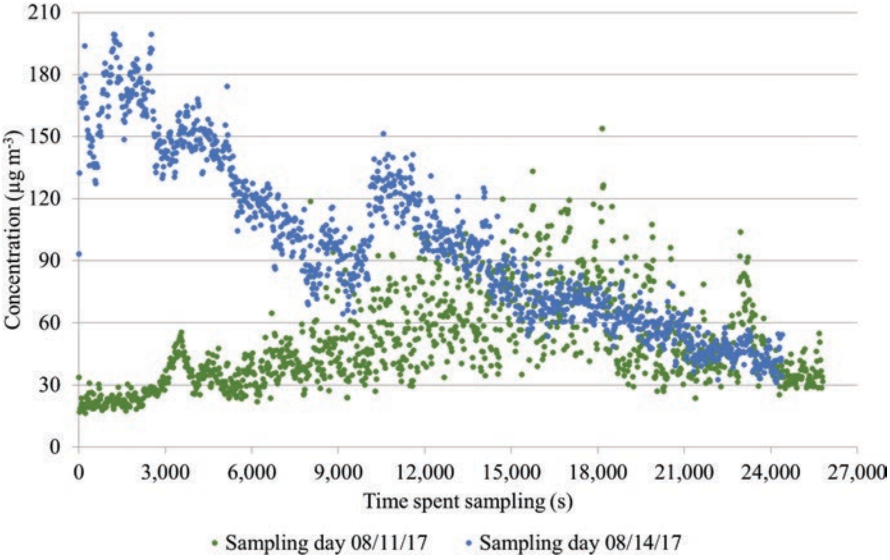

Fig. 21.1 Concentration in the function of sampling time for the days August 11, 2017 and August 14, 2017

concentration, while the mass mean diameter decreased. The smallest mass mean

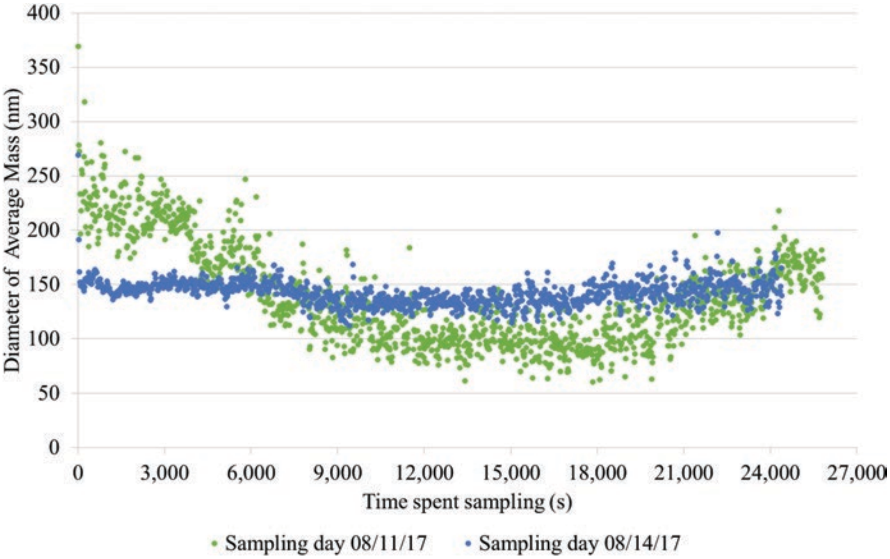

Fig. 21.2 Diameter of average mass in the function of sampling time for the days August 11, 2017 and August 14, 2017

diameter was of 140 nm, registered on March 09, 2017 and 150 nm on June 22, 2017 with concentrations of 34 and 75.6 μg m^{-3}, respectively.

On the other hand, on some days, the concentration was above average, as on August 11, 2017, August 14, 2017, and September 14, 2017, it was observed a big increase in the concentration along the sampling period. During August 11th and 14th 2017, the concentrations were above 50 μg m^{-3} during almost all the sampling time and the mass mean diameter was below 150 nm.

On September 14, 2017, it was noticed that the highest concentrations among all the sampled days. The highest sampled concentration was 202.3 μg m^{-3}, with a mass mean diameter of 160 nm.

When we compare the concentrations and the mass mean diameters of the sugarcane off-season period in the region (between February and April) and the period when the factories are operating at maximum capacity (between August and November), it was observed that the samplings between the months when the factories are at all capacity, there was an increase in the concentration of PM in relation to the off-season period.

In the period of the total capacity of the factories, the concentrations were around or above 30 μg m^{-3}, with mass mean diameter between 100 and 400 nm. While for the off-season period, the concentrations were below 10 μg m^{-3} in almost all the sampled days and with diameters between 200 and 400 nm. The usage of the sugarcane bagasse as fuel in the industries and distilleries may have affected the atmosphere of the region with PM emissions. Biomass burns in the industrial burners at high temperatures, and keeping the biomass in the flaming stage of the combustion process emits PM in high concentrations and with smaller diameters. This range of emitted diameter presents complexity in the process of capturing and cleaning the gases of industrial emission and the commonly used equipment may not be totally efficient in the collection of PM in the nanometer diameter range. However, it is necessary to evaluate the existence of different sources of PM pollution, both the industrial emissions and the open burnings of biomass, which are still happening in the country.

The concentration of the $PM_{2.5}$ sampled on August 14, 2017 and September 14, 2017 are near the values sampled by Nirmalkar and Deb (2016) for $PM_{2.5}$ of 221 ± 25.1 μg m^{-3}. The concentrations sampled during the days April 20, 2017 and June 22, 2017 are according to the results obtained by Kopanakis et al. (2012) for the concentration of the $PM_{2.5}$ of 3.6 ± 5.8 μg m^{-3}. On day August 14, 2017, it was registered that the concentrations were above the average concentrations registered by Sharma and Mandal (2017) but were below the highest concentrations sampled by these researchers. Thus, the data sampled during August 14, 2017 gives signs that the burnings that occurred in the region and Araraquara are related to the high concentrations registered on this day.

The concentrations during winter in the city of Araraquara were higher than the values obtained by Valotto et al. (2014) during the same season of the year. This way, the results obtained in Araraquara during winter may indicate the influence of the anthropogenic actions during this period.

With the objective of assessing the existence of biomass burning spots in fields and PM emission sources, data were used from the total number of burning spots in Araraquara and the state of São Paulo, besides assessing the trajectory of air masses from other regions to the sampling place.

7.4 Number of Burning Spots and Air Masses Trajectories

The data about the total number of burning spots in the city of Araraquara and the state of São Paulo were obtained in the Burning Data Bank of the National Institute of Spatial Researches, the databank allows the visualization of the places where there were burning spot.

From the information obtained in the Burning Databank from INPE, Table 21.3 was built with the total number of spots located in Araraquara and the state of São Paulo.

According to the information from Table 21.3 and the PM sampled concentrations, it was observed that there is a relation between the great number of foci present in the state, in Araraquara, and the high concentrations for the days August 11, 2017 and August 14, 2017. That is because on these days the concentration of the samples were high in relation to the other days and, the highest number of burning foci in Araraquara and the state of São Paulo was also registered.

In relation to March 09, 2017, the lowest number of foci in the state of São Paulo was registered. Thus, when we compare it with the data of concentration, it was observed that PM concentration remained low during all the sampling 10 μg m^{-3} period.

Table 21.3 Burning spots in Araraquara and the state of São Paulo.

	Fire Foci	
Analyzed period	Araraquara city	State of São Paulo
21–25/11/2016	1	216
20–24/02/2017	2	484
05–09/03/2017	0	75
12–16/03/2017	1	141
16–20/04/2017	0	182
05–09/05/2017	0	106
18–22/06/2017	0	350
29/06/2017–03/07/2017	1	486
07–11/08/2017	17	2115
10–14/08/2017	39	2385
31/08/2017–04/09/2017	14	3427
10–14/09/2017	55	5312
23–27/10/2017	1	143

The period between March 5th and 9th from 2015 was registered with the lowest number of burning, totalizing 75 foci in the state of São Paulo and no focus in Araraquara.

The period from August 10th to 14th 2017 was the period with the second highest number of burning foci registered in Araraquara, with a registered total of 39 foci in the city and 2385 foci in the state of São Paulo. The highest number of burning foci in Araraquara was between September 10th and 14th of 2017, totalizing 55 foci. In the period, it was also registered the highest number of burning foci in the state of São Paulo, totalizing 5312 foci in the state. It important to highlight that from September to October, the sugar-energy industries are in full activity and operating near the maximum production capacity.

The analysis of the air mass trajectories adds information to the influences of the burnings that occurred in certain regions and the presence of anthropogenic sources as the industries. The PM_1 can be transported through long distances through the air masses and impact regions far from its source.

For all the sampled period, it was analyzed the masses of air trajectories. In relation to the period between August 10th and 14th, it was important to analyze the trajectories of the air masses due to the great number of burnings in the state and region. It can be noticed that these did not pass near the regions where there is a big number of burning foci. However, the air masses approached cities as Ribeirão Preto and Campinas, cities that have high populational density, a high number of industries, which many use biomasses as fuel and are considered regional metropolises. The PM transport originated from cities with a high number of industries that may indicate influences from the anthropogenic actions in the composition of the sampled PM.

For September 10th and 14th, the period with an elevated number of burning foci, both in Araraquara and in the state of São Paulo, it was analyzed the route of the masses of air trajectories, which can be observed in Fig. 21.3.

The trajectories of the air masses passed through regions in which there were high numbers of burning foci during September 10th and 14th, 2017, which favors the transport of the PM originated from the burning of biomass and gives signs that the sampled PM_1 may be originated from the burning of biomass.

At the same time, the air masses trajectories passed near cities that have as their economic focus the sugar-energy industries, where the sugarcane bagasse is burned to generate electric energy. A big part of the industries in the state of São Paulo is in the central and north regions of the state.

The analysis of the air masses trajectories can be observed in other studies. Similarly, to how the analysis of the air masses trajectories between September 10th and 14th, 2017 gave signs of the influence of the PM transport originated from the biomass burning. Kopanakis et al. (2012) analyzed the trajectories of the air masses and related them to the peaks of concentration of PM_{10}, $PM_{2.5}$, and the potassium ion (K^+) with the occurrence of big forest burnings that occurred in Sicily. The researchers observed that the air masses transported the pollutants from the forest burnings to the sampled region and that on the following days, the air mass trajectories changed direction, and consequently the concentrations of PM_{10}, $PM_{2.5}$, and the

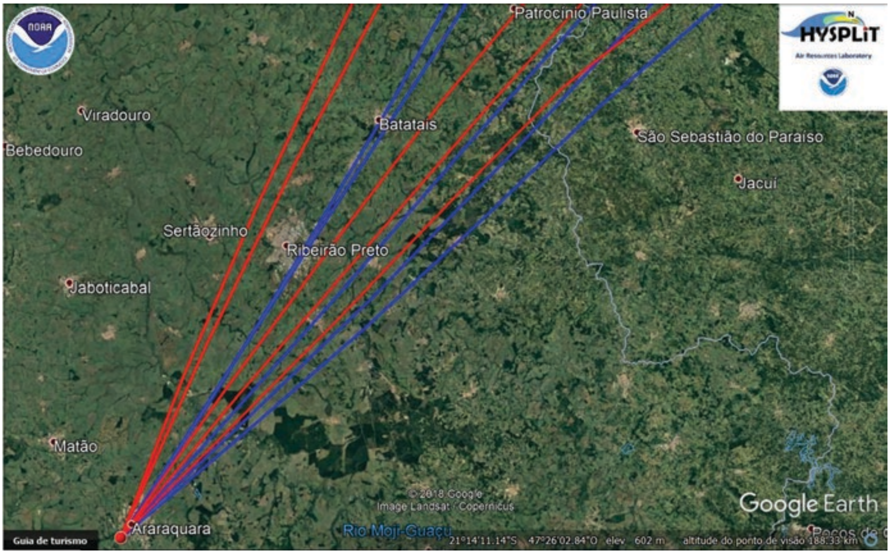

Fig. 21.3 Trajectories of the air masses in the period from 10th to 14th of September 2017. (Source—NOAA (2018))

potassium ion (K^+) reduced. Several authors carried out chemical analyzes of the soluble ions present in the PM, this chemical characterization is of big importance to the identification of the possible emitting sources and the impact that the anthropogenic actions cause on the environment.

The ionic composition of the particulate matter is related to the anthropogenic activities and with the natural processes that occur in the atmosphere of a region.

The ionic composition of the soluble ions present in the collected PM in each filter of the cascade sampler stages was determined by ionic chromatography for all the sampled days with the objective of characterizing and comparing days when there were burnings in the region and days when there were not. Tables 21.4–21.6 present the concentrations of the soluble ions present in the PM for day September 03, 2017, August 14, 2017, and September 14, 2017.

It can be observed that in PM_1 fraction of the sampled PM during March 09, 2017 it is present in the ions sulfate, calcium, potassium, sodium, chloride, nitrate, and magnesium. The ions of potassium and sulfate are used as trackers for biomass burning, mainly when they are present in the PM_1 (Cheng et al. 2013).

Comparing the concentrations of potassium, sulfur, magnesium, and sodium present on March 09, 2017 with the ones presented in the work by Valotto et al. (2014), only the concentration of sulfate on March 09, 2017 was above the concentrations sampled by Valotto et al. (2014). Valotto et al. (2014) relate the increase in the sulfate concentration to the intense photochemical activity.

Analyzing the ionic composition of the coarse PM on the sampling on August 14, 2017, the presence of nitrate, magnesium, chloride, oxalate, sodium, potassium, and calcium was verified. The ions of potassium, calcium, and magnesium, when

Table 21.4 Ions concentration by size range for the day March 09, 2017.

Diameter Range (nm)	Sodium (mg m^{-3})	Ammonium (mg m^{-3})	Potassium (mg m^{-3})	Magnesium (mg m^{-3})	Calcium (mg m^{-3})	Formate (mg m^{-3})	Chloride (mg m^{-3})	Nitrite (mg m^{-3})	Nitrate (mg m^{-3})	Sulfate (mg m^{-3})	Oxalate (mg m^{-3})	Phosphate (mg m^{-3})
9000–10,000	0	0	5.58E-05	2.66E-05	1.38E-04	0	0	0	1.67E-04	1.12E-04	5.06E-05	1.98E-06
5800–9000	0	0	0	4.58E-06	4.98E-05	0	0	0	3.15E-05	1.04E-04	8.15E-05	5.31E-06
4700–5800	0	0	1.15E-05	0	2.29E-05	0	0	0	0	4.78E-05	1.88E-05	1.10E-05
3300–4700	0	0	1.27E-06	7.75E-06	1.27E-04	0	0	0	1.85E-05	3.08E-05	5.39E-05	5.21E-07
2100–3300	0	0	2.61E-05	0	1.65E-05	0	2.36E-04	0	0	5.42E-05	2.57E-05	0
1100–2100	3.51E-05	0	2.51E-05	0	5.16E-05	0	0	4.58E-07	0	5.69E-05	0	0
700–1100	0	0	5.87E-05	0	4.67E-05	0	0	0	0	1.10E-04	0	0
400–700	8.82E-05	0	7.47E-06	0	0	0	3.52E-04	0	0	2.73E-04	8.14E-05	2.92E-07
0–400	0	0	3.11E-05	7.88E-06	7.68E-05	0	0	0	6.34E-05	5.16E-04	0	0

Table 21.5 Ions concentration by size range for the day August 14, 2017.

Diameter Range (nm)	Sodium (mg m^{-3})	Ammonium (mg m^{-3})	Potassium (mg m^{-3})	Magnesium (mg m^{-3})	Calcium (mg m^{-3})	Formate (mg m^{-3})	Chloride (mg m^{-3})	Nitrite (mg m^{-3})	Nitrate (mg m^{-3})	Sulfate (mg m^{-3})	Oxalate (mg m^{-3})	Phosphate (mg m^{-3})
9000–10,000	0	0	0	0	0	0	0	0	2.64E-05	0	0	0
5800–9000	0	0	0	0	0	0	0	0	1.82E-05	0	0	0
4700–5800	0	0	0	0	0	0	0	0	1.99E-05	0	0	0
3300–4700	0	0	0	2.51E-05	0	0	0	0	1.83E-05	0	0	0
2100–3300	3.36E-03	2.23E-06	1.45E-03	1.30E-04	8.35E-04	0	1.28E-03	1.09E-06	0	0	1.04E-05	0
1100–2100	0	1.97E-04	8.81E-04	0	0	0	2.82E-03	0	3.25E-01	0	6.99E-06	0
700–1100	2.06E-03	1.63E-04	3.25E-03	1.17E-05	2.09E-04	1.76E-04	1.92E-03	0	0	0	8.50E-06	0
400–700	2.74E-03	0	0	2.62E-05	5.98E-05	0	0	0	2.16E-05	0	0	0
0–400	0	0	0	0	0	0	0	0	1.80E-05	0	0	0

Table 21.6 Ions concentration by size range for the day September 14, 2017.

Diameter Range (nm)	Sodium (mg m^{-3})	Ammonium (mg m^{-3})	Potassium (mg m^{-3})	Magnesium (mg m^{-3})	Calcium (mg m^{-3})	Formate (mg m^{-3})	Chloride (mg m^{-3})	Nitrite (mg m^{-3})	Nitrate (mg m^{-3})	Sulfate (mg m^{-3})	Oxalate (mg m^{-3})	Phosphate (mg m^{-3})
9000–10,000	0	0	0	7.84E-06	3.32E-05	0	0	0	0	0	1.60E-06	0
5800–9000	4.29E-04	8.05E-09	2.00E-05	1.56E-05	8.49E-05	0	3.88E-04	3.37E-06	0	0	1.83E-06	0
4700–5800	3.73E-04	0	1.88E-06	5.83E-06	1.72E-05	0	4.52E-04	3.08E-06	0	0	9.42E-07	0
3300–4700	0	0	0	0	0	9.46E-06	1.50E-04	9.02E-07	0	0	6.20E-07	0
2100–3300	1.41E-03	0	6.33E-05	8.41E-06	4.30E-05	2.46E-05	8.26E-04	0	0	0	8.45E-07	0
1100–2100	8.49E-04	0	2.51E-05	0	0	6.11E-06	5.73E-04	0	1.57E-06	0	1.14E-06	0
700–1100	0	0	0	0	0	0	0	1.67E-06	0	0	7.81E-07	0
400–700	1.15E-03	6.36E-05	8.44E-05	3.18E-05	1.13E-04	1.11E-03	0	0	0	1.74E-03	0	0
0–400	0	0	0	3.37E-06	1.95E-05	0	0	0	9.74E-07	0	1.05E-06	0

found on the coarse PM originated from the resuspension of the ground dirt. Besides the nitrate and magnesium being present predominantly on the PM above 3.3 μm, they have low concentrations.

It was observed that in the PM_1 fraction of the PM sampled during August 14, 2017, it is present in the ions of nitrate, chloride, calcium, potassium, formate, ammonium, and sodium. The nitrate and the potassium, when present in the PM_1 fraction of the particulate matter, are indicatives of ions originated from the biomass burning.

The concentrations of potassium on the PM_1 sampled during August 14, 2017 are near the mean values sampled by Cheng et al. (2013) for the days when the biomass burning happened. When compared to the mean concentration sampled by Valotto et al. (2014) for potassium, the concentration obtained on August 14, 2017 was approximately six times higher.

As observed by Sharma and Mandal (2017), the ammonium and the nitrate are also present on the PM_1, but the ammonium has a lower concentration than the one sampled by Sharma and Mandal (2017). Souza et al. (2017) reported that the correlation between the ions of formate and ammonium in the PM_1 suggests that these ions are generated from the neutralization of the acids present in the atmosphere by the ammonia.

On the other hand, the presence of sulfate and nitrate together with the potassium on the PM_1 indicates that the ions of sulfate and nitrate are original from the burning of biomass (Allen et al. 2004). Like the works by Rocha et al. (2005), which also sampled the region of Araraquara, the concentrations of sulfate, formate, and chloride were higher on September 14, 2017 in comparison to March 09, 2017.

Thus, the combination of the information about the sampled PM concentration, diameter of the particles, number of burning foci, trajectories of the air mass, and composition of the PM in relation to the soluble ions, characterize the PM as possibly originated from the processes of biomass combustion. In addition to suggesting that the transport of these particles occurred by the air masses due to their trajectories pass near the burning foci and the cities that have industries that used biomass as fuel.

These concentrations of ions present on the PM are used for the calculation of the dry deposition of pollutants in the abovementioned different places, such as urban and agricultural areas.

7.5 Curves of Dry Deposition velocity and Deposition Flux

For calculating the flux of dry deposition of ions present in the atmospheric PM, it is necessary to determine the velocity of dry deposition. In this work, the velocities of depositions were determined making use of the models by Nho-Kim et al. (2004) and Zhang et al. (2001). The velocity of the wind has a big influence over the equations of the parametrization presented by Nho-Kim et al. (2004). Table 21.7 presents the velocities of the wind registered in each sampling day. It was decided to build

Table 21.7 Wind Speed registered for each sampling day.

Sampling day	Wind speed (m s^{-1})
11/25/2016	1.2
02/24/2017	2.8
03/09/2017	1.4
03/16/2017	3.1
04/20/2017	3.6
05/09/2017	1.3
06/22/2017	2.8
07/03/2017	4.6
08/11/2017	2.3
08/14/2017	1.0
09/04/2017	2.4
09/14/2017	0.8
10/27/2017	0.8

the curves of deposition velocity for the wind velocities of 1.0, 2.5, 3.0, and 5.0 m s^{-1}, so it is possible to present both the velocity of deposition and the flux of deposition in a representative way for the weather conditions of the region. The average wind velocity was 2.16 m $s^{-1.}$

Figure 21.4 presents the curves of deposition velocity with the wind velocities of 1.0 m s^{-1}, for the model by Nho-Kim et al. (2004).

Analyzing the curves of deposition velocity determined by the different wind velocities, it was observed the influence of the wind velocity in the calculations of dry deposition velocity. With the increase of the wind velocity, the smaller values of dry deposition velocity are obtained for the particles with diameters near 1.0 μm, approximating it to the model by Nho-Kim et al. (2004).

Another important aspect that may be highlighted is that the particles between 400 nm and 1.0 μm have the slowest deposition velocities. That makes those particles remain longer in the atmosphere before suffering the process of deposition, thus it increases the possibility of them being inhaled and impacting human health, due to the high penetrant power of these particles.

The same comparison was made for the model by Zhang et al. (2001). Zhang et al. (2001) made a different analysis from Nho-Kim et al. (2004). Zhang et al. (2001) calculated the deposition velocity to the same roughness length (Z_0) and the values of this were associated with the different categories of terrain.

Figure 21.5 presents the curves of deposition velocity for LUC7 SC1/SC2, LUC7 SC3 e LUC7 SC5 with the wind velocities of 1.0, 2.5, 3.0, and 5.0 m s^{-1}.

Figure 21.6 presents, respectively, the curves of deposition velocity for LUC15 SC1/SC3/SC5 with the wind velocities of 1.0, 2.5, 3.0, and 5.0 m s^{-1}. For all the types of LUC that were analyzed in this work, the deposition velocities increased with the wind velocities, like what happened on the model by Nho-Kim et al. (2004).

On the curves of deposition velocity calculated from the parametrization of Zhang et al. (2001), the smaller values of velocity were obtained for the particles with a diameter between 700 and 1.1 μm, which is close to the values obtained on

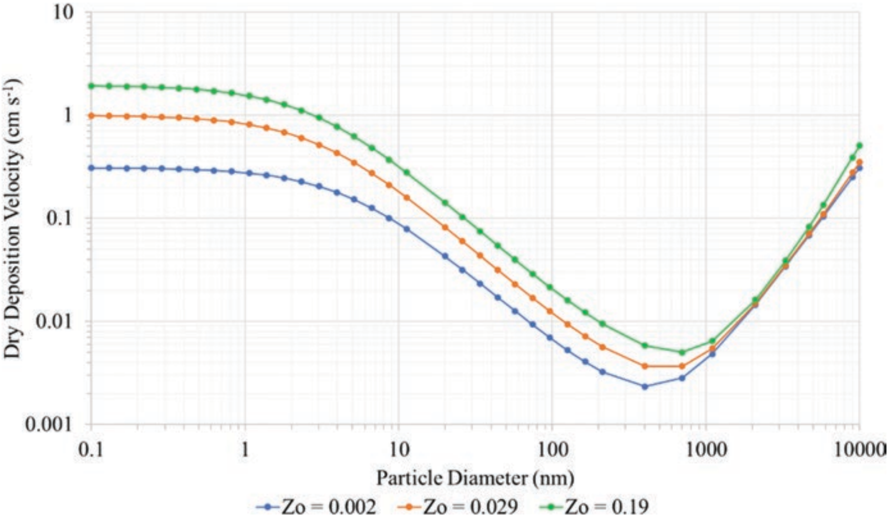

Fig. 21.4 Dry deposition velocity applying Nho-Kim et al.'s (2004) parameterization with a wind speed of 1.0 m s^{-1}.

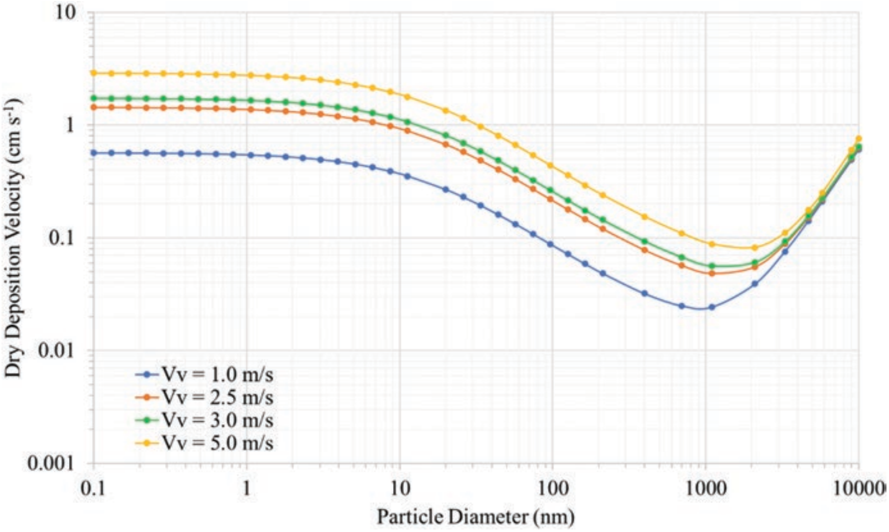

Fig. 21.5 Dry deposition velocity for LUC 7 SC3

the model by Zhang et al. (2001) of 1.0 μm. When we compare the curves of the deposition velocity of the different types of LUC, it is possible to notice that the lowest deposition velocities are obtained for the urban region. Thus, the PM remains longer on the atmosphere in regions of urban areas, consequently, the impact on human health increases.

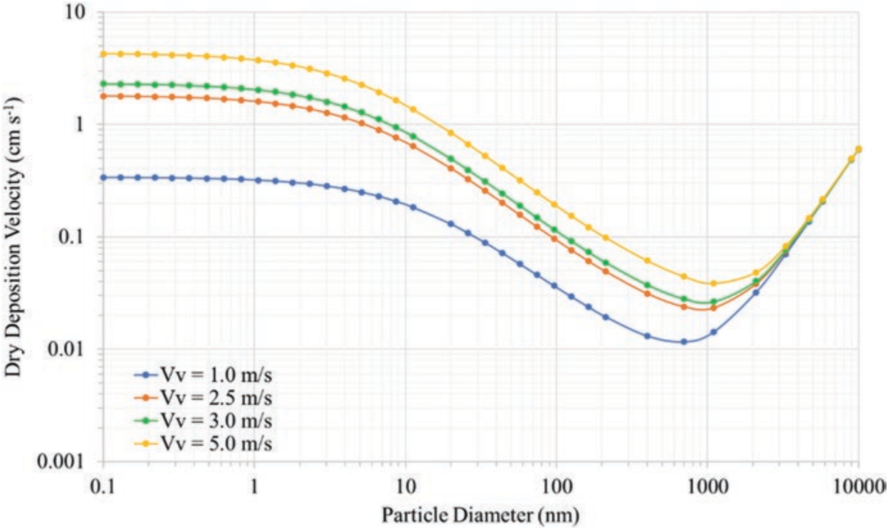

Fig. 21.6 Dry deposition velocity for LUC 15 SC1/SC3/SC5

The monitoring of the PM emission to the atmosphere, both for industrial sources and open burning is very relevant, because, according to the presented data, the most affected regions would be the urban regions, where the air masses pass transporting the PM, since the deposition velocities are smaller in these regions, mainly for particles with diameters between 400 and 1.2 μm, which are harmful to the human health.

The values of deposition velocity are incorporated in Equation (21.2) in the determination of the dry deposition fluxes of the adsorbed ions to the particulate matter. The deposition velocities were calculated referring to the category LUC 7 SC1/SC2, for the respective diameters of cut of each one of the eight stages of the cascade impactor, using the curve of the wind velocity equal to 1.0 m s^{-1}. Tables 21.8–21.10 present the deposition velocities and the deposition fluxes for the respective diameter ranges.

Comparing the obtained results of dry deposition fluxes in this work with the results obtained by Budhavant et al. (2012), the dry deposition fluxes for the potassium ion were smaller for the three analyzed days. The dry deposition flux of the nitrate ion on August 14, 2017 was 10.97 mg m^{-2} s^{-1}, while Budhavant et al. (2012) determined a deposition flux of 4.73 mg m^{-2} s^{-1} for the same ion.

Comparing the deposition fluxes calculated on this work with the results obtained by Rocha et al. (2005), in the period when the open burnings were still allowed in the state of São Paulo, it was observed that the deposition flux of the nitrate and potassium ions calculated for August 14, 2017 were approximately 2 and 9 times higher, respectively. It is worthy to highlight that the deposition flux of these ions was higher even with the open burnings being prohibited and that the sugarcane harvest came in the month of August.

Table 21.8 Dry Deposition Flux for the potassium, nitrate, and sulfate ions for the day March 09, 2017.

Diameter Range (nm)	Dry deposition velocity (m s^{-1})	Dry deposition flux Potassium (mg m^{-2} s^{-1})	Dry deposition flux Nitrate (mg m^{-2} s^{-1})	Dry deposition flux Sulfate (mg m^{-2} s^{-1})
9000–10,000	6.12E-03	3.41E-07	1.02E-06	6.85E-07
5800–9000	5.69E-03	0	1.79E-07	5.92E-08
4700–5800	2.11E-03	2.43E-08	0	1.01E-07
3300–4700	1.42E-03	1.80E-09	2.63E-08	4.37E-08
2100–3300	7.59E-04	1.98E-08	0	4.11E-08
1100–2100	3.90E-04	9.79E-09	0	2.22E-08
700–1100	2.44E-04	1.43E-08	0	2.68E-08
400–700	2.51E-04	1.87E-09	0	6.85E-08
0–400	3.25E-04	1.01E-08	2.06E-08	1.68E-07

Table 21.9 Dry deposition flux for the potassium, nitrate, and sulfate ions for the day August 14, 2017.

Diameter Range (nm)	Dry deposition velocity (m s^{-1})	Dry deposition flux Potassium (mg m^{-2} s^{-1})	Dry deposition flux Nitrate (mg m^{-2} s^{-1})	Dry deposition flux Sulfate (mg m^{-2} s^{-1})
9000–10,000	6.12E-03	0	1.62E-07	0
5800–9000	5.69E-03	0	1.03E-07	0
4700–5800	2.11E-03	0	4.21E-08	0
3300–4700	1.42E-03	0	2.61E-08	0
2100–3300	7.59E-04	1.10E-06	0	0
1100–2100	3.90E-04	3.43E-07	1.27E-04	0
700–1100	2.44E-04	7.93E-07	0	0
400–700	2.51E-04	0	5.42E-09	0
0–400	3.25E-04	0	5.85E-09	0

These data show the possible influence of the biomass burning in the deposition flux of the potassium, nitrate, and sulfate ion in the studied region. The studies of deposition flux are important because from these data it is possible to determine which ions would impact a certain region.

This is because the deposition of these ions in rivers crops and urban areas can alter the concentration of them in these different locations. In the case of rivers, the significative increase of the deposition fluxes of the nitrate and phosphate ions may cause, in the long term, eutrophication.

Table 21.10 Dry deposition flux for the potassium, nitrate, and sulfate ions for the day September 14, 2017.

Diameter Range (nm)	Dry deposition velocity (m s^{-1})	Dry deposition flux Potassium (mg m^{-2} s^{-1})	Dry deposition flux Nitrate (mg m^{-2} s^{-1})	Dry deposition flux Sulfate (mg m^{-2} s^{-1})
9000–10,000	6.12E-03	0	0	0
5800–9000	5.69E-03	1.14E-07	0	0
4700–5800	2.11E-03	3.98E-09	0	0
3300–4700	1.42E-03	0	0	0
2100–3300	7.59E-04	4.81E-08	0	0
1100–2100	3.90E-04	9.80E-09	6.12E-10	0
700–1100	2.44E-04	0	0	0
400–700	2.51E-04	2.12E-08	0	4.37E-07
0–400	3.25E-04	0	3.17E-10	0

8 Conclusions

In the study case, the PM concentrations, the mass mean diameter of the PM, the number of burning foci, the air mass trajectories, the ionic composition of the PM, the curves of deposition velocity, and the deposition flux of the ions during the studied period were analyzed. The results allowed assigning alterations of the chemical composition of the atmosphere and the PM concentrations in the atmosphere of the region to the anthropogenic action, the main one is the biomass burning.

It can be observed that the decreasing of the mass mean diameter of the PM on days with high incidences of burning foci when compared to days when there were fewer foci of burnings. The potassium ion is a tracker of biomass burning and its presence in the stages with cuts diameters smaller than 2.0 μm (PM_1) confirmed that foci of biomass burning in the region had occurred. Besides the potassium, ions of sulfate and nitrate were found in the PM1, thus, confirming the relation between these ions and the biomass burning. The high concentrations of calcium, magnesium, and potassium in the coarse PM indicated that the coarse PM was originated from the resuspension from the ground.

By analysis of the curves of deposition for slowest deposition velocities were obtained for the urban LUC, which means that the PM, mainly the ones with diameters between 400 nm and 1.2 μm, remains longer on the atmosphere and then, the probability of being inhaled increases. Due to the low dry deposition velocity and the high penetrant power of the PM1, its preoccupation with the impacts on human health increased.

Thus, the anthropogenic actions are altering the composition of the soluble ions present in the atmosphere, which may cause an imbalance in the biogeochemical cycles, modifications in the composition of the nutrients present in the ground, and may cause the eutrophication of fountainheads in the long term.

The data on air quality is becoming increasingly available for the world and many studies related to health impacts are also evolving rapidly. The considerable toxicological evidence of potential detrimental effects of particles matter on the environment and human health has been highlighted. Therefore, it is necessary to create and follow stricter air quality standards and laws in each country. The countries must adapt to the current scenario of air quality without exceeding the WHO limits.

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Chapter 22
Biochar-Based Nanocomposites: A Sustainable Solution for Water and Wastewater Treatment

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Contents

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1 Introduction

The widespread problem of increasing water pollution is one of the threats to the environment worldwide. Rapid industrialization accompanied by population growth has damaged the surface waters and also mounted pressure on the water resources. Toxic heavy metals, inorganic compounds, and organic compounds released through runoff have resulted in contamination of water bodies, threatening the health of both human beings and the environment (Sarma et al. 2016, 2017, 2019a). Numerous methods such as coagulation, photocatalytic oxidation, biodegradation, nanofiltration, and adsorption have been devised by the researchers for the treatment of water, wastewater, and microbial product (Sarma et al. 2018, 2019b). Each treatment method has its advantages and limitations governed by factors such as efficiency, stability, and cost-effectiveness (Crini and Lichtfouse 2019). Among all these methods, adsorption is mostly preferred since it is an effective, economic, and environmentally safe method for removing a wide range of contaminants (Awad et al. 2019). Various organic, inorganic, and natural materials like charcoal, clays, zeolites, silica gel, lithium chloride, and activated carbon have been characterized and tried as an adsorbent for removing different contaminants from the water and wastewater (Crini et al. 2018; Lima 2018). In pursuance of reduced the material cost and ameliorate the overall process, the use of inexpensive and waste materials as adsorbents has gained attention fueling the research on low-cost and high-capacity adsorbents that can improve water treatment (Mo et al. 2018).

Biochar, a pyrolyzed product of waste biomass is a carbon rich stable compound and it finds wide applications in various sectors including agriculture, environmental remediation, and climate change mitigation (Cha et al. 2016; Li et al. 2018; Singh et al. 2020). It has emerged as an attractive adsorbent material for the treatment of water and wastewater due to its low cost, abundant availability, and unique physicochemical properties (larger surface area, porosity, and aromaticity) (Xiang et al. 2020). Feedstock composition and pyrolysis conditions play a key role in determining biochar properties and yield (Pandey et al. 2020; Tag et al. 2016). Also, during the process of pyrolysis, there occurs the escape of hydrogen molecules that leads to a negatively charged surface of pristine biochar. This limits its sorption capacity for anionic contaminants (Cho et al. 2017). Furthermore, the separation of used biochar with adsorbed contaminants from aqueous solutions is a challenge that restricts its practical applications. In recent times, the engineering of biochar to alter its structural and physicochemical properties has gained enormous attention. One of the approaches in this context is the development of biochar nanocomposites, a new type of sorbent resulting from the combination of biochar with nanomaterials that are both eco-friendly and cost-effective (Tan et al. 2016). The biochar nanocomposites exhibit excellent sorption properties such as enhanced surface area, improved pore size distribution and pore volume, and more surface functional groups (Deng et al. 2020). Additionally, these also provide a surface capability for catalytic reactions and ease of separation making them a valuable tool for water and wastewater treatment.

2 Biochar Nanocomposites: Properties and Preparation

Biochar nanocomposites consist of nanosized metal oxides particles embedded in the biochar matrix. While the porous biochar provides stable support for a fine distribution of nanomaterial, incorporation of nanomaterial enhances the sorption properties, thermal stability, and ion exchange capacity. Depending on the nanomaterial incorporated in the biochar, the nanocomposite also has a magnetic property that enables the segregation of the used biochar from the effluent. The properties of these composites depend on multiple factors such as biomass type, pyrolysis conditions, and on the nano-material incorporated into the biochar (Huang et al. 2019).

Biochar nanocomposites are developed through three different methods namely biomass pre-pyrolysis treatment method, post-pyrolysis treatment method, and target elements enrichment method as shown in Fig. 22.1 (Tan et al. 2016; Rodriguez et al. 2019).

2.1 Pre-Pyrolysis Treatment Method

In this method, the biomass is pretreated with metal oxide/salts, iron ion, or functional nanoparticles before pyrolysis and nano-material incorporation occurs simultaneously in one step. The biomass is soaked in the solution of desired metal salts over a fixed period that allows the metal ion attachment on the surface or enters into its interior. During the process of pyrolysis, the biomass is converted into char and the attached metal ions get converted to nano-metal oxide/hydroxide, resulting in

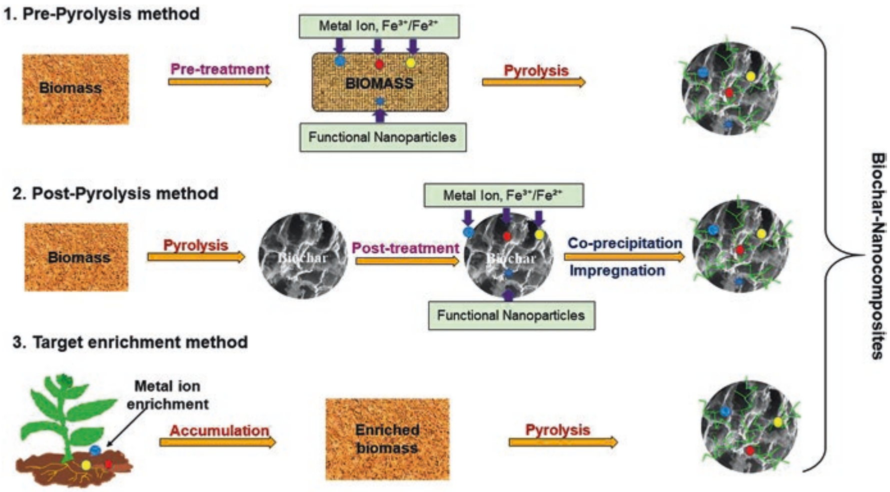

Fig. 22.1 Methods of preparation for biochar nanocomposites

the formation of a biomass matrix with embedded metal ions or biochar nanocomposites (Wei et al. 2018a). Pretreatment with metals also plays role in improving the biochar quality during the pyrolysis (Liu et al. 2013). Fang et al. (2015) synthesized Ca–Mg/biochar nanocomposites with CaO and MgO nanoparticles and abundant organic functional groups by dipping corncob biomass in a solution containing $MgCl_2$ and $CaCl_2$ followed by pyrolysis. In a similar study, pretreatment of ramie biomass with calcium ions produced Ca-impregnated biochar with improved adsorbent properties such as a higher surface area with more functional groups, enhanced hydrogen/carbon ratio, and total pore volume compared with biochar prepared from untreated ramie biomass (Liu et al. 2016). Thermal pyrolysis of $FeCl_2$- and $FeCl_3$-pretreated sludge resulted in the synthesis of magnetic biochar with nano-iron oxide particles that contributed to excellent ferromagnetic properties (Wang et al. 2017). Fe–Biochar composites synthesized from forestry wood waste biochar were successfully used for the removal of toxic contaminants from the highly saline hydraulic fracturing wastewater (Sun et al. 2019). Thus, the pre-pyrolysis method is a simple and scalable process of nanocomposite formation with a single pyrolysis step, which might be influenced by the catalytic activity of metal ions.

2.2 Post-Pyrolysis Treatment Method

In this method, biomass is first converted to biochar followed by metal oxide nanoparticles attachment onto the biochar matrix. The biochar obtained by pyrolyzing the feedstock is soaked in a metal ion solution for the synthesis of biochar nanocomposite (Wei et al. 2018b). The metal oxide particles implanted on the biochar matrix increases the surface area and act as the active sites to bind diverse contaminants from the water and wastewater. Chemical coprecipitation of metal oxides and impregnation of metal ions or functional nanoparticles on biochar is the most commonly used methods to obtain post-pyrolysis synthesis of biochar nanocomposites. Iron oxide nanoparticles onto paper sludge and wheat husks biochar resulted in magnetic biochar composites with a higher surface area and pore volume (Kayan et al. 2017). Magnetic biochar developed by introducing Fe(III)/Fe(II) solutions into mixed biochar displayed enhanced removal capabilities for glyphosate in aqueous solution (Cederlund et al. 2016). Chemical coprecipitation of $MnCl_2.4H_2O$ and $FeCl_3.6H_2O$ solution with pine needle biochar resulted in the development of $MnFe_2O_4$/biochar composite with increased specific surface area and magnetic properties (Lai et al. 2019). Copper oxide-modified biochar nanocomposites prepared by ball milling of CuO particles with Hickory wood chips biochar displayed strong interaction between CuO and biochar in diffraction and spectroscopic analyses of the nanocomposites (Wei et al. 2020). Hence, post-pyrolysis production of nanocomposites can be efficiently achieved in a two-step process by biomass pyrolysis followed by nanometal incorporation through methods of chemical coprecipitation and impregnation.

2.3 Target Elements Enrichment by Bioaccumulation

Apart from the above two methods, scientists have also tested the target element enrichment of the biomass. In this method, the feedstock biomass for biochar production is enriched with target metal elements through bioaccumulation (Yao et al. 2013b). The engineered biomass is then subjected to pyrolysis to derive metal-enriched biochar that can be used for the removal of desired contaminants. Magnesium enriched tomato plants were used to prepare engineered biochar for removal of phosphate from aqueous solution and it was observed that both precipitation and surface deposition mechanism contributed to phosphate adsorption (Yao et al. 2013a). However, this method is less preferred as the plant enriched with metals is left unfit for consumption and can also lead to contamination of the soil (Rodriguez et al. 2019).

3 Types of Biochar Nanocomposites

Biochar nanocomposites have been broadly categorized into three sub-types namely magnetic biochar composites, nanometal oxide/hydroxides–biochar composites and functional nanoparticles coated biochar composites. This categorization is based on the type of nano-material incorporated into the biochar.

3.1 Magnetic Biochar Composites

Impregnation of magnetic material (Fe_3O_4) on biochar surface results in the formation of magnetic biochar composites with excellent magnetic properties and the ability to separate easily from aqueous solutions under a magnetic field using a permanent magnet (Dong et al. 2018). Magnetic biochar is synthesized by pre-pyrolysis activation or post-pyrolysis chemical coprecipitation. Besides the general factors influencing the adsorption mechanism like pH, temperature, and adsorbent dosage, the efficiency of magnetic biochar composites also depends on pyrolysis temperature and the relative amount of raw material to magnetic material (Li et al. 2020b). An increase in pyrolysis temperature from 500 to 750°C resulted in magnetic biochar with increasing congo red dye removal capabilities of up to 94%, while there was a decrease in adsorption capacity of magnetic biochar derived beyond 800°C (Thines et al. 2017). The proportion of magnetic material and raw material used during the impregnation process also affects the adsorption. Mercury removal capacity of magnetic biochar prepared from impregnation in sawdust biochar significantly improved when the impregnation mass ratio of $FeCl_3$ from 0.5 to 1.5, but decreased further (Yang et al. 2016). Adsorption of heavy metal pollutants on magnetic biochar is mediated mainly through electrostatic attraction, surface complexation, ion exchange, and O-containing groups (Li et al. 2020b). Biochar composites composed of siderite and rice husk biochar displayed higher surface area along with impressive magnetic properties (Li et al. 2019). γ-Fe_2O_3–biochar composite derived from banana peels displayed magnetic property and excellent bisphenol A degradation owing to the higher surface area, embedded Fe ions, and numerous oxygen functional groups (Rong et al. 2019). However, magnetic biochar prepared by precipitating Fe_3O_4 on douglas fir biochar surfaces indicated a loss in surface area (Navarathna et al. 2019). Zhang et al. (2020b) prepared biochar-based mesoporous composites from coconut shells using four different iron oxides for phosphate removal from aqueous media and observed changes in the pore structure and an increased number of active sites for phosphate adsorption. Magnetic biochar composites produced by coprecipitation of Fe_3O_4 magnetic nanoparticles with biochar from sewage sludge and woodchips displayed high efficiency in removal of both metal (Cr(VI)) and dye (Acid orange7) from water even after five cycles (Santhosh et al. 2020). Overall, magnetic biochar nanocomposites can be applied for the cost-effective removal of toxic pollutants with ease of separation in presence of an external magnetic field.

3.2 Nanometal Oxide/Hydroxides Biochar Composites

These comprise of biochar with a coating of functional nanoparticles like nanometallic oxides/hydroxide (Song et al. 2014). Nanometal oxide/hydroxide biochar composites can be prepared by enrichment of the target element of the biomass followed by pyrolysis or by dipping the biomass into metal ions solution that attaches metal ions on the surface of biomass and is converted into nanometal hydroxide or metal oxide after pyrolysis. Post-pyrolysis insertion of metal oxide nanoparticles on to the biochar can also be used that results in the formation of biochar nanocomposites with impregnated metal ions and is based on methods of evaporative and heat treatment (Rodriguez et al. 2019). The wide range of nanoparticles embedded in the biochar matrix provides unique properties, such as ferromagnetism, enhanced surface area, porosity, and surface reactive groups, and so on, which increases the adsorption efficiency for contaminants removal. Biochar composites with impregnated cobalt nanoparticles were used for degradation of acetaminophen using peroxymonosulfate (Yang et al. 2019a). Zinc–biochar nanocomposites prepared by pretreating sugarcane bagasse with zinc nitrate solution displayed up to twofold increase in the removal efficiency for Cr(VI) ions as compared to pristine biochar (Gan et al. 2015). Watermelon rind biomass pretreated with $MgCl_2$ using excessive impregnation was pyrolyzed to produce MgO modified watermelon rind biochar with significantly enhanced surface area and Pb removal capacity (Zhang et al. 2020a). Manganese oxide nanoparticles embedded on peanut shell-derived biochar through in situ precipitation technique displayed higher sorption capacity for antimony and copper (Wan et al. 2020). A biochar/AlOOH composite prepared by treating hickory wood chips biochar with aluminum chloride solution showed an increased surface area and strong adsorption ability for phosphorous from wastewater (Zheng et al. 2019). Mn(II)-impregnated biochar particles prepared by treating peanut shell-based biochar with $MnSO_4{\cdot}4H_2O$ solution displayed promising sorption ability for Pb(II) and Cd(II). The oxygen-containing groups in the biochar contribute to nonspecific outer-sphere surface complexation while the impregnated hydrated manganese oxide nanoparticles mediate specific inner-sphere complexation (Wan et al. 2018). Millet bran biochar functionalized with phosphoric acid was treated with hydrated $MnCl_2$ to produce sulfide loaded functional biochar composite via a facile hydrothermal reaction showed excellent removal capacity of aqueous Cd(II) (Fan et al. 2020). Thus, nanometal oxide/hydroxides biochar composites can be developed through all three methods and serve as excellent materials for extended applications through sorption and catalysis.

3.3 Functional Nanoparticles Coated Biochar Composites

These are composites produced by coating the biochar surface with functional nanoparticles such as nanoscale zero-valent iron, chitosan, carbon nanotubes, graphene, and graphene oxide. These hybrid materials offer efficient sorption properties, leading to enhanced sorption of contaminants (Wei et al. 2018b). These are synthesized by prior treatment of biomass with functional nano-materials or post-pyrolysis infusion of functional nanomaterials. In the pre-pyrolysis method, the biomass is mixed with a nanoparticle solution before pyrolysis. Biochar–carbon nanotube composite developed by dip-coating biochar in carbon nanotubes suspension in presence of sodium dodecylbenzenesulfonate prior to pyrolysis and increased the removal of sulfapyridine and lead significantly in comparison of native biochar (Inyang et al. 2015). Chestnut shell biochar supported carbon nanotube composites derived by the pre-pyrolysis method demonstrated higher surface area and porosity and heavy metal removal capacity than the pristine biochar (Yang et al. 2020b). Similarly, biochar derived from sludge and coated with multiwalled carbon nanotube composite improved the sorption properties of the biochar that contributed to increased removal of sulfamethoxazole from water (Ma et al. 2020).

In the post-pyrolysis method, biochar is used to disperse and stabilize engineered nanoparticles like chitosan and zero-valent iron nanoparticles to enhance their reaction activity (Rodriguez et al. 2019). A graphene–biochar composite prepared by the pre-pyrolysis treatment of wheat straw by graphene displayed an increase in surface area and surface functional groups, which increased the adsorption efficiency for removal of phenanthrene and mercury over normal biochar (Tang et al. 2015). Nano zero-valent iron (nZVI)/biochar composites have efficient organic contaminant removal tendency combined with catalytic reduction capabilities. The high surface area and functional active sites on the biochar surface in nZVI/biochar composite enhances mass transfer of organic contaminant while adsorption is governed by four factors including segregation into the organic matrix fraction of the biochar, hydrophobic interactions, electrostatic attraction, and diffusion through the pores of biochar (Wang et al. 2019). Biochar supported zero-valent iron nanoparticles synthesized by treatment of biochar with a mixture of hydrated ferrous sulfate and carboxymethyl cellulose solution significantly enhanced the removal of Cr (VI) and the removal was stable over a wide concentration of carboxymethyl cellulose solution (Zhang et al. 2019). Rice straw pretreated with a graphene solution was used to prepare Fe_3O_4–graphene–biochar composite by chemical coprecipitation of $FeCl_2$ and $FeCl_3$. The obtained composite showed enhanced adsorption capacity for crystal violet dye (Du et al. 2020). Although functional nanoparticles coated biochar composites combine the benefits of biochar and carbonaceous materials, the high cost of materials such as carbon nanotubes and graphene restrict their practical applicability.

4 Application in Treatment of Water and Wastewater

Owing to their excellent physicochemical properties, biochar nanocomposites offer the potential for removal of diverse contaminants ranging from various organic contaminants to different inorganic pollutants from water and wastewater (Fig. 22.2).

4.1 Organic Contaminants

Diverse organic compounds, such as dyes, phenolic compounds, pesticides, and pharmaceuticals are pollutants of the water. These organic contaminants originate from industrial effluents, domestic sewage, agriculture wastewater, and urban runoff. Besides the potential toxicity, their bioaccumulation ability and environmental persistence make them a cause of concern (Kanaujiya et al. 2019; Behera and Prasad 2020). Different types of biochar nanocomposites find application in the removal of these organic contaminants. Various mechanisms are involved in the removal of organic pollutants by the biochar nanocomposites, which include electrostatic interaction, hydrogen bonding, hydrophobic interactions, and π–π interactions.

4.1.1 Dyes

Textile effluents contain a notable amount of recalcitrant organic dyes that are lethal in nature and toxic to plant and aquatic life (Holkar et al. 2016). Biochar nanocomposites have been effectively used as material for the sorption of pollutant dyes. Nanoscale zero-valent iron biochar composite was prepared by the reduction of ferrous iron by borohydride on biochar and used for the removal of acid orange showing 95.2% dye degradation within 10 min (Quan et al. 2014). Removal of methylene blue from contaminated synthetic wastewater was carried out using Fe_2O_3 biochar nanocomposite prepared from pulp and paper sludge. A 1.5 fold rise

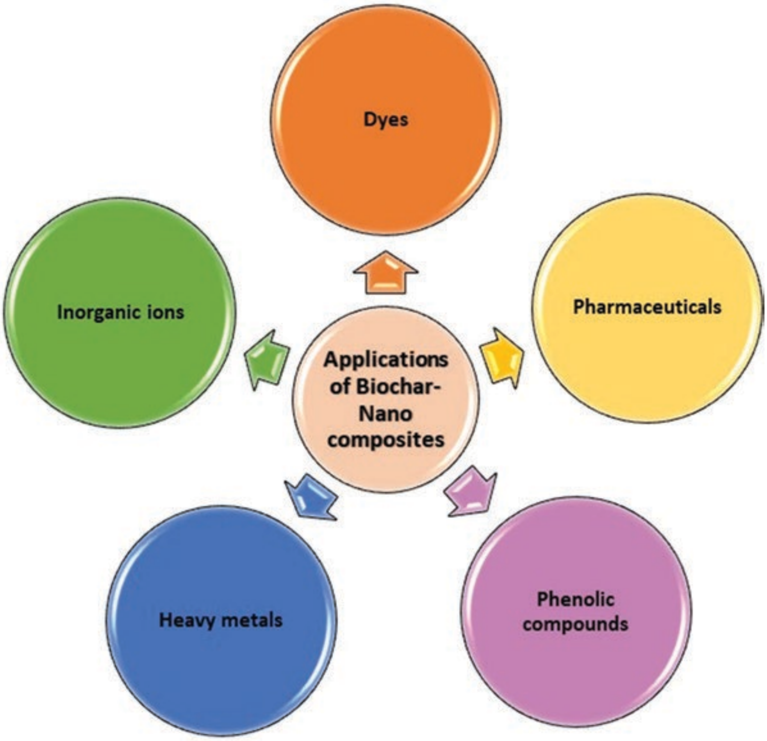

Fig. 22.2 Application of biochar nanocomposites in water and wastewater treatment

in the maximum adsorption capacity of the nanocomposite was observed owing to dual adsorption on the biochar matrix and Fe_2O_3 nanoparticles (Chaukura et al. 2017). Iron oxide–biochar nanocomposite prepared by post-pyrolysis treatment of paper and pulp sludge biochar with $FeCl_3$ solution showed higher adsorption capacity for methyl orange as compared to biochar that shows a weak adsorbent toward anions. In 30 min, 100% methyl orange removal was achieved using 100 mg of Fe_2O_3–biochar while only 30.61% removal was observed with 250 mg biochar (Shumba et al. 2019). Du et al. (2020) prepared a graphene coated biochar by treating rice straw with graphene solution and converted it to Fe_3O_4–graphene–biochar by chemical coprecipitation using $FeCl_2$ and $FeCl_3$. The composite exhibited improved sorption properties that resulted in improved adsorption of crystal violet dye as compared to uncoated graphene biochar. The interaction between aromatic centers of the functional groups played a role in the adsorption mechanism. Ball milling of CuO particles with biochar resulted in the formation of CuO-modified biochar nanocomposites and exhibited excellent adsorption for reactive red dye with a 46% removal efficiency that was much higher as compared to pristine biochar that showed 20% (Wei et al. 2020). Overall, greater surface area and functional reactive groups provided by biochar nanocomposite contribute to increased adsorption sites resulting in efficient removal of dye contaminants.

4.1.2 Pharmaceuticals

Pharmaceutical compounds such as antibiotics, hormones, anti-inflammatory drugs, antidepressants are emerging contaminants that enter into the natural environment through domestic waste, sewage, septic tank, and often directly from pharmaceutical and chemical manufacturing facilities and pose potential risks to both aquatic and human life (Balakrishna et al. 2017). Magnetic biochar composite developed by precipitation of iron oxide nanoparticle on douglas fir biochar was used to remove anti-inflammatory drugs ibuprofen and acetylsalicylic acid. Various interactions such as hydrogen bonding, electrostatic interactions, and dipole–dipole interactions were responsible for the adsorption of studied anti-inflammatory drugs over a wide pH range and adsorption capacities (39.9, and 149.9 mg/g for ibuprofen and acetylsalicylic acid, respectively) (Liyanage et al. 2020). Essandoh et al. (2017) prepared iron oxide–biochar with magnetic properties by treating the switchgrass biochar with an aqueous Fe^{3+}/Fe^{2+} solution followed by NaOH treatment. The adsorption capacity of magnetic biochar was 205 mg/g while that of pristine biochar was 223 mg/g indicating that magnetization of the biochar could be achieved with an insignificant loss of adsorption capacity with a maximum monolayer. Magnetic biochar derived from municipal sludge could achieve removal efficiency up to 86% for antibiotic tetracycline (Zhou et al. 2019). Magnetic biochar nanocomposites prepared from bagasse biochar demonstrated enhanced adsorption capacity for 17β-estradiol of up to 50.24 mg/g (Dong et al. 2018). A graphene oxide coated magnetic citrus peel biochar nanocomposite showed better adsorbent properties with improved thermal stability and efficient removal capability for the selected antibiotics. Adsorption mechanism was governed by multiple mechanisms and adsorption capacity up to 283.44 and 502.37 mg/g was achieved for ciprofloxacin and sparfloxacin, respectively (Zhou et al. 2019). MnO_2–biochar composite prepared from rice husk biochar with manganese dioxide nanoparticles, revealed a remarkable increase in pore volume and specific surface area with increased tetracycline hydrochloride and doxycycline removal capabilities and excellent regeneration ability (Li et al. 2020b). Hence, nanocomposites can carry out the removal of pharmaceuticals compounds in an efficient and cost-effective manner.

4.1.3 Phenolic Compounds

Phenolic compounds with the presence of characteristic phenol units are another class of contaminants that enter water systems through natural, industrial, domestic, and agricultural activities. These compounds have known toxic effects on different life forms and their interaction with other organic and inorganic compounds can produce compounds with worse toxicity (Anku et al. 2017). Removal of various phenolic compounds was performed using rice straw biochar coated with zero-valent iron applied. The biochar surface provided surface area while the inner Fe(0) converted the sorbed contaminants into reductive products. Also, the functional moieties present on the surface of biochar augmented the catalytic electron transfer (Oh et al. 2017). Iron-functionalized biochar composite was prepared by pretreating sawdust and with $FeCl_3 \cdot 6H_2O$ solution, and was used to activate peroxymonosulfate for efficient removal of bisphenol A (Jiang et al. 2019). nZVI/biochar composites derived from rice stalk biochar coated with nanoscale zero-valent iron demonstrated monochlorobenzene removal efficiency of up to 98.8% (Yang et al. 2020a). Magnetic $CuZnFe_2O_4$–biochar composite showed high adsorption of bisphenol A in natural freshwater resources. The adsorption mechanism included hydrogen bonding, hydrophobic interactions, and π–π interactions. The adsorption capacity of Cu–Zn–Fe-loaded biochar was found to be 263.2 mg/g, while that of pristine biochar was 185.2 mg/g owing to enhanced physicochemical properties (Heo et al. 2019). Overall, different types of interactions are involved in the mechanism that play role in the adsorptive removal of phenolics by biochar nanocomposite.

4.2 *Inorganic Contaminants*

Inorganic contaminants consist of ions like nitrate, phosphate, fluoride that occur naturally or have an anthropogenic origin. Excessive concentrations of these inorganic contaminants in an aquatic environment enhances the growth of flora in any receiving waters (Verma and Ratan 2020). Biochar-based nanocomposites have shown the potential to remove inorganic contaminants from water. Magnetic nanocomposites prepared by treatment of douglas fir biochar with $FeCl_3$ was used for the removal of nitrate and fluoride ions from water. The α-Fe_2O_3 and Fe_3O_4 particles dispersed on treated biochar caused magnetization and generated most adsorption sites, with adsorption capacities of 15 mg/g for nitrate and 9 mg/g for fluoride (Dewage et al. 2018). Magnetic nanocomposites developed by coprecipitation of Fe_3O_4 on douglas fir biochar exhibited phosphate adsorption capacity of ~90.0 mg/g from water, which is approximately 20 times higher than that reported for bare magnetite. Adsorption was governed by chemisorption and the electrostatic factors (Karunanayake et al. 2019). Nano zero-valent iron/biochar composite was prepared by treating bagasse biochar with $FeSO_4 \cdot 7H_2O$ and sodium borohydride and used to remove nitrate. The nZVI/biochar was able to remove nitrate efficiently (75.0–97.0%) in a wide pH range (Wei et al. 2018a). MgO coated magnetic biochar composite was made by chemical coprecipitation of Mg^{2+}/Fe^{3+} on biochar prepared from the residue of anaerobic digestion. The composite exhibited Fe_2O_3 nanoparticles deposited onto the surface of biochar. The composite displayed a maximum adsorption capacity of 149.25 mg/g for phosphate governed by mechanisms of physical absorption, surface electrostatic attraction, surface complexation, and precipitation (Liu et al. 2019). Magnesium oxide–biochar composite derived from pretreatment of wood waste with $MgCl_2$ was used to recover inorganic ions (NH^+ and PO_4^{3-}) from human urine. The composite demonstrated high removal capacities of 47.5 and 116.4 mg/g for ammonium and phosphate, respectively. Ammonium removal was facilitated by the precipitation of struvite on the biochar surface while phosphate removal was governed by both surface adsorption and primary precipitation mechanism (Xu et al. 2018). Thus, inorganic contaminants from water can be effectively removed by the use of biochar nanocomposites through mechanisms involving surface complexation, coprecipitation, electrostatic adsorption, precipitation, and ligand exchange.

4.3 Heavy Metals

Heavy metal contamination of water bodies has increased rapidly in the last decades due to increasing industrial activity that discharges a variety of toxic metals (Kamal et al. 2010; Thakare et al. 2021). Solubility of these heavy metals in water makes their contamination a serious concern as these are toxic to both animals and plants when present above permissible concentrations (Mishra et al. 2019). The use of biochar nanocomposites for remediation of heavy metal from water is an upcoming research area. MnO_2–biochar composite derived by MnO_2 modification of swine manure biochar showed an enhanced surface area and pore volume resulting in higher adsorption capacity of up to 268.0 and 45.8 mg/g for Pb^{2+} and Cd^{2+} respectively as compared to 127.75 and 14.41 mg/g for pristine biochar (Liang et al. 2017). Nanoscale zero-valent iron immobilized on biochar derived from sewage sludge could remove up to 90% and 82% of Cr^{6+} and Pb^{2+} respectively from contaminated water within 30 min in a process that occurred as a result of combined effects of adsorption, reduction, and precipitation of both Cr^{6+} and Pb^{2+} over the particles (Diao et al. 2018). MoS_2-modified magnetic biochar prepared by the hydrothermal method was used for the withdrawal of Cd(II) from aqueous systems. The composite had a higher surface area, abundant surface functional groups, and 7.81-fold higher adsorption capacity around than that of pristine biochar (Khan et al. 2020). Humic acid/Fe–Mn oxides-loaded biochar composite synthesized by $Fe(SO_4)_2$ treatment of rice husk biochar exhibited efficient adsorption capacities of up to 67.11 and 35.59 mg/g for Cd(II) and As(V), respectively as compared to 11.06 and 0 mg/g, respectively for pristine biochar. The adsorption mechanisms involved in Cd(II) sorption on the composite was chelation and deposition while As(V) bound through ligand exchange (Guo et al. 2019). Biochar supported nanoscale zerovalent iron prepared from pinewood biomass was effectively utilized to eliminate heavy metals from synthetic stormwater. The nZVI–biochar composite could achieve a 97% and 40% increase in adsorption capacity for Cd^{2+} and Zn^{2+} respectively compared to original biochar. The removal mechanism by biochar–nZVI was governed by chemical reduction and surface complexation (Hasan et al. 2020). Magnetic biochar composite derived from pyrolysis of siderite and rice husk displayed larger specific surface area and porous structures. The composite material displayed strong adsorption (52.63 mg/g) for U(VI) involving simultaneous adsorption and reduction of U(VI) to U(IV) by Fe_3O_4 (Li et al. 2019). Ball milling of micron grade iron powder with biochar resulted in Fe^0–biochar composite. Ball milling enhanced the amalgamation of Fe^0 and biochar and exposed the functional groups of biochar. The composite was used for removal of Cr(VI) and could achieve enhanced removal of up to 97.8% (Wang et al. 2020). Hence, high removal capacities can be achieved for removal of both cationic and anionic heavy metals using biochar nanocomposites involving mechanisms of electrostatic adsorption, coprecipitation, complexation with surface functional groups, and π–π interaction.

Some of the recent developments in biochar-based nanocomposites for water and wastewater treatment along with their applications are presented in Table 22.1.

5 Benefits and Challenges

Incorporation of nanomaterials on biochar has several advantages. The adsorption efficiency of the biochar nanocomposite is enhanced due to the cumulative effect of the individual properties of biochar and nanomaterial. The composites exhibit increased surface area, porosity, functional groups, and thermal stability (Tan et al. 2016). Biochar nanocomposite can adsorb anions from aqueous solutions for which pristine biochar has a low efficiency. Magnetic biochar composites offer adsorptive removal of organic and inorganic pollutants and heavy metals from water (Li et al. 2020c). The functional nanoparticles coated biochar composites enable simultaneous catalytic degradation and adsorption of organic contaminants overcoming the problem of saturation of sorbent due to the accumulation of contaminants. The magnetic property of the composites enables their easy separation from water. The overall cost-effective nature of these biochar derived nanocomposites make them promising adsorbents for treatment.

However, there remain challenges that need to be overcome. Disposal of biochar containing adsorbed contaminants remains a challenge (Dai et al. 2019). Furthermore, there are concerns about the unintentional release of nanomaterials during the use of composites for water treatment that can cause detrimental effects (Kaphle et al. 2018). Moreover, the synthesis of the nanocomposite has to be regulated so that the nanocomposite can be tailored for target contaminants.

6 Conclusion and Future Prospects

Biochar nanocomposites are hybrid materials that offer a synergistic approach of biochar with nanotechnology. With their excellent sorption capabilities and ease of separation, they have great potential to be used for water and wastewater treatment. Nevertheless, their application at the industrial level warrants more information about the knowledge gaps such as the effect of biochar production methods on the properties of composite, stability, and recycling of the composite material.

Table 22.1 Recent developments in biochar nanocomposites for wastewater treatment

Feedstock	Nanomaterial	Pore size dia.	Surface area	Synthesis technique	Target contaminant	Adsorption capacity	References
Water hyacinth	ZnO	4.6 nm	469.6 m^2/g	Post-pyrolysis impregnation	Chromium Cr(VI)	43.48 mg/g	Yu et al. (2018)
Wheat straw	Fe_3O	5.78 nm	114.85 m^2/g	Post-pyrolysis, coprecipitation	N and P (NH_4^+ and PO^{3-})	5.45×10^9 cells/g	He et al. (2017)
Sewage sludge	SBC α-Fe_2O_3 and MSBC α-FeOOH	SBC-13.833 nm MSBC-9.168 nm	SBC-24.21 m^2/g MSBC-34.99 m^2/g	Post-pyrolysis	Ni	Ni adsorption capacity of SBC and MSBC are 20.38 mg/g and 35.50 mg/g	Yang et al. (2019a b)
Corn husks	Fe-loaded	–	PI- 94.9 m^2/g IP- 112.45 m^2/g	Pre- pyrolysis impregnation (PI) and post-pyrolysis impregnation (IP)	Antibiotics tetracycline (TC) and levofloxacin (LEV)	TC adsorption of IP and PI are 102.0 mg/g, 149.1 mg/g. For LEV IP and PI are 56.6 mg/g and 273.7 mg/g	Chen et al. (2019)
Peanut shell	Hydrated MnO	13.8 nm	3.57 m^2/g	Post-pyrolysis impregnation	Pb^{+2} and Cd^{+2}	Pb-67.9 mg/g and Cd-22.3 mg/g	Wan et al. (2018)
Rice husk	MnO_x	2.46 nm	340 m^2/g	Pre- pyrolysis	Pb^{+2}	86.5 mg/g	Faheem et al. (2016)
Quinoa crop biomass	Fe nanoparticle	–	–	Post-pyrolysis	Cr(VI)	77.35 mg/g	Imran et al. (2020)
Watermelon rinds	Fe_3O_4/C	94.860 nm	111.194 m^2/g	Post-pyrolysis	Thallium (I)	1123 mg/g	Li et al. (2020a)
Rice husk	Fe nanoparticle	–	–	Post-pyrolysis coprecipitation	Crystal violet (CV)	185.6 mg/g	Luyen et al. (2020)
Corn straw	MgO–biochar	2.132 nm	273.817 m^2/g	Pre- pyrolysis	Phosphate	60.95 mg P/g	Zhu et al. (2020)
Sewage sludge	$CaCO_3$	3.4 nm	25.6 m^2/g	Post-pyrolysis	Cd(II)	36.5 mg/g	Zuo et al. (2017)

Feedstock	Nanomaterial	Pore size dia.	Surface area	Synthesis technique	Target contaminant	Adsorption capacity	References
Dairy manure	Ca	–	2.6 ± 0.1 m^2/g	Post-pyrolysis impregnation	Phosphate	13.6 mg/g	Choi et al. (2018)
Water hyacinth	Fe_2O_3	–	1038.48 m^2/g	Pre-pyrolysis chemical coprecipitation	Cu^{+2} and Zn^{+2}	First and second-order kinetic parameters for Cu^{+2}–1.41, 3.24 mg/g and Zn^{+2}–7.43, 8.09 mg/g	Nyamunda et al. (2019)

Furthermore, more studies need to be conducted on the specificity of biochar nanocomposites for contaminant removal from real wastewater samples as it will contain a variety of pollutants that might compete with the target pollutant. Simultaneous catalytic degradation and adsorption that is reported in one type of biochar nanocomposites also demand more research in terms of novel composites that can be developed and utilized for catalysis. Additionally, incorporation of multiple nanomaterials can also be tested for a synchronized removal of multiple contaminants. All these issues need to be addressed in future studies to determine the economic feasibility for use of nanobiochar at an industrial scale.

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Correction to: Biobased Nanotechnology for Green Applications

Hemen Sarma, Sanket J. Joshi, Ram Prasad, and Josef Jampilek

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Owing to an error on the part of the editor and corresponding chapter author, the author Hossein Motamedi has been removed from the chapter 7 Biosynthesis of Nanoparticles from Bacteria and Thallophytes: Recent Advances and chapter 9 Microbial Nanotechnology in Life Sciences: An Opportunity for Green Applications. The author list has now been updated by removing Hossein Motamedi in the chapter opening pages, table of contents, and wherever applicable throughout the book.

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