Nanotechnology in the Life Sciences

Ram Prasad *Editor*

Plant Nanobionics

Volume 2
Approaches in Nanoparticles, Biosynthesis, and Toxicity

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Nanotechnology in the Life Sciences

Series Editor

Ram Prasad
School of Environmental Science and Engineering, Sun Yat-sen University,
Guangzhou, China
Amity Institute of Microbial Technology, Amity University,
Uttar Pradesh, Noida, India

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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Editor
Ram Prasad
School of Environmental Science and Engineering
Sun Yat-sen University
Guangzhou, China

Amity Institute of Microbial Technology
Amity University
Uttar Pradesh, Noida, India

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Foreword

The twentieth century has witnessed the exponential growth of world population demanding higher agricultural productivity to feed the increasing population. It is, therefore, required to use the modern technologies which can help agriculture to improve crop productivity as well as revenue. Nanotechnology is considered a perspective shifter which, by manipulating matter at atomic and/or molecular scale, enables us to develop new materials or devices that have unique properties beyond the realm of conventional ones. Among the several branches of nanotechnology, nanobiotechnology is believed to be one of the rapidly developing areas. As nanobiotechnology develops, focus is shifting towards farming that involves the use of nanomaterials to increase food quality, food quantity, plant protection, detection of plant diseases, monitoring plant growth, biosensors for monitoring soil quality, plant biosystems and reduce waste for "sustainable amplification." Hence, we must rethink the uses of nanobiotechnology approaches especially in plant nanobionics.

The present book *Plant Nanobionics: Approaches in Nanoparticles Biosynthesis and Toxicity* is a very timely publication, which intends to provide state-of-art information in the area of nanotechnology, broadly involving plant-based innovation and applications. The book comprises of 16 chapters. The first chapter by Sim et al. reviews on the carbon dots from green precursors with amplified photoluminescence: synthesis, characterization, and its applications in the bioimaging, sensing, photocatalysis, and biomedicine, while the second chapter presented by Lim et al. highlights the preparation, characterization, and application of perovskite oxides-based photocatalysts and applications in environmental remediation to energy conversion. In Chap. 3, García-Rosales et al. describe the use of biogenic material (pineapple peel) with iron nanoparticles for As(V) removal by sorption process. Chapter 4, discussed by R.P. Singh, highlights the biogenic plant-mediated synthesis of iron and iron oxide nanoparticles and their use in the treatment of cancer, drug delivery, MRI agents, catalysis, detection of toxicants/pollutants, and removal of pesticides from potable water. Also, in Chap. 5, he highlights the applications of eco-friendly biogenic copper and copper oxide-nanostructured materials as antimicrobial agent, cytotoxic activity against cancer cell lines, and several biomedical, pharmaceutical, and agricultural systems. Chapter 6 by Enamala et al. throws light on recent advances in plant nanobionics where the engineered nanomaterials are combined with plant organelles with synthetic nanoparticles to enhance the function of plants and various applications. In Chap. 7, Marin-Bustamante et al. carry out an extensive review on the development of nanostructured materials applications in the design of edible films, functional polymers, and smart packaging for its use in the food sector industry. González-Reza et al. in Chap. 8 emphasize polymeric nanoparticles applications in food science. In Chap. 9, Rasool et al. highlight the applications as well as the role of nanomaterials in enhancing future crop production and protection. Djiwanti and Kaushik, in Chap. 10, discuss the promising nanoformulation procedures to be considered as future development of effective, efficient, and safe nanopesticide for plant protection. Hajong et al. describe the potential use of nanomaterials in crop protection for better eco-friendly management against biotic stresses in plants and agricultural practices in Chap. 11. Butnariu and Butu, in Chap. 12, present an overview of applications of nanobiosensors in plant biology. In Chap. 13, Peyravi et al. present an overview of toxicity of nanomaterials in plant and aquatic environments, especially carbon-based and metal/metal oxide nanomaterials. George et al. describe the use of nanocellulose (nanostructure composite material), which could be exploited to its advantage in polymer science as a promising reinforcement candidate due to its intrinsic chemical nature, aspect ratio, and degree of crystallinity, in Chap. 14. Rani et al. present the applications of different inorganic nanomaterials in the field of bioimaging techniques such as magnetic resonance imaging, X-ray computed tomography, positron emission tomography, ultrasound imaging, fluorescence imaging, and photoacoustic imaging in Chap. 15. Finally, Mufamadi and Mulaudzi, in Chap. 16, discuss the potential benefits of green engineered silver nanoparticles in plant protection, food quality, and economic impact for developing countries, especially sub-Saharan Africa.

Overall, it is a great effort by Dr. Ram Prasad as well as by experts from nine countries to make this book a highly resourceful, up-to-date, and worthwhile for the students, researchers, scientists, and academicians working in the field of plant and/or agriculture nanotechnology. I do hope that readers will find this book highly useful and interesting.

Professor Kamal Prasad
University Department of Physics
Tilka Manjhi Bhagalpur University
Bhagalpur, Bihar, India

Biography of Kamal Prasad

Kamal Prasad, Ph.D. is a Professor at the University Department of Physics and Director of Computer Centre, T.M. Bhagalpur University, Bhagalpur, India. He has 25 years of teaching experience in many organizations such as SLIET Longowal (Punjab), Central University of Jharkhand Ranchi, and Aryabhatta Knowledge University Patna – a technical university. Prof. Prasad has successfully guided 12 Ph.D. and 2 M.Tech. students and is working as the Associate Editor of *IET Nanodielectrics* and Editorial Board member of different journals including *Colloids and Surface B*. He has over 150 publications to his credit including 2 books, dozens of book chapters, and 15 X-ray diffraction reference data in JCPDS-ICDD, USA. His current research interests include synthesis and characterizations of eco-friendly ferroelectric/piezoelectric ceramics as well as ceramic-polymer composites and advanced nanomaterials for different industrial applications. He is an active peer of different internationally reckoned journals. He has delivered more than 30 invited lectures in different national and international conferences/workshops.

Preface

The purpose of this book is to describe the state of the art in research on smart nanoparticle synthesis from plants and toxicity effect on environment. This work on nanomaterials and nanotechnologies (herbicides, pesticides, sensors, and nanomaterials, among others) covers the main fields, like plant biology, agriculture, and technological improvements to increase crop yields, with special emphasis on sustainable management and the environmental impacts of nanopesticides.

I am confident that this book provides cutting-edge knowledge on both theoretical and applied features of green synthesis nanoparticles, characterization, formulation, application, and management, as well as the effects of nanoparticles on soil properties and plant characteristics, and some biotic interactions. This book is designed for undergraduate and postgraduate students, researchers, policy-makers, and other professionals in plant biology-/nanotechnology-related disciplines.

The use of plants to synthesize biogenic nanoparticles has been of great interest. Active ingredients in plants can change the oxidation state of metals, and these physiological processes have opened up new opportunities for us to explore novel applications, for example, the biosynthesis of metal nanomaterials. In contrast to chemical and physical methods, green approaches for synthesizing nanomaterials can be achieved in aqueous phase under gentle and environmental-friendly benign conditions. This approach has become an attractive focus in plant nanotechnology research toward resource-efficient and sustainable development. The book covers the synthesis of nanoparticles by plants and the mechanisms involved in such biosynthesis and a unique template for the synthesis of tailored nanoparticles targeted at therapeutics, medicine, agriculture, and biofuel and toward new applications that integrate biological system with nanomaterials to produce biohybrids and the next generation of bionic architectures.

This book should be immensely useful to nanobiotechnology, especially plant biologists, nanotechnologists, researchers, technocrats, and scientists of plant biology and agriculture. I am honored that the leading scientists who have extensive, in-depth experience and expertise in plant systems and nanobiotechnology took the time and effort to develop these outstanding chapters. Each chapter is written by internationally renowned researchers/scientists, so the reader is given an up-to-date and detailed account of our knowledge of the nanobiotechnology and innumerable applications of plant biology.

I wish to thank Eric Stannard, Senior Editor, Springer; Anthony Dunlap, Springer Nature, USA; Rahul Sharma, Project Coordinator, Springer Nature; and Santhamurthy Ramamoorthy Project Manager, SPi Global, for their generous assistance, constant support, and patience in initializing the volume. I give special thanks to my exquisite wife, Dr. Avita, for her constant support and motivations in putting everything together. I in particular am very thankful to Professor Ajit Varma, Amity University, for the constant encouragement. And, I also give special thanks to my esteemed friends and well-wishers and all faculty colleagues of the School of Environmental Science and Engineering, Sun Yat-sen University, China, and AIMT, Amity University, Uttar Pradesh, India.

Guangzhou, China Ram Prasad
Noida, Uttar Pradesh, India

Contents

Contributors

P. Avila-Pérez Instituto Tecnológico de Toluca, Departamento de Posgrado, Metepec, Mexico

Azrina Abd Aziz Faculty of Engineering Technology, Universiti Malaysia Pahang, Kuantan, Pahang, Malaysia

Monica Butnariu Chemistry & Biochemistry Discipline, Banat's University of Agricultural Sciences and Veterinary Medicine "King Michael I of Romania" from Timisoara, Calea Aradului, Timisoara, Romania

Alina Butu National Institute of Research and Development for Biological Sciences, Splaiul Independentei, Bucharest, Romania

R. G. Cásarez-Santiago Instituto Politécnico Nacional, Escuela Nacional de Ciencias Biológicas, Unidad Profesional Adolfo López Mateos, Av. Wilfrido Massieu s/n Instituto Politécnico Nacional, Mexico City, Mexico

J. J. Chanona-Pérez Instituto Politécnico Nacional, Escuela Nacional de Ciencias Biológicas, Unidad Profesional Adolfo López Mateos, Av. Wilfrido Massieu s/n Instituto Politécnico Nacional, Mexico City, Mexico

Murthy Chavali Shree Velagapudi Ramakrishna Memorial College (PG Studies-Autonomous), Acharya Nagarjuna University, Guntur, Andhra Pradesh, India

MCETRC, Guntur, Andhra Pradesh, India

Manashi Debbarma School of Crop Protection, College of Post-Graduate Studies, Central Agricultural University (Imphal), Umiam, Meghalaya, India

Nongthombam Olivia Devi School of Crop Protection, College of Post-Graduate Studies, Central Agricultural University (Imphal), Umiam, Meghalaya, India

P. Divya Sruthi ITC Spices (ITC Agri Business Division), Guntur, Andhra Pradesh, India

Setyowati Retno Djiwanti Indonesian Agency for Agricultural Research and Development (IAARD), Indonesian Spice and Medicinal Crop Research Institute (ISMECRI), Plant Protection Division, West Java, Indonesia

Manoj Kumar Enamala Bioserve Biotechnologies (India) Private Limited, Hyderabad, Telangana, India

Ali Bali Eslami Department of Chemical Engineering, Babol Noshirvani University of Technology, Babol, Iran

G. García-Rosales Instituto Tecnológico de Toluca, Departamento de posgrado, Metepec, Mexico

Benu George School of Biotechnology, National Institute of Technology, Calicut, Kerala, India

Ricardo M. González-Reza Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Departamento de Ingeniería Bioquímica, Mexico City, Mexico

N. Göemes-Vera Instituto de Ciencias Agropecuarias, Universidad Autónoma de Hidalgo (CICyTA), Av. Universidad s/n Rancho Universitario, Tulancingo, Mexico

Monika Hajong School of Crop Protection, College of Post-Graduate Studies, Central Agricultural University (Imphal), Umiam, Meghalaya, India

Humberto Hernández-Sánchez Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Departamento de Ingeniería Bioquímica, Mexico City, Mexico

Mohsen Jahanshahi Department of Chemical Engineering, Babol Noshirvani University of Technology, Babol, Iran

Suresh Kaushik Soil Science and Agricultural Chemistry, Indian Agricultural Research Institute, New Delhi, India

Jia Min Khor Department of Environmental Engineering, Faculty of Engineering and Green Technology, Universiti Tunku Abdul Rahman, Kampar, Perak, Malaysia

Bhulakshmi Kolapalli Prathista Industries Limited, Secunderabad, Telangana, India

Chandrasekhar Kuppam Green Processing, Bioremediation and Alternative Energies (GPBAE) Research Group, Faculty of Environment and Labour Safety, Ton Duc Thang University, Ho Chi Minh City, Vietnam

Nidhi Lal School of Biotechnology, National Institute of Technology, Calicut, Kerala, India

Jie Yet Lee Department of Environmental Engineering, Faculty of Engineering and Green Technology, Universiti Tunku Abdul Rahman, Kampar, Perak, Malaysia

Kah Hon Leong Department of Environmental Engineering, Faculty of Engineering and Green Technology, Universiti Tunku Abdul Rahman, Kampar, Perak, Malaysia

Ping Feng Lim Department of Environmental Engineering, Faculty of Engineering and Green Technology, Universiti Tunku Abdul Rahman, Kampar, Perak, Malaysia

L. C. Longoria-Gándara Division for Latin America/Department of Technical Cooperation International Atomic Energy Agency, Vienna, Austria

C. López-Reyes Instituto Nacional de Investigaciones Nucleares, Ocoyoacac, Mexico

Dipali Majumder School of Crop Protection, College of Post-Graduate Studies, Central Agricultural University (Imphal), Umiam, Meghalaya, India

M. Q. Marin-Bustamante Instituto Politécnico Nacional, Escuela Nacional de Ciencias Biológicas, Unidad Profesional Adolfo López Mateos, Av. Wilfrido Massieu s/n Instituto Politécnico Nacional, Mexico City, Mexico

J. A. Mendoza-Pérez Instituto Politécnico Nacional, Escuela Nacional de Ciencias Biológicas, Unidad Profesional Adolfo López Mateos, Av. Wilfrido Massieu s/n Instituto Politécnico Nacional, Mexico City, Mexico

Majid Peyravi Department of Chemical Engineering, Babol Noshirvani University of Technology, Babol, Iran

Nanotechnology Research Institute, Babol Noshirvani University of Technology, Babol, Iran

Ruma Rani ICAR-National Research Centre on Equines, Hisar, India

Aadil Rasool Department of Bioresources, University of Kashmir, Hazratbal, Srinagar, India

Reiaz Ul Rehman Department of Bioresources, University of Kashmir, Hazratbal, Srinagar, India

C. A. Reséndiz-Mora Instituto Politécnico Nacional, Escuela Nacional de Ciencias Biológicas, Unidad Profesional Adolfo López Mateos, Av. Wilfrido Massieu s/n Instituto Politécnico Nacional, Mexico City, Mexico

L. E. Rojas-Candelas Instituto Politécnico Nacional, Escuela Nacional de Ciencias Biológicas, Unidad Profesional Adolfo López Mateos, Av. Wilfrido Massieu s/n Instituto Politécnico Nacional, Mexico City, Mexico

Pichiah Saravanan Department of Environmental Science and Engineering, Indian Institute of Technology (ISM), Dhanbad, Jharkhand, India

Silpi Sarkar Department of Biotechnology, Vignan University, Guntur, Andhra Pradesh, India

Khushboo Sethi ICAR-National Research Centre on Equines, Hisar, India

Wasifa Hafiz Shah Department of Bioresources, University of Kashmir, Hazratbal, Srinagar, India

Lan Ching Sim Department of Environmental Engineering, Faculty of Engineering and Green Technology, Universiti Tunku Abdul Rahman, Kampar, Perak, Malaysia

Geeta Singh Department of Biomedical Engineering, Deenbandhu Chhotu Ram University of Science and Technology, Sonipat, India

Ravindra Pratap Singh Department of Biotechnology, Indira Gandhi National Tribal University (Central University), Amarkantak, MP, India

T. V. Suchithra School of Biotechnology, National Institute of Technology, Calicut, Kerala, India

Inayatullah Tahir Department of Botany, University of Kashmir, Hazratbal, Srinagar, India

Jun Yan Tai Department of Environmental Engineering, Faculty of Engineering and Green Technology, Universiti Tunku Abdul Rahman, Kampar, Perak, Malaysia

Jing Lin Wong Department of Environmental Engineering, Faculty of Engineering and Green Technology, Universiti Tunku Abdul Rahman, Kampar, Perak, Malaysia

María L. Zambrano-Zaragoza Universidad Nacional Autónoma de México, Facultad de Estudios Superiores Cuautitlán, Laboratorio de Procesos de Transformación y Tecnologías Emergentes de Alimentos, Cuautitlán Izcalli, Mexico

About the Author

Ram Prasad, PhD is associated with Amity Institute of Microbial Technology, Amity University, Uttar Pradesh, India, since 2005. His research interests include applied microbiology, plant-microbe interactions, sustainable agriculture, and nanobiotechnology. He has more than one hundred fifty publications to his credit, including research papers, review articles, and book chapters and five patents issued or pending, and edited or authored several books. He has 12 years of teaching experience and has been awarded the Young Scientist Award (2007) and Prof. J.S. Datta Munshi Gold Medal (2009) by the International Society for Ecological Communications; FSAB Fellowship (2010) by the Society for Applied Biotechnology; the American Cancer Society UICC International Fellowship for Beginning Investigators, USA (2014); Outstanding Scientist Award (2015) in the field of Microbiology by Venus International Foundation; BRICPL Science Investigator Award (ICAABT-2017); and Research Excellence Award (2018). He serves as Editorial Board Member of *Frontiers in Microbiology*, *Frontiers in Nutrition*, and *Academia Journal of Biotechnology* and as Series Editor of Nanotechnology in the Life Sciences, Springer Nature, USA. Previously, Dr. Prasad served as Visiting Assistant Professor, Whiting School of Engineering, Department of Mechanical Engineering, at Johns Hopkins University, USA, and, presently is working as Research Associate Professor at the School of Environmental Sciences and Engineering, Sun Yat-Sen University, Guangzhou, China.

Chapter 1
Carbon Dots Synthesized from Green Precursors with an Amplified Photoluminescence: Synthesis, Characterization, and Its Application

Lan Ching Sim, Jun Yan Tai, Jia Min Khor, Jing Lin Wong, Jie Yet Lee, Kah Hon Leong, Pichiah Saravanan, and Azrina Abd Aziz

Contents

L. C. Sim (✉)
Department of Environmental Engineering, Faculty of Engineering and Green Technology, Universiti Tunku Abdul Rahman, Kampar, Perak, Malaysia
e-mail: simcl@utar.edu.my

J. Y. Tai · J. M. Khor · J. L. Wong · J. Y. Lee · K. H. Leong
Department of Environmental Engineering, Faculty of Engineering and Green Technology, Universiti Tunku Abdul Rahman, Kampar, Perak, Malaysia

P. Saravanan
Department of Environmental Science and Engineering, Indian Institute of Technology (ISM), Dhanbad, Jharkhand, India

A. A. Aziz
Faculty of Engineering Technology, Universiti Malaysia Pahang, Kuantan, Pahang, Malaysia

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1.1 Carbon Dots (CDs)

Recently, carbon- or graphite-based quantum dots have gained growing attention in environmental applications, owing to its unique optoelectronic properties, broadband optical absorption, bright fluorescence emissions, favorable photoinduced electron transfer properties, and cost-effectiveness in synthesis routine (Yan et al. 2016). Accidentally discovered by Xu et al. in 2004 during purification of single-wall carbon nanotubes (SWCNTs) (Xu et al. 2004), carbon dots (CDs) have recently emerged as a new class of semiconductor due to its distinct properties, e.g., excellent photostability, excitation wavelength dependent fluorescence, low toxicity, effective infrared-responded upconverted photoluminescence (UCPL), and tunable fluorescence emission (Essner et al. 2016; Sachdeva and Gopinath 2015; Jelinek 2017). They are known as quasi-spherical shape nanoparticles with sizes below 10 nm that encompass a carbonegic core with surface functional group (Wang et al. 2017). CDs consist of graphitic carbon (sp^2 carbon) and graphene oxide sheets where the diamond-like sp^3-hybridized carbon is present, stabilizing the CDs three-dimensional network (Demchenko and Dekaliuk 2013). The carboxyl groups on the surface of CDs provide great water solubility and enable the advance functionalization with chemically reactive group and surface passivation with organic, inorganic, polymeric, or biological materials to CDs that could enhance fluorescence properties of CDs (Lim et al. 2015; Baker and Baker 2010).

CDs possess excellent fluorescence characteristic and high photostability against photobleaching and blinking which potentially become an alternative to heavy metal-based semiconductor quantum dots (SQDs) currently in use (Wang et al. 2011). Although SQDs like CdSe, CdS, and PbSe were widely used due to their strong photostability, fluorescence, and tunable emission, their high toxicity has raise safety concern of environment and human's health, restricting both biological and environmental application. The differences between CDs and SQDs are that luminescence of CDs emits from the surface, whereas in the latter case, luminescence originates from the core of the nanocrystals (Štěpánková et al. 2015). So by attaching the carboxyl, hydroxyl, and amino groups on the surface of CDs, the optical property and biocompatibility as well as the selectivity and sensitivity could be enhanced. CDs are able to emit PL under near-infrared (NIR) light excitation that given a potential for light energy conversion, photovoltaic devices, and related applications (Wang et al. 2009). The PL intensity of CDs tends to reduce when the pH turns alkaline, making it suitable for cellular imaging (Pandey et al. 2013). CDs are also used as bio-sensing for visual monitoring of glucose, potassium, nucleic acid, copper, and pH (Namdari et al. 2017).

The photoluminescence (PL) of CDs is dependent on quantum effect of nanoparticles with various sizes, emissive traps on the surface of CDs, excitation wavelength (λ_{ex}), or other unknown factors (Wang and Hu 2014; Baker and Baker 2010). The PL of CDs can be efficiently quenched by electron acceptor or donor molecules in solution, indicating that photoexcited CDs exhibit excellent electronic properties as electron donor and acceptor (Zhang and Yu 2015). Besides that, it also can act as an electron mediator, photosensitizer, and spectral converter due to its UCPL property (Wang et al. 2009a). Thus, it is not surprising that the applications of CDs have been extended to photocatalysis of water splitting and removal of organic pollutants in recent years. Nevertheless, the mass fabrication and selection of an appropriate precursor that is low cost, sustainable, high carbon yield, and easily available for long period of time (Zhu et al. 2013) are the main challenges facing by CDs.

1.2 Carbon Dots Synthesized from Green Precursors

Recently, CDs derived from green precursors (green CDs) have gained attention from numerous researchers because of its excellent properties and also environmentally friendly synthesis routine (Yan et al. 2016). The "green precursors" are defined as derivatives of renewable natural products or processes or naturally occurring (Sharma et al. 2017). Green CDs show much more promise in greener and sustainable future development as most of the natural resources can be obtained economically and also synthesized using versatile method (Shen and Liu 2016). In past researches, various chemical precursors such as glucose (Ma et al. 2012), citric acid (Ju et al. 2014; Schneider et al. 2017), ethylene glycol (Wang et al. 2017b), and EDTA (Liu et al. 2017) were widely reported. Since CDs are mainly applied for biomedicine application such as drug delivery, biosensing, bioimaging, and gene transfer, the switch from chemical precursors to "green precursors" is more appropriate. The green precursors can be obtained from natural resources such as sugarcane juice (D'souza et al. 2016; Sim et al. 2018), pomelo peels (Lu et al. 2012), willow bark (Qin et al. 2012), and bagasse (Du et al. 2014) (Fig. 1.1). Hydrothermal carbonization method is widely used to prepare CDs from green materials due to its low cost, nontoxic nature, and environmentally friendly process. The quantum yield (QY) of CDs is based on the type of green precursors and preparation method used, as shown in Table 1.1.

Nitrogen doping in CDs has been reported recently to increase the QY and to improve the intrinsic low emission efficiency. Liu et al. (2012) successfully increased the QY of grass-derived CDs from 2.5% to 6.2% after doping with nitrogen. One-pot hydrothermal carbonization method was used by Liao et al. (2016) to produce water-soluble nitrogen-doped CDs (N-CDs) from the mixture of natural peach gum polysaccharide (PGP) and ethylenediamine. The QY of N-CDs was enhanced from 5.31% to 28.46% after surface passivation of CDs with nitrogen (Liao et al. 2016). Ethylenediamine was also used as a nitrogen source to produce N-CDs from onion wastes (Bandi et al. 2016) with QY of 28%. Liu et al. (2017a)

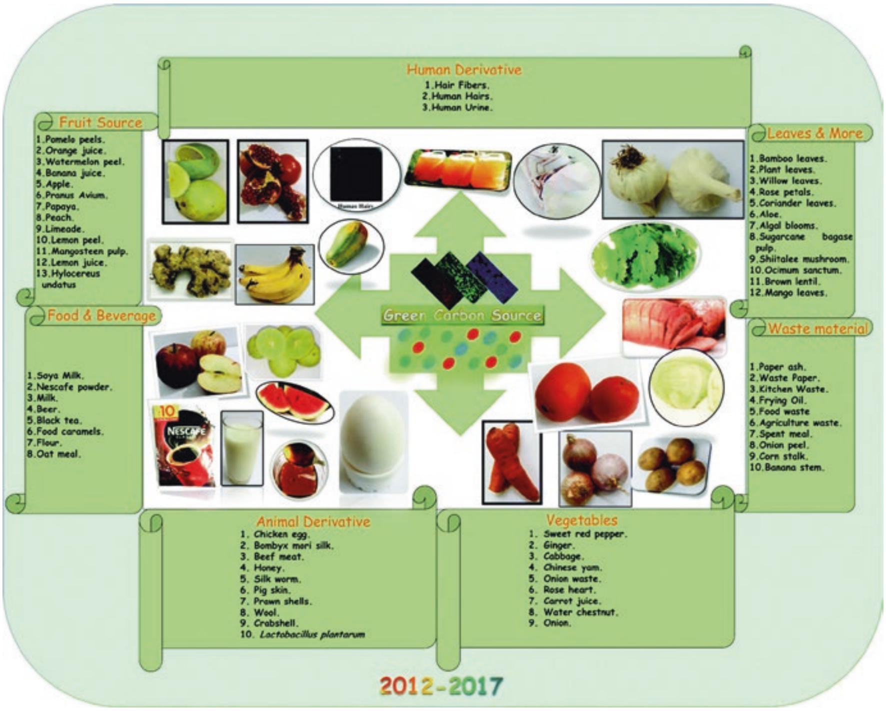

Fig. 1.1 Green precursors used to produce CDs. (From Sharma et al. 2017)

used ammonia as nitrogen source to dope CDs derived from rose-heart radish and achieved a QY of 13.6%. Ding et al. (2017) used pulp-free lemon juice as intrinsic nitrogen source to prepare CDs with high QY (28%) and intense red luminescence. High-protein sources such as milk (Wang and Zhou 2014), chicken egg (Wang et al. 2012), oatmeal (Yu et al. 2015), hair (Guo et al. 2016), etc. were used as intrinsic nitrogen sources for the self-passivation of CDs. Among these intrinsic sources, oatmeal successfully produced N-CDs with the highest QY (37.4%) due to the highest N/C ratio prepared at 200 °C (Yu et al. 2015). Besides N-doping of CDs, other researchers also produced the nitrogen- and sulfur-co-doped CDs (N-S-CDs). Sun et al. (2013) developed a large-scale synthesis of N-S-CDs by using sulfuric acid carbonization and etching of hair fiber. They claimed that higher reaction temperature at 140 °C was favorable to form N-S-CDs with smaller size, higher S content, and longer wavelength of photoluminescence emissions. A greener method was reported by Zhao et al. (2015), where N-S-CDs were prepared using garlic as intrinsic source for N and S doping without using harmful chemicals like sulfuric acid as sulfur source. The obtained CDs possess good water dispersibility and quantum yield of 17.5%.

Table 1.1 Synthetic method and quantum yield of different precursors

Precursor	Synthetic method	Quantum yield (%)	Particle size (nm)	References
Orange juice	Hydrothermal treatment at 120 °C	26	1.5–4.5	Sahu et al. (2012)
Strawberry juice	Hydrothermal treatment at 120 °C	6.3	5.2	Huang et al. (2013)
Sugarcane juice	Hydrothermal treatment at 120 °C	5.76	3	Mehta et al. (2014)
[a]Grass	Hydrothermal treatment at 150–200 °C	2.5–6.2	3–5	Liu et al. (2012)
Orange peels	Hydrothermal 180 °C for 12 h.	36	2–7	Prasannan and Imae (2013)
Waste paper	Hydrothermal with urea, 150 °C for 50 min	–	–	Fadllan et al. (2017)
Papaya juice	Hydrothermal 150 °C for 12 h.	7	3	Kasibabu et al. (2015)
Tulsi leaves	Hydrothermal 180 °C for 4 h	9.3	4–7	Kumar et al. (2017)
[a]Milk	Hydrothermal treatment at 180 °C	12	2–4	Wang and Zhou (2014)
Hair	Carbonization at 200 °C	10.75	2–8	Guo et al. (2016)
Coriander leaves	Hydrothermal treatment at 240 °C	6.48	4.1	Sachdeva and Gopinath (2015)
Sweet potatoes	Hydrothermal treatment at 180 °C	2.8	1–3	Lu et al. (2013)
Pomelo peels	Hydrothermal treatment at 200 °C	6.9	2–4	Lu et al. (2012)
Cabbage	Hydrothermal treatment at 140 °C	16.5	2–6	Alam et al. (2015)
Willow bark	Hydrothermal treatment at 200 °C	6	5–25	Qin et al. (2012)
[a]Oatmeal	Hydrothermal treatment at 200 °C	37.4	20–40	Yu et al. (2015)
Bagasse	Hydrothermal treatment at 180 °C	9.3	12.3	Du et al. (2014)
[a]Soy milk	Hydrothermal treatment at 180 °C	2.6	–	Zhu et al. (2012)
Banana juice	Heating in oven at 150 °C for 4 h	8.95	3	De and Karak (2013)
Apple juice	Hydrothermal treatment at 150 °C	4.27	4.5	Mehta et al. (2015)
[a]Peach gum	One-pot hydrothermal carbonization of the mixture of natural peach gum polysaccharide (PGP) and ethylenediamine	28.46	2–5	Liao et al. (2016)

(continued)

Table 1.1 (continued)

Precursor	Synthetic method	Quantum yield (%)	Particle size (nm)	References
[a]Lemon juice	Hydrothermal treatment at 190 °C for 10 h	28	4.5	Ding et al. (2017)
[a]Chicken egg	Direct plasma treatment at radio-frequency power of 120 W (voltage = 50 V, current = 2.4 A)	8	2.04–3.39	Wang et al. (2012)
Urine	Carbonization at 200 °C	5.3	10–55	Essner et al. (2016)
[a]Onion	Hydrothermal treatment at 120 °C	28	7–25	Bandi et al. (2016)
[a]Rose-heart radish	Hydrothermal treatment at 180 °C for 3 h	13.6	1.2–6	Liu et al. (2017a)
[b]Hair fiber	Sulfuric acid carbonization and etching of hair fiber	11.1	3.1–7.5	Sun et al. (2013)
[b]Garlic	Hydrothermal treatment at 200 °C for 3 h	17.5	11	Zhao et al. (2015)

[a]CDs doped with nitrogen (N-CDs)
[b]CDs doped with sulfur and nitrogen (N-S-CDs)

1.3 Synthesis

Numerous synthesis approaches of CDs reported can be categorized into two major routes: top-down and bottom-up approaches. CDs can be produced and modified via physical, chemical, or electrochemical techniques during preparation or posttreatment period (Namdari et al. 2017). The unique characteristics of each CDs synthesis method were summarized in Table 1.2. During CDs synthesis, three main issues such as carbonaceous aggregation, size control and uniformity, and surface properties are needed to be addressed to create CDs with optimum properties for various applications (Wang and Hu 2014).

1.4 Top-Down Approaches

The top-down route generally involves the breaking down process of relatively large carbon structures such as activated carbon, carbon nanotubes, carbon soot, graphite, graphite oxide, and nanodiamonds via arc discharge, chemical oxidation, and electrochemical and laser ablation (Xu et al. 2014; Liu et al. 2016). The top-down approaches are typically conducted as their simple operation, and abundant raw materials allowed mass production of CDs. However, these approaches require specific treatments and would produce low yield from graphite source as most graphites have relatively large graphitic structures which are hard to be broken down to

Table 1.2 The unique characteristics of each CDs synthesis method

Approaches	Synthesis techniques	Advantages	Disadvantages	References
Top-down	Arc discharge	High production of low-defect products Environmentally benign	Low quantum yield	Liang et al. (2017), Zuo et al. (2015)
	Electrochemical	Less synthesis reaction time Does not need costly reagents, further surface modification, high temperature, and strong acid	Low quantum yield	Hou et al. (2015)
	Laser ablation	Cheap Convenient Trouble-free	Lower quantum yield Poor control over sizes	Shahidi et al. (2018), Namdari et al. (2017)
Bottom-up	Combustion	Does not use external heating sources Short reaction duration Rapid product cooling process	Requires appropriate raw material for morphology control	Baker and Baker (2010), Hossain and Islam (2013)
	Hydrothermal/ solvothermal	Environmentally friendly Low cost Nontoxic	Required high temperature	Wang and Hu (2014), Hu et al. (2010)
	Microwave irradiation	Cost-effective Energy-conservative Time-saving	Low production	Guo et al. (2017), Wang et al. (2017a)

less than 10 nm in diameter. Dong et al. (2010) found that this drawback can be slightly reduced by altering the carbon source with amorphous carbon form that contained abundant tiny crystalline graphite fragments via a suitable synthesis method. Hence, the discussion of top-down approaches is done to allow better visualization on top-down approaches.

1.4.1 Arc Discharge

Arc discharge approach is a popular method to synthesize carbon nanomaterials due to its high production of low-defect products with environmentally benign properties. The morphologies and productivity of CDs can be controlled with arc satiability and precursor temperature history as they determine the interaction at the anode boundary (Liang et al. 2017). Arora and Sharma (2014) elaborated that the arc discharge process involved the electrical breakdown of a gas to produce plasma by using electric current in alternating or direct current. The generated plasma

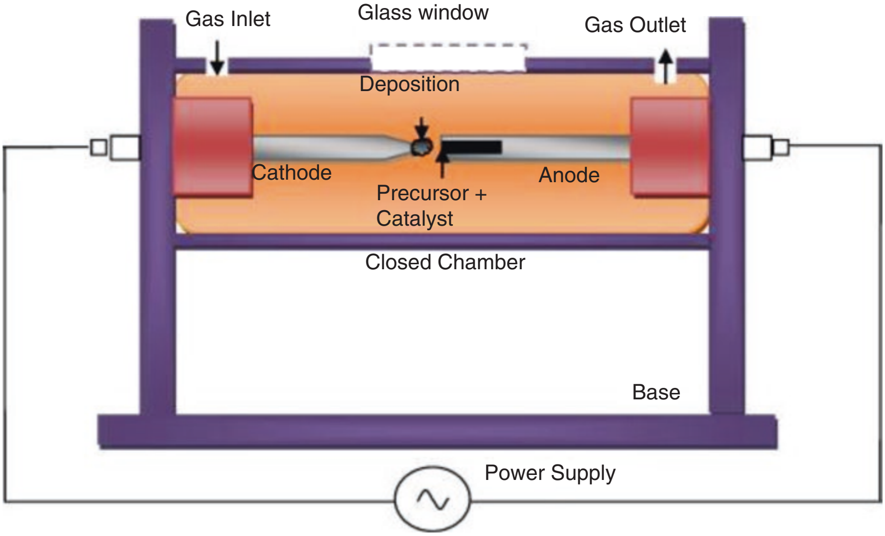

Fig. 1.2 Schematic drawing of an arc discharge setup. (From Arora and Sharma 2014)

(4000–6000 K temperature) with high heat flux or thermal energy would then sublime the bulk carbon precursor to create carbon vapors. Next, the carbon vapors would undergo phase change and transform into liquid at cooler temperature. Figure 1.2 shows the schematic drawing of an arc discharge setup. Xu et al. (2014) discovered the production of stable black and crude suspension with arc-discharge soot oxidation with nitric acid precursor and sediment extraction with sodium hydroxide aqueous solution. The black suspension separated an average of 18 nm diameter fluorescent CDs after gel electrophoresis purification method. Moreover, Bottini et al. (2006) showed that the blue to yellowish-green fluorescent range CDs were produced via arc discharge from carbon nanotubes. The discovery of argon gas breakdown in a fluid form for CDs production was pioneered by Sun et al. (2016) and allowed the elimination of agglomerated CDs by frequency adjustment. Despite that, CDs yield via arc discharge approach is still low (Zuo et al. 2015).

1.4.2 Electrochemical Carbonization

Electrochemical carbonization method is another widely employed nonselective method in top-bottom approach (Zhao et al. 2008; Ming et al. 2012). Bulk carbons such as carbon nanotubes, carbon fiber electrodes, and graphite are used in the production of carbon quantum dots. Deng et al. (2014) employed a conventional three-electrode system composed of two Pt sheets with a dimension of 4 × 4 cm^2 as working and counter electrode and reference electrode. The reference electrode is a calomel electrode that is mounted on freely adjustable Luggin capillary. The applied voltage in the setup can affect size, carbon content, and UV-vis absorption and brightness of CDs similar with Bao et al.'s (2011) study. Another study done by Li et al. (2010) showed that the electrochemical carbonization synthesis of CDs was assisted by alkali. An alkaline environment played a major factor as it aids in judicious cutting of carbon honeycomb layer into ultrasmall carbon particles due to the presence of hydroxyl (OH^-) group from alkali suspension. Zhou et al. (2007) reported that the structure evolution of bulk carbon changed upon the number of cycles of electrochemical treatment. Multiwalled carbon nanotubes at 100th electrochemical treatment cycles had entangled with curled and swelling features, while 1000th electrochemical treatment cycles had caused serious deformation and tube wall openings. Therefore, the number of electrochemical treatment cycles influenced the active area and surface reaction of CDs. In comparison with other methods, this method reduces synthesis reaction time and does not need costly reagents, further surface modification, high temperature, and strong acid (Hou et al. 2015). However, the quantum yield of CDs is low with electrochemical carbonization (Zuo et al. 2015).

1.4.3 Laser Ablation

According to Shahidi et al. (2018), the laser ablation method is a convenient, cheap, and trouble-free method. This method utilizes pulsed laser with high pulse energy on target surface immersed in a liquid medium for vaporization and flume formation which contains high kinetic energy cluster, as well as atomic and ionic particles (Gondal et al. 2013). The flume would react with the liquid medium to produce CDs. However, the laser ablation in liquid medium required an additional process for common materials and did not utilize the merits of high temperature synthesis (Kazemizadeh et al. 2017). Therefore, the generation of CDs using laser ablation method was done in vacuum method to prevent the problems present in liquid medium. Gonçalves et al. (2010) stated that the laser ablation method was optimized with variation of distance between focusing lens and carbon target. The increased distance between focusing lens and carbon target increased the area of irradiated carbon target and influence which ultimately result to wider size dispersion. Sun et al. (2006) first reported that the produced CDs from laser ablation method in water with argon carrier gas showed bright luminescence upon attaching simple organic species. Simple organic compounds like diamine-terminated oligomeric polyethylene glycol (PEG_{15000N}) were used before acid treated at 120 °C for 72 h. The attachment process allowed surface passivation to occur which resulted to emissive surface energy traps upon stabilization. Kazemizadeh et al. (2017) elaborated that the middle energy levels of CDs caused thermal quenching and prevented elimination of photoluminescence radiation after surface passivation. Quantum confinement of these emissive surface energy traps also played a part as the large surface-to-volume ratio was needed for brighter luminescence. Despite their attractive merits, the laser ablation method was reported to have a lower quantum yield and poor control over sizes (Namdari et al. 2017).

1.5 Bottom-Up Approaches

Alternatively, the bottom-up approaches form selected molecular precursor to "quantum-sized" particles via combustion, hydrothermal/solvothermal, and microwave irradiation methods (Xu et al. 2013). The bottom-up approaches offered great advantages as morphology and size distribution of the product can be precisely controlled for surface passivation. The selection of precursors and synthesis methods in bottom-up approaches is needed to be addressed and discussed.

1.5.1 Combustion

Nersisyan et al. (2017) defined that the combustion technique is a complex process which involves self-sustaining chemical activities with rapid release of heat in the high-temperature reaction front form. The primary factors of the combustion process application in synthesis method are heat, light, and engines. In comparison with other techniques with high temperature, combustion technique does not use external heating sources and has short reaction duration with rapid product cooling process which allowed the production of non-equilibrium products that have unique biological, electrochemical, mechanical, and physical properties. The combustion method used soot-derived sources from candles or natural gas to synthesize CDs (Baker and Baker 2010). Soot carbon was referred to as the carbonaceous aerosol dark component which consisted of pure elemental carbon with highly polymerized organic material by Cachier et al. (1989). Hossain and Islam (2013) stated that the incomplete combustion process created nonuniform size and shape CDs. Incomplete combustion typically occurs when oxygen was insufficient for complete reaction with fuel to produce water (H_2O) and carbon dioxide (CO_2). Incomplete combustion was utilized to produce carbon soot. An example of incomplete combustion of dodecane was shown in the equation below. In reality, actual combustion process produced a wide range of major and minor products such as carbon monoxide (CO) and pure carbon (C).

$$C_{12}H_{26} + O_2 \rightarrow C + CO_2 + CO + H_2O \tag{1.1}$$

This simple and effective synthesis via combustion method was reported by Tian et al. (2009). Combustion soot of natural gas produced 5 nm diameter CDs that exhibited indirect bandgap semiconductor material behavior and electrochemical activities. Another study conducted by Rahy et al. (2012) synthesized CDs by combusting an aromatic compound in a controlled environment of a Pyrex® glass container. The aromatic compounds used are benzene, toluene, and xylene. The morphology of CDs can be controlled by usage of raw materials. Kshirsagar et al. (2017) compared different organic precursor such as almond flames, burnt almond char, clarified butter, and mustard oil for the CDs synthesis. Their study discovered that the saturated fatty acids present in fats or oils contained high percentage of carbon for CDs synthesis. These findings would allow the utilization of food products into CDs synthesis via combustion technique.

1.5.2 Hydrothermal/Solvothermal

Hydrothermal/solvothermal synthesis method is the most widely used bottom-up method as it allowed formation of high pressure and temperature in an autoclave condition to obtain good crystal morphology of CDs (Xu et al. 2013). Hydrothermal method utilized water solvent, whereas solvothermal method used organic solvents such as benzene, dimethylformamide (DMF), or dimethyl sulfoxide (DMSO). These synthesis methods were also reported by Wang and Hu (2014) to be low cost, environmentally friendly, and nontoxic as their precursor used were of chemical or biological origins. Chemical materials such as citric acid and Tris were used in production of CDs as they were relatively cheap and environmentally friendly (Zhou et al. 2015). The citric acid- and Tris-derived CDs exhibited strong fluorescence upon contact with Fe^{3+} ions and hypotoxicity toward living cells. Other chemicals such as ethanol in hydrogen peroxide solution were able to synthesize CDs that were temperature sensitive and able to detect hypochlorite ions at high quantum yield of 38.7% without surface passivation or even heteroatom doping as described in Hu et al.'s (2016) study. The ethanol solution was used as the carbon source as it is the most common and cheap reagent in the laboratory. Similarly, nontoxic and nonimmunogenic polyethylene glycol can act as passivating solvent to produce bright, photostable, and tunable photoluminescence-emitted CDs (Fan et al. 2014). According to Sharma et al. (2017), biological materials used as green precursors for hydrothermal/solvothermal synthesis are fruits, fruit juices, fruit peels, vegetable, spices, plant leaves, beverages, animal, animal and human derivatives, and waste materials. A study by Sim et al. (2018) had reported that the CDs produced using sugarcane juices enhanced the solar photocatalytic performance of g-C_3N_4 upon coupling. Besides that, vegetables such as broccoli were also used to produce CDs that detected Ag^+ ions, as per a study by Arumugam and Kim (2018). *Bombyx mori* silk that was made up of sericin and fibroin was able to produce CDs at hydrothermal condition for cell imaging application as shown in Fig. 1.3 (Wu et al. 2013). CDs can also be synthesized using waste materials like cigarette filters to detect Sudan I dye with a high selectivity and sensitivity (Anmei et al. 2018). Despite hydrothermal/solvothermal advantages, Hu et al. (2010) reported that the hydrothermal/solvothermal method required high temperature in the synthesis method which would create impracticality in large-scale production. The low-temperature hydrothermal/solvothermal method, however, required additional metal ions or templates to produce different morphologies of carbon materials for optimization of their applications.

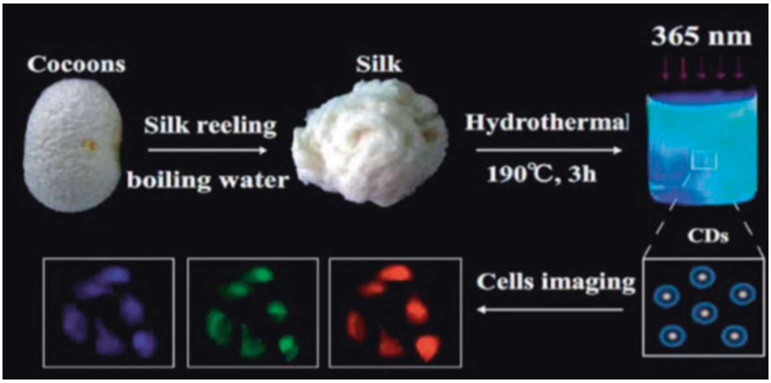

Fig. 1.3 Illustration of CDs formation for *Bombyx mori* silk. (From Wu et al. 2013)

1.5.3 Microwave Irradiation

Guo et al. (2017) stated that microwave irradiation method is an efficient synthesis method as it is time-saving, cost-effective, and energy-conservative. Microwave irradiation is located between infrared irradiation (0.001 m) and radio waves (1 m) in the electromagnetic spectrum. Microwave irradiation had a strong penetrating ability in various mediums and caused charged particle interaction (Zhang et al. 2007). The charged particle interaction changed thermodynamics function by reducing activation energy of materials and weakening the chemical bond intensities. Materials that produce heat after interaction with microwave irradiation are known as microwave absorbers. Carbon was reported to be a good microwave absorber as it generates heat upon contact with microwave irradiation, as per a research by Menéndez et al. (2010). This synthesis method was described to have a faster reaction time as compared with conventional hydrothermal/solvothermal methods (Pham-Truong et al. 2018). L-lysine-derived CDs produced in Choi et al.’s (2017) study had strong blue photoluminescence after 5 min of microwave irradiation. The produced CDs from L-lysine can be used for biological application as it had a 97% cell viability assay with KB and MDCK cells and can be exploited in cellular imaging with successful uptake through endocytosis. In addition, Wang et al. (2011) reported that the CDs produced from graphite oxide had a higher absorption and lifetime of 3.72 ns through microwave heating route. The microwave irradiation allowed materials to grow uniformly as it was able to produce force upon charge particle to move or polarize. Subsequently, the molecular movement would cause friction and collisions and, thus, generate rapid heating which eliminates temperature gradient effect. In another study done by Yang et al. (2015a), CDs produced from folic acid and urea via microwave route had good biocompatibility and cytotoxicity as they distinguished GES-1 normal cell and HeLa cancer cell. However, the present CDs production from microwave irradiation was low as it was less than 40%, and it would significantly hinder the practical application of CDs (Wang et al. 2017a).

1.6 Structural Properties

The surface properties of green precursor-derived CDs are investigated using the X-ray photoelectron spectroscopy (XPS) and Fourier-transform infrared spectroscopy (FTIR). The internal structural properties are analyzed using high-resolution transmission electron microscopy (HRTEM), Raman spectroscopy, and X-ray powder diffraction (XRD).

1.6.1 Surface Properties (XPS and FTIR)

Both XPS and FTIR results can be used to confirm the functional groups in the CDs. Figure 1.4a, b shows the CDs prepared from orange peels consist of various oxygen-containing functional groups such as C=C/C–C, C–OH/C–O–C, C=O, O–C=O, C–O, C=O, and C–OH/C–O–C. The XPS results are consistent with the FTIR spectra (Fig. 1.4c) which detected the C=C stretching of polycyclic aromatic hydrocarbon and carbonyl groups (C=O). Besides, the signals arising from the furan rings of 5-hydroxymethylfurfural and nonaromatic compounds were also detected by nuclear magnetic resonance (NMR) (Prasannan and Imae 2013). For sulfur- and nitrogen-doped CDs (S–N–CDs) derived from hair fiber, Sun et al. (2013) reported the additional existence of $–SO_3^-$, C–N, C–S, N–H, and S–H bonds in FTIR spectra which is in consistence with the XPS spectrum. The presence of –C–S- covalent bond of the thiophene-S is confirmed by the peaks at 163.5 and 164.6 eV, while the pyridinic N and pyrrolic N were observed at 398.5 and 399.7 eV. The N-CDs derived from onion are highly soluble in water and able to serve as linkers for the attachment of biomolecules owing to the presence of different functional groups such as –OH, –COOH, and –NH in N-CDs. The XPS N 1 s spectrum indicated the presence of C–N–C (398.5 eV) and N–H (400.2 eV) bonds in N-CDs which was consistent with –N–H stretching vibrations (3200–3400 cm^{-1}) and C–N stretching vibrations (1340 cm^{-1}) in FTIR spectrum (Bandi et al. 2016).

1.6.2 Internal Structural Properties (HRTEM, Raman, and XRD)

As shown in Table 1.1, the particle size of CDs varies with the type of precursors used to produce the CDs, ranging from 1 to 40 nm. Yu et al. (2015) synthesized oatmeal-derived CDs with larger particle size between 20 and 40 nm with relatively good quantum efficiency of 37.4% (Fig. 1.5a, b). Most of the reported CDs exhibit a broad diffraction peak at 25° with d-spacing ranging from 0.32 to 0.34 nm which is attributed to highly disordered carbon atoms (Zhu et al. 2013; Ding et al. 2017). The shift of diffraction peak to 22.6° and the increase of d value to 0.39 nm

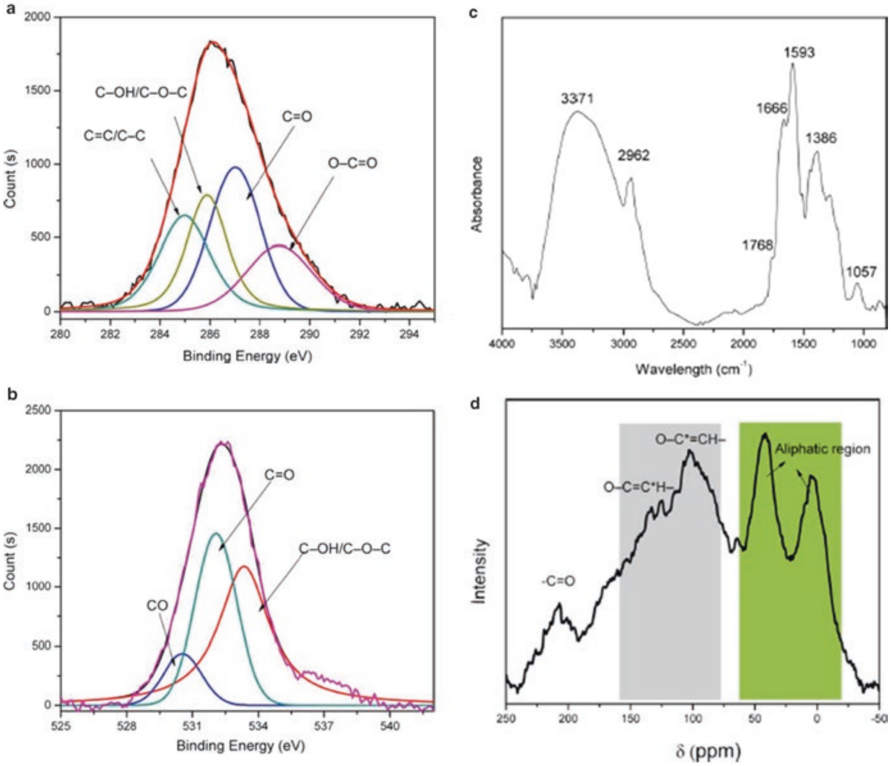

Fig. 1.4 XPS scans (**a**) C1s, (**b**) O1s regions of CDs, (**c**) FTIR spectra of CDs, and (**d**) ^{13}C solid-state NMR spectrum of CDs. (From Prasannan and Imae 2013)

(Fig. 1.5c) suggested the amorphous nature of CDs and the introduction of oxygen functional groups during the synthesis (Yu et al. 2015). Similar results were also reported by other researchers (Alam et al. 2015). The absence of lattices in CDs due to the amorphous nature was also reported by other researchers (Liao et al. 2016; Essner et al. 2016). Nevertheless, lattice spacing of 0.226 nm was observed in N-CDs derived from rose-heart radish, indicating the graphitic nature of N-CDs (Liu et al. 2017a). Alam et al. (2015) found that the lattice spacing of cabbage-derived CDs is 0.21 nm, which corresponds to sp^2 (1120) graphitic crystal phase of graphene. CDs possess several defects which can be observed in Raman spectrum. Two obvious peaks at D band (~1360 cm^{-1}) and G band (~1580 cm^{-1}) (Fig. 1.5d) are attributed to the partially disordered graphite-like structure of sp^3 and sp^2 hybrid carbons, respectively (Li et al. 2013; Yu et al. 2015).

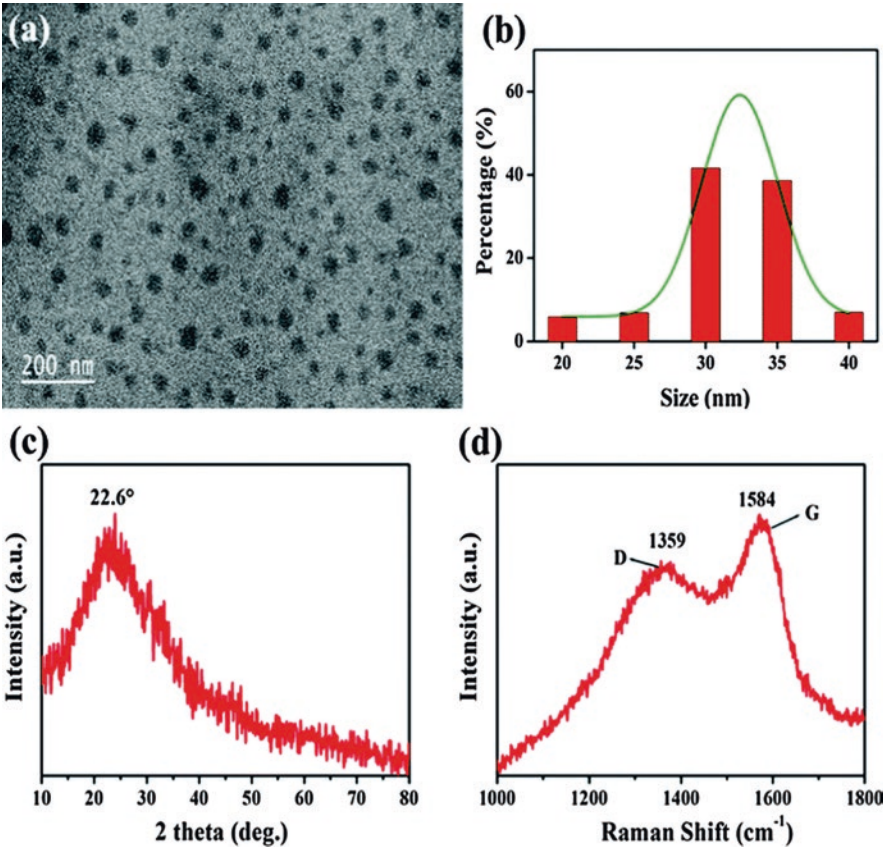

Fig. 1.5 TEM image (**a**), size distribution histogram (**b**), XRD pattern (**c**), and Raman spectrum (**d**) of the CNPs. (From Yu et al. 2015)

1.7 Other Properties

Other properties of CDs such as optical absorption, photoluminescence, upconverted photoluminescence (UCPL) properties, separation of charge carriers, and quantum yield will be discussed in following sections.

1.7.1 Optical Absorption

For coriander leaf-derived CDs solution, Sachdev and Gopinath (2015) observed two absorption peaks at 273 nm and 320 nm which were ascribed to π–π* transition of C=C bonds and n–π* transition of C=O bonds in Fig. 1.6b. Similar observation was reported by earlier researchers (Sachdev et al. 2014; Sachdev et al. 2013; Park

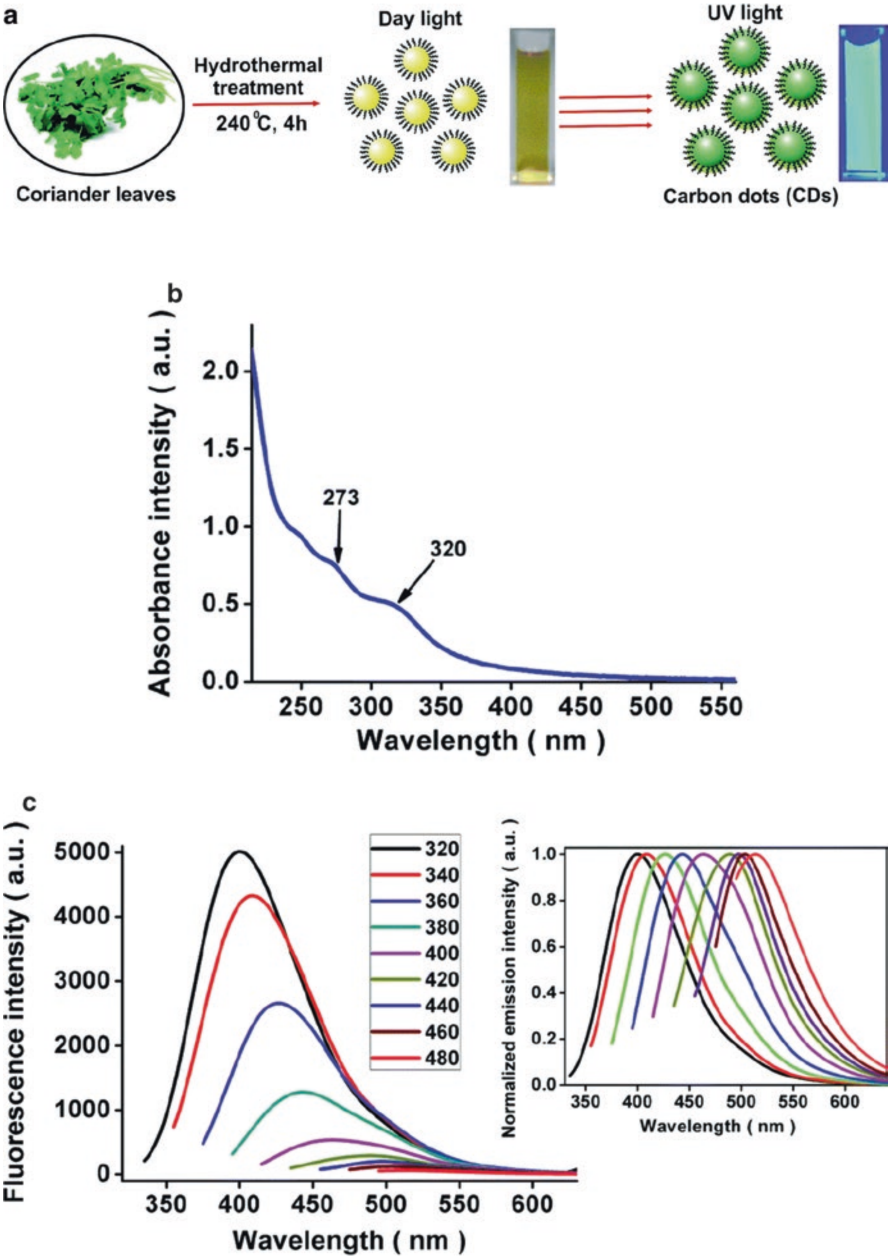

Fig. 1.6 (**a**) Schematic illustration depicting one-step synthesis of CDs from coriander leaves. (**b**) UV-vis absorption spectrum of CDs. (**c**) Fluorescence emission spectra of CDs at different excitation wavelengths ranging from 320 nm to 480 nm with increments of 20 nm (inset: normalized emission intensity). (From Sachdev and Gopinath 2015)

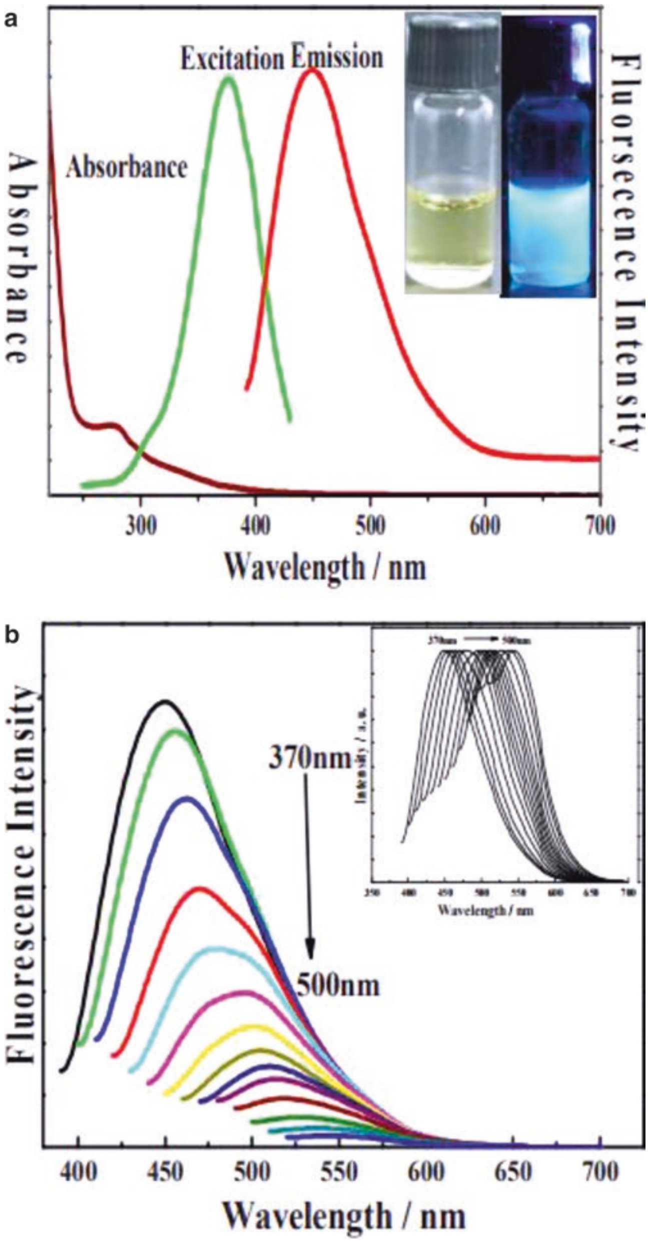

Fig. 1.7 Characteristic optical spectra of CDs. (**a**) UV-vis absorption 10 spectrum and photoluminescent spectra. Inset: photograph taken under daylight (left) and 365 nm UV light (right). (**b**) Emission spectra of CDs recorded for progressively longer excitation wavelength in 10 nm increment from 370 nm to 500 nm. Inset: the normalized PL emission spectra. (From Wu et al. 2013)

et al. 2014). Some researchers observed a maximum absorption peak in the range of 230–278 nm with a tail extending toward the visible region in Fig. 1.7a (Wu et al. 2013; Ramanan et al. 2016; Wei et al. 2014).

1.7.2 Excitation Wavelength-Dependent Fluorescence

The fluorescence emission of CDs depends on the excitation wavelength. Most of the studies show that the maximum emission tends to shift toward higher wavelength with decreasing intensity when the excitation wavelength increases (Figs. 1.6c and 1.7b) (Sachdev and Gopinath 2015; Wu et al. 2013; Liu et al. 2012). This indicates that the emission of CDs could be tuned by altering the excitation wavelength. It was previously reported that the radiative recombinations of the surface-confined electrons and holes contributed to the fluorescence emission of CDs (Cao et al. 2012a; Sk et al. 2014; Zhang et al. 2015). The doping of CDs with nitrogen or sulfur could increase the QY fluorescence due to the formation of new surface states, which trapped the electrons and caused the radiative recombination (Dong et al. 2013). The chemical and electrical structure of CDs is proportionally dependent on the amount of nitrogen and phosphorus doping, thus increasing the fluorescence property of CDs (Zhu et al. 2013). Till now, the origin of the fluorescence of CDs is still not fully understood. Other researchers claimed that this behavior is caused by bond disorder-induced energy gaps (Luo et al. 2009), quantum confinement, and different energy levels associated with surface states arising from the presence of surface functional groups like C-O, C=O, and O=C-OH (Chandra et al. 2012; Bao et al. 2011; Sahu et al. 2012; Li et al. 2011).

1.7.3 Upconverted Photoluminescence (UCPL)

The UCPL properties arise from the multiphotons activation process and cause the simultaneous absorption of two or more photons. Such emission is called anti-Stokes photoluminescence, where the emission wavelength is shorter than the excitation wavelength (Fig. 1.8) (Wang and Hu 2014; Mehta et al. 2014). This feature renders CDs ability to absorb near-infrared light (NIR) and emit UV and visible light which is suitable for the photocatalysis application under sunlight irradiation. A recent work by Sim et al. (2018) found that the sugarcane juice-derived CDs did not exhibit detectable upconversion fluorescence when the excitation wavelength exceeded 540 nm (Fig. 1.9a). Similar results are reported by Wen et al. (2014). They suggested that the frequently obtained UCPL properties could be contributed by the normal fluorescence excited by the leaking component from the second diffraction in the monochromator of the fluorescence spectrophotometer.

1.7.4 Electron Transfer Property

Sim et al. (2018) reported that the incorporation of sugarcane juice-derived CDs into g-C_3N_4 promoted the efficient separation of electron and hole pairs. However, the separation efficiency dropped if the concentration of CDs was excessive

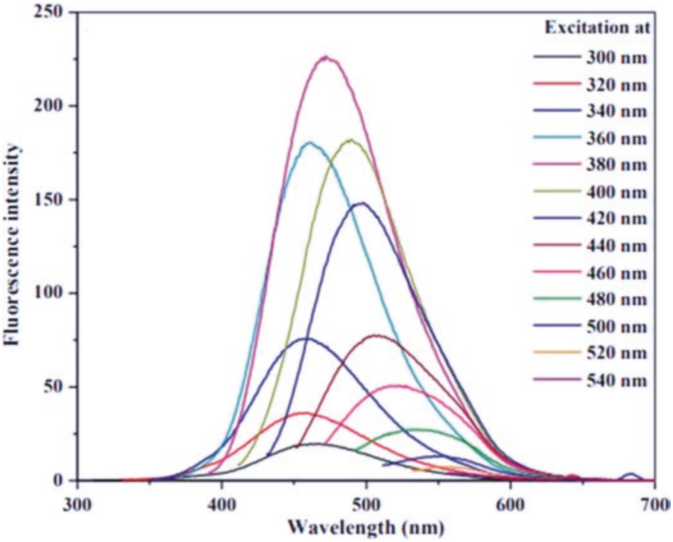

Fig. 1.8 Fluorescence emission spectra of CDs obtained at different excitation wavelengths progressively increasing from 300 nm to 540 nm with a 20 nm increment. (From Mehta et al. 2015)

(Fig. 1.9b). Their work also mentioned that the π-conjugated CDs act as a photosensitizer to sensitize g-C_3N_4 and donate electrons to g-C_3N_4 (Fig. 1.10). The electron transfer property of CDs enables their wide applications in metal ion detection. According to Roshni and Praveen (2017), the electron or energy transfer from CDs surface groups to metal ions like Hg (III) significantly quenched the fluorescence emission of CDs. Such electron transfer process is induced by the presence of hydroxyl and carboxyl or carbonyl groups on the surface of CDs, resulting in the strong binding interaction between the metal ion and these functional groups (Roshni and Praveen 2017; Zhou et al. 2012).

1.8 Applications

CDs have obviously emerged to become an important research field that is still experiencing rapid advances, as reflected by the large number of recent publications. The CDs possess unique features such as tunable fluorescence, easy functionalization, high aqueous solubility, and excellent optical and biological properties which enable their wide applications in different fields. This section summarizes the application of CDs in bioimaging, sensing, photocatalysis, drug delivery, and gene transfer.

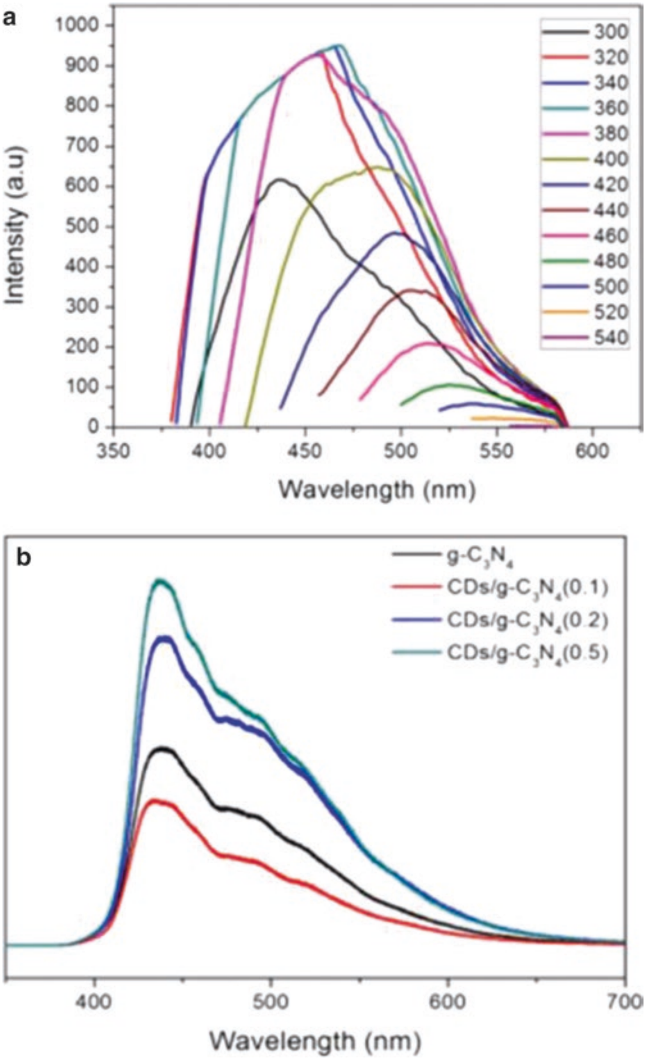

Fig. 1.9 (**a**) The photoluminescence (PL) emission spectrum of CDs at different excitation wavelengths and (**b**) PL spectra of the composites. (From Sim et al. 2018)

1.8.1 *Bioimaging*

Martynenko et al. (2017) defined that the bioimaging process occurred with labeling of target biomolecule with contrast agent via specific biochemical techniques for read-out system detection. An ideal contrast agent is soluble and stable in suitable buffers or biomatrices and has good analytical signal and photophysics data with

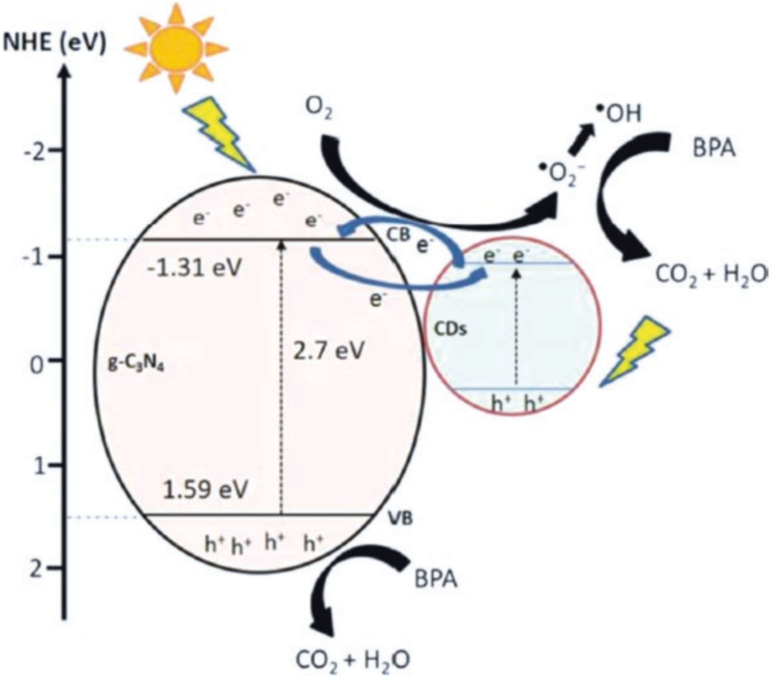

Fig. 1.10 Electron transfer mechanism of CDs/g-C_3N_4. (From Sim et al. 2018)

easy application in practical bioimaging process. CDs were reported to be able to fulfill the requirements as an ideal contrast agent due to their excellent photoluminescence property and biocompatibility to target biomolecule (Peng et al. 2017). The distinctive advantages of CDs in bioimaging such as excellent photostability, multicolor emission profile, and small size were also described by Zhang and Yu (2015). Fluorescent CDs derived from 2-propanol in Angamuthu et al.'s (2018) study showed clear zone of HeLa cell nuclei upon excitation of 488 nm wavelength in confocal microscopy imaging. The 2-propanol-derived CDs also exhibited low cytotoxicity and positive biocompatibility upon HeLa cell incubation which conformed to the advantages of CDs. Another research by Lin et al. (2014) demonstrated that the CDs synthesized from shrimp eggs exhibited blue, green, and red fluorescences at cell membrane and cytoplasm of SK-Hep-1 cells upon delivery for 24 h, shown in Fig. 1.11. The multicolor emission of CDs performed better in bioimaging application compared with traditional fluorescent protein with single fluorescence characteristic. Yang et al.'s (2009) study was able to develop highly fluorescent CDs as prominent contrast agent for optical imaging in vivo for the first time. The PEGylated CDs was injected subcutaneously into female mice and imagined in Lumazone FA in vivo imaging system with 470 nm and 525 nm emission filters. Figure 1.12 shows the intravenous injection of CDs into the mice. It was demonstrated that the fluorescence from CDs was readily detected in urine which

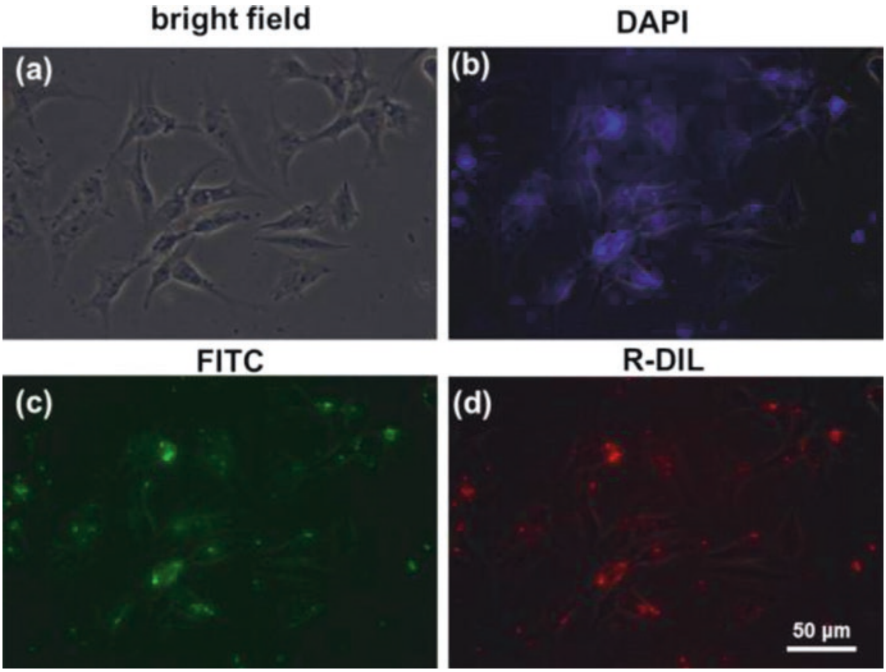

Fig. 1.11 Images of bright-field and fluorescence images of SK-Hep-1 cells treated with CDs derived from shrimp eggs. (From Lin et al. 2014)

suggested urine excretion of CDs from the mice body after 3 h postinjection. This deduced that the CDs would be excreted after injection which reduced its toxicity in the mice. Furthermore, Cao et al. (2012) also confirmed Yang et al. (2009) report of applied CDs in mice for bioimaging. They presented that fluorescence signals of CDs injected in subcutaneous layer of female mice would diffuse and fade slowly within 24 h. The CDs also migrated along the arm of mice with consistent fluorescent emission. Cao et al. (2012) also compared with conventional CdSe/ZnS QDs in bioimaging of mice and discovered that the resulting fluorescence images of both CDs and CdSe/ZnS QDs were similar in brightness and fluorescent quantum yields. However, CDs had a better advantage compared with CdSe/ZnS QDs as it is nontoxic to the mice.

1.8.2 Sensing

Han et al. (2017) stated that the sensing based on fluorescence had received huge attention due to its excellent sensitivity, low cost, and short response time. The fluorescence sensing mechanism involved four different mechanisms such as photoinduced electron transport (PET), resonance energy transfer (RET), photoinduced

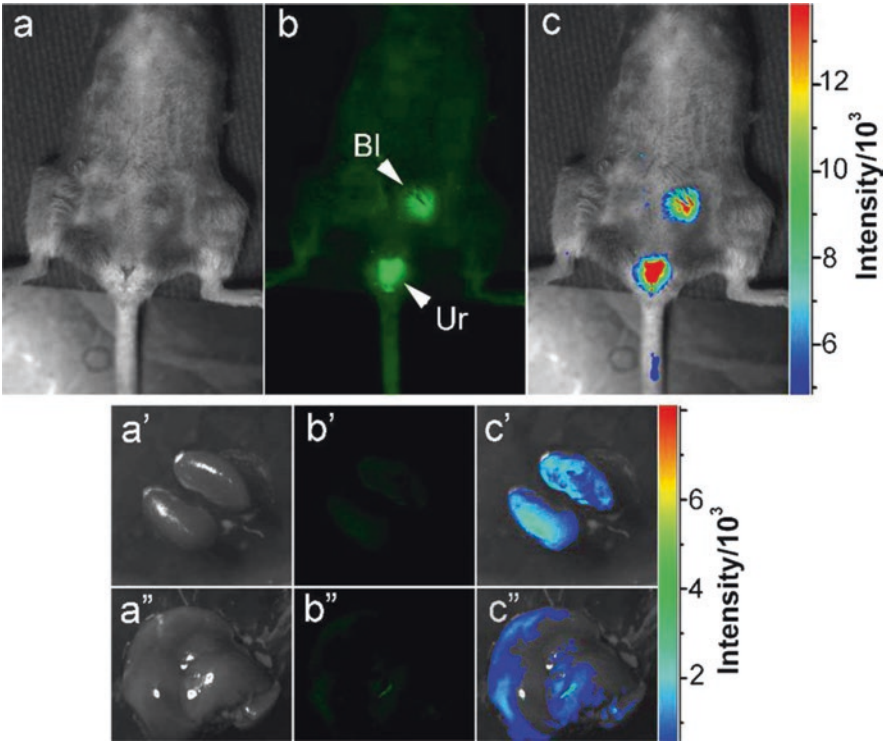

Fig. 1.12 Intravenous injection of (**a**) bright field, (**b**) as-detected fluorescence (Bl (bladder) and Ur (urine)), and (**c**) color-coded images. Similar order for the images of the dissected kidneys at the lower left and liver at lower right. (From Yang et al. 2009)

charge transfer (PCT), and inner filter effect (IFE) (Sun and Lei 2017). The PET process involved the internal redox reaction, while RET used long-range dipolar interaction between excited state of CDs and another species to produce fluorescence emission. In addition, PCT mechanism transfer electrons from electron donor to acceptor in partial charge transfer of fully conjugated π system. The IFE process differed from the rest of the mechanism as this mechanism utilized quenching, which allowed fluorescence lifetime to be independent of total intensity. CDs can be used as an effective sensing agent as it is abundant, benign, and low cost. In comparison with other traditional semiconductor QDs, CDs had higher solubility, chemical inertness, resistance toward photobleaching, and facile modification. Han et al. (2018) described that the synthesized CDs with various functional group were able to detect multiple compounds such as hydrogen peroxide, glutathione, mercury ion (Hg^{2+}), silver ion (Ag^{+}), tetracycline, and enrofloxacin hydrochloride. Furthermore, the fungus-derived CDs were able to recover 105.0% of hyaluronidase in human urine (Yang et al. 2017). Hyalurondase is an enzyme that degraded hyaluronic acid and had been recognized as a new tumor marker type which allowed the fungus-derived CDs to detect tumor in human body. Li et al. (2017) also reported

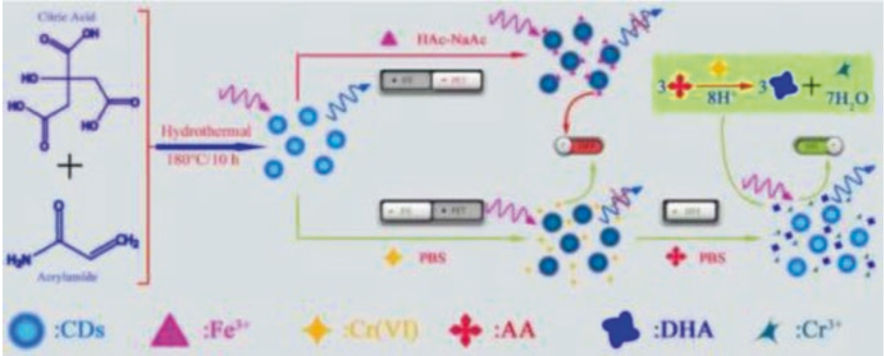

Fig. 1.13 Hydrothermally synthesized CDS in three sensing modes for Fe^{3+}, Cr (VI), and ascorbic acid via different methods including PET, IFE, and elimination IFE mechanism type. (From Li et al. 2017)

hydrothermally synthesized CDs were able to detect iron ion (Fe^{3+}), chromium (Cr(VI)) ion, and ascorbic acid in lake water and industrial water via PET, IFE, and elimination IFE mechanisms. These mechanisms were shown in Fig. 1.13. Fluorescent CDs produced from carnation in Zhong et al. (2016) exhibited colorimetric response from pH ranging from 12.8 to 4.6 and under different light sources of daylight and UV light. The fluorescent CDs that corresponded to the different pH values showed that CDs act as a colorimetric and fluorescent sensor for pH sensing. Hematin that bound to the membrane of red cell and caused any related sickle-cell anemia was sensed by p-aminobenzoic acid-synthesized CDs in human blood sample using IFE (Zhang et al. 2018). Therefore, the CDs were able to distinguish hematin from complex solution and act as good and stable as fluorescence nanoprobe.

1.8.3 Biomedicine (Drug Delivery and Gene Transfer)

The fluorescence property of CDs had allowed the application of biomedicine in targeted drug delivery and gene therapy owing to their aqueous solubility, facile synthesis, and quantum yield (Jaleel and Pramod 2017). Drug delivery significantly determined the therapeutic efficiency and nonproductive distribution of specific treatments. Yuan et al. (2017) detailed that the chemotherapeutics with reduced drug delivery can lead to increase drug dosages and undesirable side effects during treatment. CDs were able to aid the chemotherapeutic treatment as they exhibit superb loading, release, target, and tracking of drug properties. Carrot root-derived CDs were reported by D'souza et al. (2018) to effectively hold and deliver mitomycin drug to cancer cell due to their biocompatibility and ultrasmall size. The green-synthesized CDs acted as optimal drug vehicles by offering excellent selectivity and specificity for mitomycin drug delivery system development. Feng et al. (2016)

described that the modification of single surface property of CDs formed charge-convertible property in mildly acidic tumor extracellular microenvironment at approximately pH 6.8. The CDs with the addition of polyethylene glycol allowed pH-responsive characteristics by changing the charge to negative at normal physiological environment at pH 7.4 and reverse to positive charge at tumor extracellular microenvironment. These properties allowed the CDs to have a prolonged blood circulation time, enhanced permeability and retention (EPR) effect, enhanced tumor cell internalization, less side effects at normal physiological condition, improved endosome escape, and controlled cytotoxic release of cisplatin, an anticancer drug in cancer cell as shown in Fig. 1.14.

Alternatively, the high photoluminescence property allowed the CDs to act as a promising probe for gene therapy. The gene therapy developed gene carriers which were initially done via virus. Viruses were effective transfection vectors but had issues with carcinogenicity, immunogenicity, and ammation. Therefore, CDs were developed to overcome virus limitation as CDs had high transfection efficiency and low toxicity (Yang et al. 2017). Sodium alginate-derived CDs were synthesized and acted as a gene vector for plasmid TGF-β1 delivery in Zhou et al.'s (2016) study. The green CDs were compared with Lipofectamine 2000, branched PEI, and semiconductor QDs in transfection efficiency, and the results showed that the CDs had a higher transfection efficiency due to its low toxicity, small size, positive surface charge, and strong condensation effect on pDNA macromolecule that prevented pDNA enzymolysis. Zhang et al. (2016) stated that the fluorescent CDs with small interfering RNA (siRNA) conjugate were able to deliver 1/30 of siRNA amount in comparative with gold nanoparticles. The fluorescent CDs-based siRNA conjugate

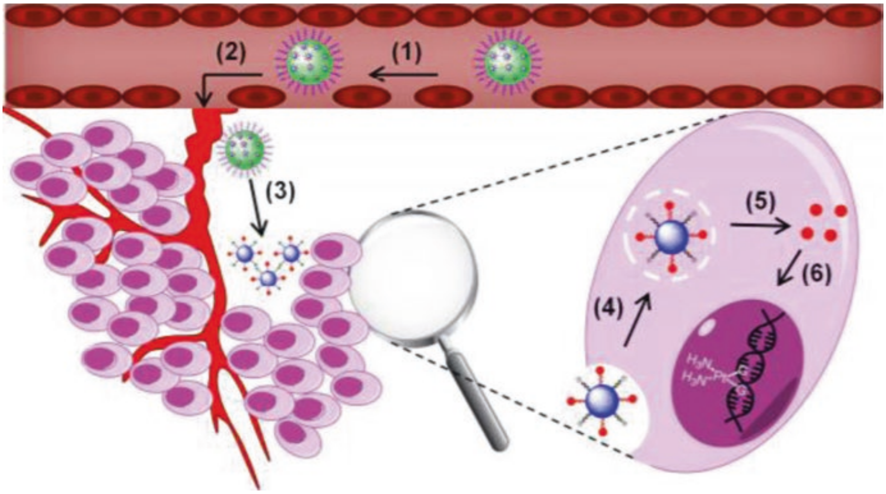

Fig. 1.14 Illustration for the drug delivery process of CDs-modified polyethylene glycol: (1) prolonged blood circulation time, (2) enhanced permeability and retention (EPR) effect, (3) enhanced tumor cell internalization, (4) less side effects at normal physiological condition, (5) improved endosome escape, and (6) controlled cytotoxic release of cisplatin, an anticancer drug in cancer cell. (From Feng et al. 2016)

reduced approximately 80% of A375 cells via cellular Plk1 mRNA treatment which led to induce apoptosis in 31.90% of A375 cells and 20.33% of MCF-7 cells. These apoptosis induction efficiency was higher than commercially available Lipofectamine 200, which further proved the efficiency of CDs-based siRNA conjugate in gene delivery and therapy.

1.8.4 Photocatalysis

Han et al. (2018) described that photocatalysis involved the synergistic effect of light and catalyst during energy conversion material process which degraded contaminates and obtained hydrogen energy. An ideal photocatalyst for photocatalysis process should have a wide light absorption range and high photogenerated charge carrier separation efficiency for enhanced overall quantum efficiency and practical applications. Photocatalysis process can be utilized in water splitting technologies which generate hydrogen generation and pollutant removal remediation methods. CDs were able to produce photogenerated charge carriers under light irradiation and had unique properties of low cost, excellent photoelectric properties, enhanced adsorption capacity, and nontoxic nature. Besides that, CDs were reported by Yu et al. (2016) to be a viable alternative in comparison to the expensive platinum group metal-modified photocatalyst as CDs had an intrinsic bandgap owing to quantum confinement and edge effect which enhanced the separation of photogenerated charge carrier (Lu et al. 2016). As reported by Yang et al. (2015), pure CDs produced without any modification and co-catalyst generated hydrogen from pure water at a higher rate of 34.8 times compared with commercial TiO_2 Degussa P25 when methanol was utilized as the sacrificial reagent. The enhanced photocatalytic ability of pure CDs in water splitting was due to CDs big band gap, low photoluminescence intensity, strong oxidation and reduction potential which ultimately, lowered the recombination rate of photogenerated charge carriers and increased the photocatalytic activities. For optimization of photocatalytic process, the CDs were required to adopt two material design approaches such as the band alignment and interfacial properties manipulation and properties tuning on heteroatom doping, particle size and surface state. The first approach of band alignment manipulation was difficult to be achieved singly as the highest unoccupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) was governed by size and shape factors. Hu et al. (2016) explained that the doping of heteroatom in CDs was able to tailor the charge distribution of CDs surface which facilitate better photogenerated charge carrier separation. The synthesized chlorine (Cl) and phosphorus (P) functionalized CDs showed higher photocatalytic efficiency in methylene blue and methyl orange dye under visible light irradiation. Another study done by Sim et al. (2018) showed that the CDs and graphitic carbon nitride (g-C_3N_4) composite completely degraded Bisphenol A (BPA) pollutant after 90 min under solar irradiation due to its superb visible light absorption capability. The approach of CDs application in photocatalytic treatment of recalcitrant pollutant would prove to be a renewable and sustainable method for future treatments.

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Chapter 2
Perovskite Oxide–Based Photocatalysts for Excellent Visible Light–Driven Photocatalysis and Energy Conversion

Ping Feng Lim, Kah Hon Leong, Lan Ching Sim, Pichiah Saravanan, and Azrina Abd Aziz

Contents

P. F. Lim · K. H. Leong (✉) · L. C. Sim
Department of Environmental Engineering, Faculty of Engineering and Green Technology, Universiti Tunku Abdul Rahman, Kampar, Perak, Malaysia
e-mail: khleong@utar.edu.my

P. Saravanan
Department of Environmental Science and Engineering, Indian Institute of Technology (ISM), Jharkhand, India

A. A. Aziz
Faculty of EngineeringTechnology, Universiti Malaysia Pahang, Kuantan, Pahang, Malaysia

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2.1 Introduction

Perovskite oxides are the class of compounds presenting the general formula ABO_3. Perovskites derive their name from a mineral that has a composition of $CaTiO_3$, were discovered by a Russian geologist Gustav Rose in 1839, and were named after a Russian mineralogist Count Lev Aleksevich von Perovski (Tanaka and Misono 2001). Theoretically, an ideal perovskite oxide structure has a cubic unit cell of side length about 3.9 Å, with space group Pm-3 m and contains one formula unit. Generally, perovskite crystal structure is composed of cations with a large ionic radius having 12 coordination of oxygen atoms and occupy the A sites. Cations with a smaller ionic radius have six coordination of oxygen atoms and occupy the B sites. A corner-sharing network of BO_6 octahedra , with B ion in its center while at the corners of the unit cell, an ion is assigned on a dodecahedral site at the body center of the cube. Oxygen ions are at the middle of the edges, and the schematic structure is shown in Fig. 2.1 (Kanhere and Chen 2014). The perfect connection of octahedral structure will result in a perfect cubic lattice.

The atoms are well arranged and touch one another in a perovskite structure. In an ideal condition, the B–O distance is equivalent to $a/2$, whereas the A–O distance is $\sqrt{2}\left(a/2\right)$ (a = cubic unit cell length). Hence, the relation between the ionic radii can be shown in the following equation:

$$\left(r_A + r_O\right) = \sqrt{2}\left(r_B + r_O\right) \tag{2.1}$$

where r_A is the radius of A-site cation, r_B is the radius of B-site cation, and r_O is the radius of oxygen anion. Even though perovskite crystals are mostly found in cubic structure and retained in ABO_3 compounds, a real perovskite ABO_3 always exhibits

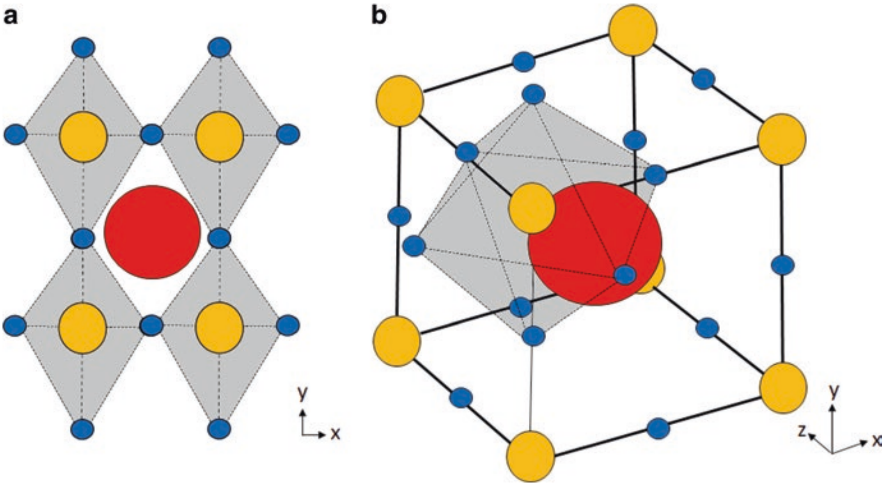


Fig. 2.1 (**a**) BO_6 octahedra, (**b**) crystal structure of simple perovskite oxides with ABO_3 (A-site cation: red; B-site cation: yellow; oxides: blue)

lattice distortion to varying degrees; hence, the abovementioned relation is not exactly obeyed. As a result of the deviation, Victor Moritz Goldschmidt introduced a “tolerance factor,” *t*, defined as an indicator to denote the stability and distortion of perovskite crystal structures. The tolerance factor can be described in the following equation:

$$t = \left(r_{\text{A}} + r_{\text{O}}\right) / \sqrt{2}\left(r_{\text{B}} + r_{\text{O}}\right) \tag{2.2}$$

The tolerance factor is a dimensionless number or unity. A perovskite structure is usually found in lower *t* values ($0.75 < t \leq 1$). In this manner, the transformation of perovskite crystal phases varies in the following sequences: orthogonal, rhombohedral, tetragonal, monoclinic, and triclinic phase, which is mainly dependent on octahedral rotations. Moreover, in a stable perovskite lattice, the limits of cationic radii were set in which $r_{\text{A}} > 0.90^{-}$ and $r_{\text{B}} > 0.51^{-}$ (Verma and Jindal 2011).

Many different cations can be embedded in perovskite structure by virtue of their tolerance factor, allowing the development of diverse engineered materials. Factors such as the ionic radii, electronegativity of A- and B-site cations, and tilting of the BO_6 octahedra may give rise to high or low symmetry crystal structures. Depending on the type of cations occupying the lattice sites, the interactions between A and B sites with oxygen can be varied, and thus different perovskite crystal geometries with different properties can be yielded. The A-site elements in ABO_3 are usually rare earth or alkaline earth metal, and B-site elements are mostly transition metals in the periodic table. Although perovskite has two cation sites, the catalytic activity is mainly determined by the transition metals. Besides, the degree of distortion which correlates with the tilting angle of BO_6 octahedra can determine its crystal fields and results in different electronic and optical properties. In the field of advanced oxidation process, specifically photocatalysis, the performance of photocatalytic activity can be affected by several factors. The mobility of electron–hole within the lattice and electron–hole separation can be influenced by effective separation of electron–hole pairs, excitation lifetime, and excitation binding energy. Distortion in the lattice, defect-induced energy states, and localization of electrons at specific defect sites can determine the production of photoexcited electron–hole pairs. In perovskite oxides, the degrees of tilting can affect the band structure of nanocomposites, electron and holes mobility properties, photoluminescence, redox reaction, and dielectric behavior that influence the entire photocatalytic process. This is due to the fact of valence and vacancy controls of B-site elements, B—O bond length. This is influenced by octahedral rotations and B—O—B angle due to the shift of oxygen ions from the edges of the perovskite structure (Lüders et al. 2014).

2.2 Synthesis Methods of Perovskite Oxides

The synthesis route plays a crucial role in the physical and chemical properties of perovskite oxides. It can be a simple yet comprehensive or complex method, concerning the types of parameters such as precursor, chemicals purity, reaction time, pH, temperature, and pressure. The approach to synthesize perovskite oxides also must be studied in relation to the specific demands of activity and selectivity, both of which depend on the arrangement of atoms within its structure. The all-time challenge is none other than to transform the starting precursor into a highly porous perovskite oxide without segregation of different elements that would contain tiny parts with different properties.

2.2.1 Solid-State Method

Solid-state reaction route is one of the simplest methods to synthesize perovskite oxides. The techniques involved in this conventional method only consist of few simple steps, which are mixing, grinding, or ball-milling the mixed oxides, either in dry or wet slurry, and finally calcinate the mixture at high temperatures of about 600–1000°C. Solids do not react well together at room or low temperature, and thus it is necessary to heat the mixture at high temperature. It is believed that the reaction can be completed once the reaction temperature reaches two-third of the melting point of the solid reactants (Wold and Dwight 2012; Rives 2016). One of the advantages of using this method is that no solid by-products are formed. However, it should be noted that the whole process sometimes needs to be repeated for a few times in order to obtain a complete and pure perovskite oxide. The grinding or milling process is important as the conditions such as rotation area, grinding time, and grinding atmosphere can have a significant effect on the perovskite surface area and catalytic performances (Szabo et al. 2003). However, this process is not suitable in the long run and not so preferable, despite its easy operation.. The onventional method could produce wide grain size distributions and bad homogenous phases, meanwhile rising calcination temperature consumes more energy yet likely to cause agglomeration and shows relatively low surface area (Zhu and Chen 2011).

2.2.2 Coprecipitation Method

Apart from the solid-state method, precursors can be homogeneously mixed if they are prepared in liquid or gaseous phase. Liquid phase precursor is more convenient due to its short-range chemical structure, allowing a better distribution at molecular scale. Moreover, the movement and strength of molecule in the liquid state are of the magnitude of Van der Waals forces or hydrogen bond forces, which are smaller when compared to the diffusion of solids of which loosening the ionic forces or breaking the covalent bonds. Therefore, perovskite oxides synthesized by coprecipitation method can produce fine and homogeneous composites with relatively high specific surface areas. Generally, the metal source containing nitrates, carbonates, and oxalates are most commonly used, while sodium hydroxide (NaOH), potassium hydroxide (KOH), or aqueous ammonia (NH_3) are used as precipitant agents. Selection of precipitant is very important to prevent the negative effect of foreign ions on the synthesized catalyst. The basic steps of coprecipitation method are easily understood whereby precursor mixtures will firstly undergo a nucleation and growth stage, then precipitation occur, followed by filtration of catalyst, and then calcination to finally obtain the desired product. During the nucleation and growth stage, stirring rate and temperature are the two major factors that will affect the formation of the catalyst. However, precipitation points for each perovskite oxides are different; hence, it is difficult to control the stoichiometry and homogeneity of cationic distribution in the grains (Delmon 2007).

2.2.3 Hydrothermal Method

Hydrothermal synthesis can be defined as the method of synthesizing single crystals depending on the solubility of minerals in hot water under high pressure. In the past decade, many studies have been carried out using hydrothermal synthesis and achieved various advancements (Wang et al. 2005). The typical procedure of the hydrothermal method is the addition of precursors and proper agents that are capable of regulating or templating the crystal growth to distilled water with appropriate ratio. The mixture is then transferred into a closed vessel of stainless steel autoclave for the crystallization reaction. The reaction takes place at an elevated temperature, time, and high autogenous pressure. The desired component is formed after the hydrothermal process. Temperature and time play a vital role throughout the process. The crystal size generally increases as a result of Ostwald ripening whereby small particles dissolve faster than the large particles and contribute to the growth of larger crystals. This process usually proceeds until the solubility of the large and small particles are very close to each other. In addition, there is another method similar to hydrothermal synthesis, which is solvothermal synthesis. Both hydrothermal and solvothermal syntheses involve high pressure and temperatures over a prolonged time to get artificially formed crystals. The only difference is the solution used in hydrothermal is water (aqueous) and solvothermal is solvent (non-aqueous) (Li et al. 2016). As for the synthesis of perovskite oxides, different structures can be formed depending on the reactant's nature and ratio, pH, temperature, and time. The main advantage of this method is that heating and pressurizing the system close to critical points can make lots of materials to be soluble in water. Consequently, a number of raw materials are suitable to synthesize the desired products by means of this approach (Rao et al. 2003; Xia et al. 2003; Vayssieres 2004; Wang et al. 2005; Deng et al. 2011).

2.3 Overview of Perovskite Oxides in Photocatalysis

The performance of photocatalytic activity has always being held back by several factors. Properties such as optical absorption and band edge potentials determine the feasibility of photo-induced reactions under light irradiation, electron and holes effective mass, excitation lifetime, electron–hole separation, and mobility within lattice that can strongly influence the efficiency of photocatalytic activity. The defect in lattice and induced energy states and localization of electrons can decide the fate of the photoexcited electron–hole pairs. To date, numerous efforts and time have been dedicated to understand and improve the electronic properties of perovskite oxides, taking into account their band gap energy and unique crystal structure that show excellent potential for efficient photocatalysis. Moreover, perovskite oxide structures provide decent frameworks to tune their band gap values to enable visible light absorption and band edge potentials. The following sections discuss some groups of perovskite oxides that have shown promising photocatalytic activity under visible light irradiation.

2.3.1 Titanium-Based Perovskite Oxides

In the past decade, titanate-based perovskite oxides have been studied for photocatalytic application due to its interesting electronic, optical, magnetic, and photocatalytic properties. Most of the titanate perovskite oxides have wide band gap energy value more than 3.0 eV and show great efficiency of photocatalytic properties only under UV radiation, which account for only a small portion of solar light (Maeda 2011). Using these titanates as host materials, various modifications have been used to alter the optical properties and induce visible light absorption. Moreover, titanates also offer excellent resistance to photocorrosion and high thermal stability, resulting in characterizing them as a promising material for sustainable development (Alammar et al. 2015). Some titanate-based perovskite oxides, which have a more negative energy, enable them to be a suitable candidate for hydrogen generation or water splitting process (Kavan et al. 1996). In the selection of A-site cation of $ATiO_3$, elements such as calcium (Ca), strontium (Sr), barium (Ba), manganese (Mn), iron (Fe), cobalt (Co), nickel (Ni), cadmium (Cd), and lead (Pb) are reported to be showing good visible light–based photocatalysis. Strontium titanate oxide ($SrTiO_3$) and calcium titanate oxide ($CaTiO_3$) are the most common titanate-based perovskite oxides used for research and development. $SrTiO_3$ is a well-known simple cubic perovskite oxide (Pm-3 m, $a = 3.9$ Å) with an indirect band gap of 3.25 eV (Van Benthem et al. 2001). $SrTiO_3$ has been studied extensively as an important n-type semiconductor for its outstanding physical properties (stability, wavelength response, and current voltage response), and its morphology is shown in Fig. 2.2. Its practical applications in various fields such as water splitting (Liu et al. 2006; Guan and Guo 2014), solar cells (Burnside et al. 1999), oxygen gas sensors (Hu et al. 2004, 2005), and photocatalysis prove the stability of this perovskite oxide photocatalyst (Konta et al. 2004; Cao et al. 2011; Huang et al. 2014). On the other hand, $CaTiO_3$ is similar to $SrTiO_3$ with a band gap of 3.6 eV. Many studies have been carried out using $CaTiO_3$ and doping of foreign elements onto it to enhance its photocatalytic activity (Nishimoto et al. 2006; Zhang et al. 2010, 2012). These studies are very useful to give an insight into the photocatalytic activities of the doped system.

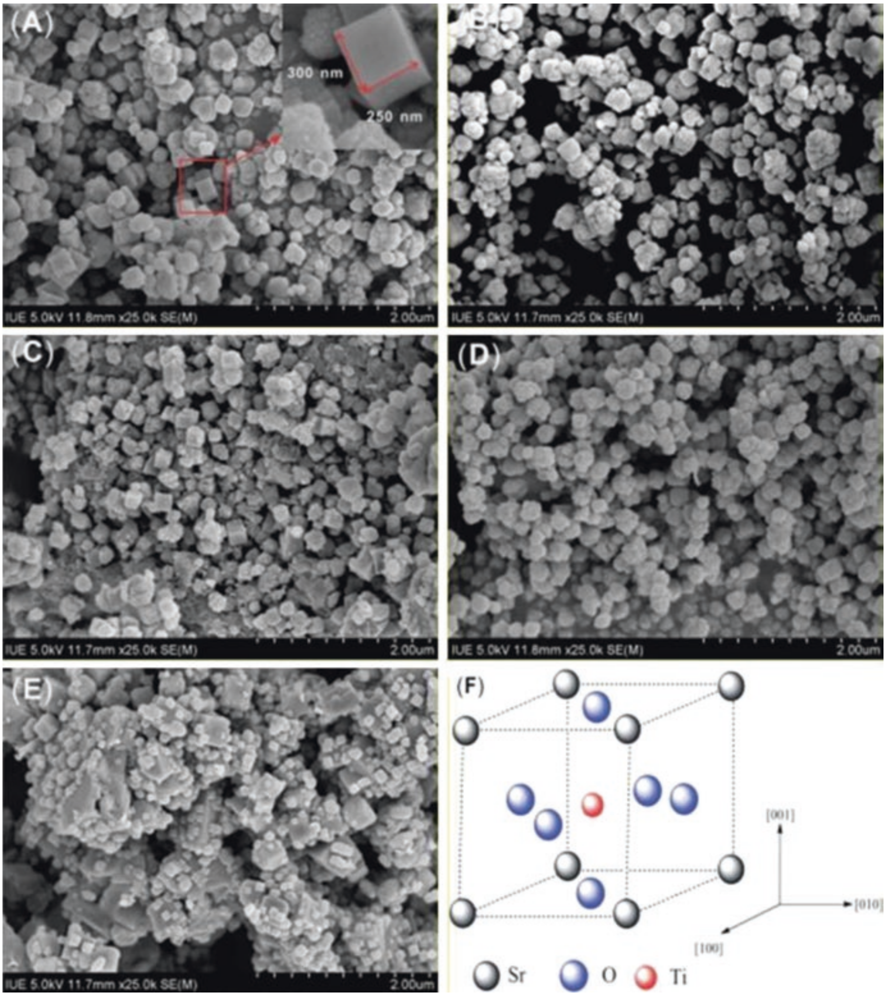


Fig. 2.2 FESEM images of $SrTiO_3$ with different weights of hexamethylenetetramine (**a**, **b**) 5 g, (**c**) 10 g, (**d**) 15 g, (**e**) 20 g, and (**f**) crystal structure (Xu et al. 2014)

2.3.2 Tantalum-Based Perovskite Oxides

Tantalate perovskites often possess high photocatalytic activity attributed to their suitable valance band (VB) and conduction band (CB) potential level, consisting of Ta_{5d}, and the efficient carrier delocalization caused by the proper distortion of TaO_6 connections (Zou et al. 2000; Kato and Kudo 2001). This is mainly associated with the crystalline structure of tantalate perovskite oxides, which can be dependent on the synthesis route. Figure 2.3 illustrates the images of $NaTaO_3$ morphology.

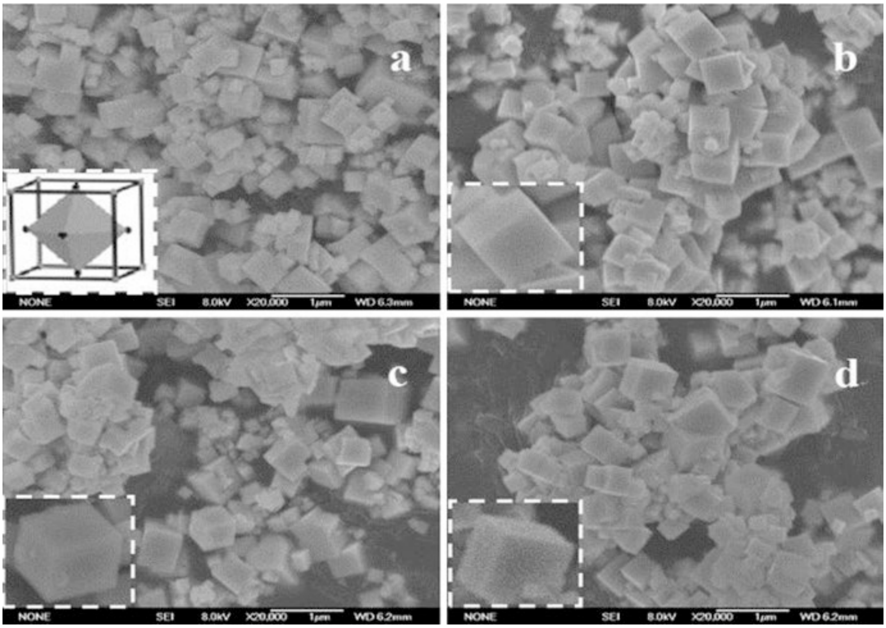


Fig. 2.3 FESEM images of $NaTaO_3$ (Liu et al. 2011)

To date, the most popular methods used are templating, sol–gel, hydrothermal, and hydrothermal–electrochemical. These methods could ensure better crystallinity and fine particle size, which in turn, result in better photocatalytic performance (Osterloh 2007; Li and Zang 2009; Reitz et al. 2012). Of all the tantalate perovskites, sodium tantalate oxide ($NaTaO_3$) and potassium tantalate oxide ($KTaO_3$) are the most efficient photocatalysts. However, a few studies have been carried out on tantalate perovskites to enable visible light photocatalysis as compared to titanate perovskites. $NaTaO_3$ attracts more attention due to its stable, layered structure, and excellent charge separation, which can promote the high efficiency of photocatalytic system (Kanhere et al. 2013). However, $NaTaO_3$ is reported to be inactive under visible light irradiation due to the VB of $NaTaO_3$, which predominantly consists of O_{2p} orbitals whose potential energy levels are positioned at a deep position about 3 V against a normal hydrogen electrode (NHE) (Grabowska 2016) (Table 2.1). Therefore, studies on doping with other elements in order to narrow the band gap and utilize the visible light photocatalytic application have been carried out (Yang et al. 2010; Zhou et al. 2011; Kanhere et al. 2013).

Table 2.1 Band gap energy and crystal structure of perovskite oxides photocatalysts (Grabowska 2016)

Perovskite-type oxides		Band gap	Crystal structure
(A) TiO_3	$SrTiO_3$	3.1–3.7	Cubic
	$BaTiO_3$	3.0–3.3	Cubic
	$CaTiO_3$	3.6	Cubic or orthorhombic
	$MnTiO_3$	3.1	Rhombohedral
	$CoTiO_3$	2.28	Rhombohedral
	$FeTiO_3$	2.8	Rhombohedral
	$PbTiO_3$	2.75	Tetragonal
	$CdTiO_3$	2.8	Rhombohedral
	$NiTiO_3$	2.18	Rhombohedral
	$ZnTiO_3$	2.87–3.7	Cubic, hexagonal, rhombohedral
(B) TaO_3	$KTaO_3$	3.4–3.6	Cubic or orthorhombic
	$NaTaO_3$	4.2	Orthorhombic, monoclinic, cubic
	$AgTaO_3$	3.4	Rhombohedral
	$LiTaO_3$	4.7	Cubic or rhombohedral
(C) NbO_3	$KNbO_3$	3.14–3.24	Cubic, orthorhombic, rhombohedral, tetragonal
	$NaNbO_3$	3.0–3.5	Orthorhombic, tetragonal, cubic
	$AgNbO_3$	2.7	Orthorhombic
	$CuNbO_3$	2.0	Monoclinic
	$LiNbO_3$	3.78	Rhombohedral
	$SrNbO_3$	2.79	Cubic

2.3.3 Niobium-Based Perovskite Oxides

Similarly, niobium-based perovskites show good photocatalytic activity but limited UV irradiation. The most commonly found niobium-based perovskites are sodium niobite oxide ($NaNbO_3$) and potassium niobate oxide ($KNbO_3$). These two semiconductors each have band gap energy values of 3.08 eV and 3.14 eV, respectively (Liu et al. 2007). The morphology of $KNbO_3$ is portrayed in Fig. 2.4. However, modification on the band structure can enhance the visible light absorption and hence improves the photocatalytic activity. Furthermore, niobium-based perovskites also exhibit many other attractive properties such as ferroelectricity, piezoelectricity, ionic conduction, and photorefraction. Both $NaNbO_3$ and $KNbO_3$ are highly stable, nontoxic, and suitable for photocatalytic purposes. Nitrogen doping in niobium-based perovskites has been studied on the degradation of 2-propanol, water splitting, and organic pollutant degradation (Wang et al. 2013). Doping of non-metallic elements and loading metal nanoparticles were also been studied with the aim of fully utilizing the solar spectrum in the photocatalytic process (Lan et al. 2011; Shi et al. 2014). However, to date, complete detailed studies on photocatalysis using niobium-based photocatalysts are still lacking.

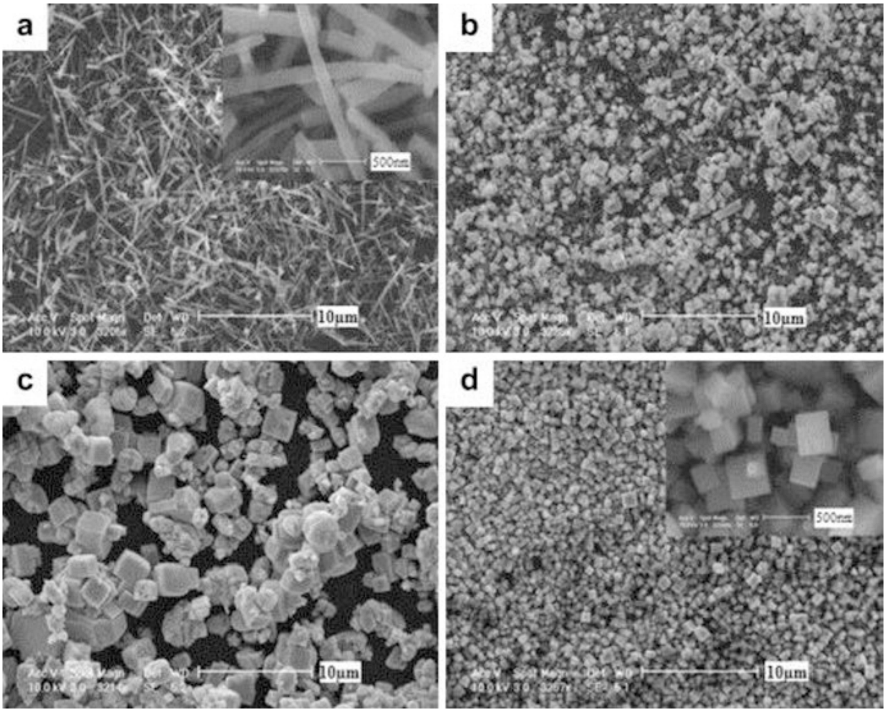


Fig. 2.4 FESEM images of $KNbO_3$ obtained from various KOH concentrations (**a**) 10 M, (**b**) 13 M, (**c**) 16 M, and (**d**) 30 M. (Wang et al. 2013)

2.4 Applications and Catalytic Studies of Perovskite Oxides

Perovskites are one of the most important families of materials that exhibit a wide range of ferroelectric, piezoelectric, and pyroelectrical properties and electro-optical effects. They have been used as electronic, structural, magnetic, and refractory materials in numerous technological applications. From the point of view of photocatalytic activity, perovskite oxides are capable of utilizing its broad features in enhancing the photocatalytic effect. Photocatalysis is a type of chemical reaction that involves the process of utilizing energy input from incident radiation by the catalyst. Furthermore, catalytic properties of the material surface to carry out chemical reactions without being consumed in the process. To date, numerous studies on photocatalysis have been carried out to achieve a new breakthrough, especially in the field of energy generation and environmental cleaning applications. Thus, understanding the basic mechanism of photocatalytic process is of utmost importance in order to design and enhance the perovskite oxide–based photocatalysts.

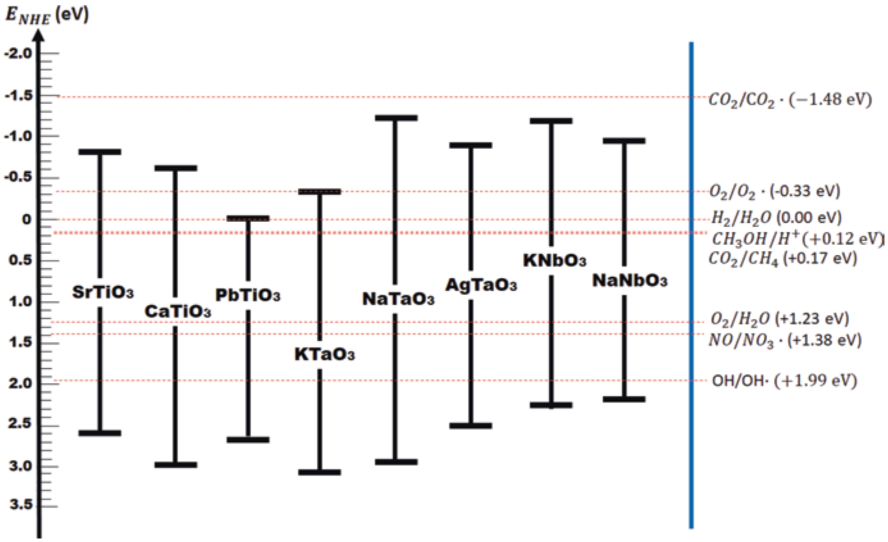


Fig. 2.5 Photocatalytic reaction energy levels of perovskite oxides with respect to NHE

A photocatalyst is initiated by the absorption of photon with energy equal to, or greater than the band gap of the semiconductor, which then photogenerated electron–hole pairs, as shown in the following equation:

$$\text{Photocatalyst} + h_{\text{v}} \rightarrow e_{\text{cb}}^{-} + h_{\text{vb}}^{+} \tag{2.3}$$

where h_{v} is photon energy, cb is conduction band, and vb is valence band (Rauf and Ashraf 2009). Subsequently, the photoexcited semiconductor can act as either an electron donor or acceptor in the surrounding medium. However, these photogenerated electrons and holes can recombine and release energy as heat, with no chemical effect. Otherwise, these electron–hole pairs will participate in redox reactions with adsorbed species at the surface, where the valence band hole is strongly oxidizing while the conduction band electron is strongly reducing (Al-Rasheed 2005). Figure 2.5 shows the reduction and oxidation levels of some of the common perovskite oxides with reference to the normal hydrogen electrode (NHE). It is believed that these values can provide an insight for future research. It is noted that the energy of photoexcited electron in the reduction reaction should be higher than the redox level. Therefore, the CB potential of the photocatalyst should be located at a higher energy value than the VB oxidation potential.

2.4.1 Photocatalytic Water Splitting

Hydrogen (H_2) production from photocatalytic water splitting is one of the most potential routes to address energy and clean environment concerns. In the recent decades, there has been remarkable progress in using semiconductor-based photocatalysts under ultraviolet (UV) light and visible light irradiation (Liu et al. 2006). Figure 2.6 presents the schematic of water splitting process. In the water-splitting reaction, electron and hole pairs will be photogenerated upon light irradiation of photon with suitable wavelength on the surface of perovskite oxide photocatalyst. Direct oxidation of water molecules occurs at the valence band, and this interaction results in the liberation of an oxygen molecule and four positively charged hydrogen ions. These hydrogen ions latter migrate to the conduction band where the photoexcited electrons can carry out reduction to form hydrogen molecules in line with the following equations (Tang et al. 2008):

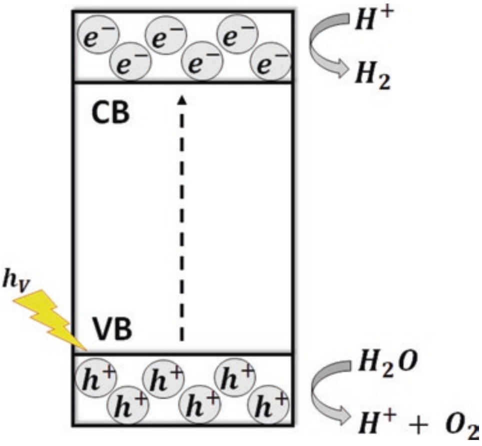
$$2H_2O \rightarrow 4H^+ + O_2 \tag{2.4}$$

$$4H^+ + 4e^- \rightarrow 2H_2 \tag{2.5}$$

$$2H_2O \rightarrow 2H_2 + O_2 \tag{2.6}$$

Evolution of hydrogen and oxygen through water splitting can be considered as one of the most promising ways to produce hydrogen as clean and renewable energy. However, there are three major steps involved in the photocatalytic overall water splitting process, which are light absorption in producing electron–hole pairs, charge separation, and surface catalytic reactions. Among these steps, charge separation and surface catalytic reactions are more vital to improve the efficiency of water to hydrogen conversion. For given semiconductor materials, perovskite oxides can be proposed as an effective semiconductor to overcome these issues and consequently enhance the energy conversion efficiently (Mu et al. 2016).

Fig. 2.6 Schematic diagram of water splitting reaction mechanism



2.4.2 Photodegradation of Organic Pollutants

Many organic pollutants can be oxidized through photocatalysis reaction, where direct oxidation via photogenerated holes or indirect oxidation via hydroxyl ions takes place. Figure 2.7 shows the mechanism of photodegradation of organic pollutants by active radical species. A great number of researches have been carried out hitherto on using perovskite oxide photocatalytic activity to mineralized pollutants such as organic dyes, aliphatic and aromatic hydrocarbons, phenolics, and organic acids to carbon dioxide (CO_2) and water molecule (Mahmoodi et al. 2006; Sadik et al. 2007). In most cases, the photogenerated valence band holes can easily react with water (H_2O) on the catalyst surface to produce hydroxyl radicals (•OH) that are strong oxidants. Meanwhile, the electrons at the conduction band react with the most easily available electron acceptor, oxygen (O_2) to form superoxide radical ions ($•O_2^-$) (Elmolla and Chaudhuri 2010).

$$H_2O + h_{vb}^{+} \rightarrow \cdot OH + H^{+} \tag{2.7}$$

$$O_2 + e_{cb}^{-} \rightarrow \cdot O_2^{-} \tag{2.8}$$

The complete oxidation–reduction reaction would prevent the recombination of the electrons and holes. The hydroxyl radicals and superoxide radicals produced can then further react with the organic pollutants to complete the mineralization process.

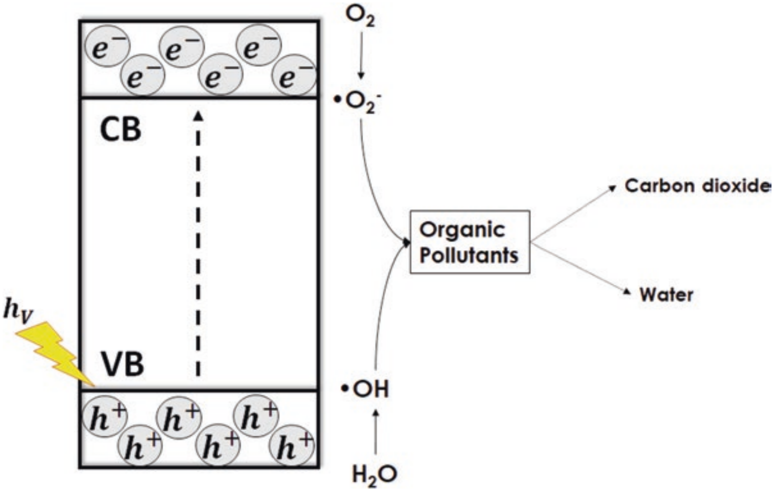


Fig. 2.7 Mechanism of photodegradation of organic pollutants

2.4.3 Photocatalytic Conversion of Carbon Dioxide to Fuels

Global warming is one of the major environmental concerns that needs much attention. Carbon dioxide is one of the largest contributors to the global climate change due to greenhouse effect. An increase in the atmospheric concentration of carbon dioxide has led to the rising of global temperature through absorption of infrared light and re-emitting it to the surroundings. The emission of carbon dioxide is mostly from the fossil fuel combustion intended for energy generation, and fossil fuel is inevitably depleting as energy demand is increasing. Therefore, it is crucial to address this environmental issue as well as meeting the increasing energy demand. In the past decade, photocatalytic conversion of CO_2 into fuels has driven many research activities in this area. Figure 2.8 presents a schematic diagram of CO_2 photoreduction over perovskite oxide photocatalyst. With proper adsorption and photocatalytic processes, the conversion of CO_2 in the presence of water can be performed to produce hydrocarbon fuels despite CO_2, which is a thermodynamically inert and stable compound (Li et al. 2014; Tu et al. 2014). The following equations depict the possible chemical reactions of CO_2 photocatalytic conversion.

$$\mathrm{CO_2} + 2\mathrm{H}^+ + 2e^- \rightarrow \mathrm{CO} + \mathrm{H_2O} \tag{2.9}$$

$$\mathrm{CO_2} + 6\mathrm{H}^+ + 6e^- \rightarrow \mathrm{CH_3OH} + \mathrm{H_2O} \tag{2.10}$$

$$\mathrm{CO_2} + 8\mathrm{H}^+ + 8e^- \rightarrow \mathrm{CH_4} + \mathrm{H_2O} \tag{2.11}$$

It could be noticed that different hydrocarbons can result from different numbers of protons in the reactants. Among those reactions, conversion of CO_2 to methane (CH_4) is significantly attractive (Habisreutinger et al. 2013). Hence, the photocatalyst must possess enough band potential for proton generation that can be succeeded by perovskite oxides, as its unique structure gives broader extent to reconstruction and modification.

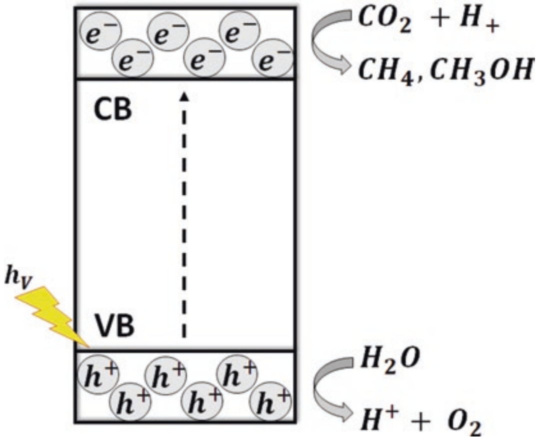


Fig. 2.8 Photoreduction of CO_2 over a photocatalyst surface

2.4.4 Other Applications

Perovskite oxides with specific structures can also exhibit other excellent properties and beneficial in other applications such as gas sensing, nitrogen oxide (NO_x) removal, nitrogen fixation, VOC removal, and dry reforming of methane. Due to the chemical and thermal stability, a number of perovskite oxides have been used as gas-sensing materials. Owing to the presence of oxygen vacancies in the perovskite structure, the sensitivity toward sensing atmospheric oxygen is stronger. Gas-sensing performance is also mediated by surface properties. Cubic-like perovskite oxide proves that it has more active centers for trapping the target gas than bulk perovskite oxide due to its smaller size and higher surface area. This could decide the sensitivity toward gases such as ethanol, ammonia, acetone, hydrogen peroxide, and so on (Cheng and Lu 2008; He et al. 2009). In addition, NO_x gases can be oxidized through photocatalysis. Hydroxyl radicals and superoxide radicals generated from photoexcited photocatalyst can further oxidize the NO_x to nitrogen dioxide or nitrate as shown in the following equations (Dalton et al. 2002).

$$NO + 2 \cdot OH \rightarrow NO_2 + H_2O \tag{2.12}$$

$$NO_2 + \cdot OH \rightarrow NO_3^- + H^+ \tag{2.13}$$

$$NO_x + \cdot O_2^- \rightarrow NO_3^- \tag{2.14}$$

In addition, nitrogen fixation is a conversion process of nitrogen into ammonia that is very useful in agricultural applications. However, ammonia production usually requires high pressure and temperature, which limits its development in practical application. Therefore, photocatalytic nitrogen fixation is an alternative low energy consumption and eco-friendly process to produce ammonia. The mechanism of nitrogen fixation is relatively similar to that of the abovementioned conversion of CO_2, where chemically adsorbed nitrogen molecule reacts catalytically with protons to form ammonia as shown in the following equation (Feng et al. 2018).

$$N_2 + 6H^+ + 6e^- \rightarrow 2NH_3 \tag{2.15}$$

In addition, dry reforming of methane is a promising approach to reduce two greenhouse gases, CO_2 and CH_4 in the atmosphere and produces synthesis gas, which is a mixture of hydrogen (H_2) and carbon monoxide (CO).

$$CH_4 + CO_2 \rightarrow 2CO + 2H_2 \tag{2.16}$$

Synthesis gas is conventionally produced via steam reforming. However, due to the increased concerns of greenhouse gases in the recent years, dry reforming of methane is gaining interest as a chemical energy transmission system by providing a good approach to utilize the biogas and natural gas with a great amount of CO_2 reduction. The mechanism for the dry reforming of methane is very dependent on the nature of the catalyst, and this provides a pathway for using perovskite oxides. To date, numerous studies using perovskite oxides have been carried out on various aspects of dry reforming of methane (Arora and Prasad 2016; Abdullah et al. 2017).

2.5 Future Perspectives

With the promising characteristic of perovskite oxide photocatalyst in environmental remediation and energy conversion, fabrication of perovskite-based photovoltaic and energy storage devices could be the future outlook. Recent progress witnessed a major engineering advancement in modifying interface features and electrical contact of perovskite layers. These properties are vital for the enhancement of perovskite-based devices. Moreover, tuning of band gap energy unveiled a highly efficient solar cell that can fully maximize its potential. At the present, some appropriate light harvester characteristics such as enhanced light absorption, lower recombination rate of electron and hole pairs, and superficial flaw levels are sufficient to advance into photovoltaic and energy storage devices. However, narrowing the band gap energy and plasmonic photovoltaics are expected to eventually open a new dimension in the field of photovoltaic technologies for better light harvesting that span across the entire solar spectrum. This future outlook will promote an alternative sustainable solar cell for a greener environment. Bera and group reported that perovskite oxide $SrTiO_3$ has efficient electron mobility for hybrid perovskite solar cells. They revealed that it could enhance the efficacy of solar cells to 25% as compared to the non-perovskite oxide solar cells (Bera et al. 2014). A schematic that illustrated the cell configurations of solid oxide cells for energy storage and conversion is shown in Fig. 2.9. Perovskite-based photocatalyst will pave a new direction in the near future for various sustainable applications.

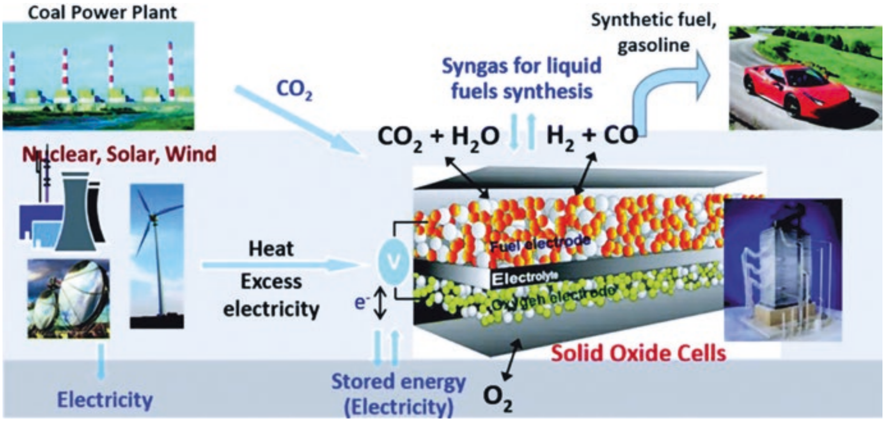


Fig. 2.9 Schematic diagram of cell configuration for energy storage and conversion. (Zhang et al. 2017)

2.6 Conclusion

This chapter revealed the theory of perovskite oxide–based photocatalysts for various environmental and energy conversion applications specifically under light irradiation. Furthermore, the different types of synthesis route together with its pros and cons are explained. The understanding of perovskite oxide characteristics is crucial in enhancing the different types of applications. With the strong oxidation and reduction power, perovskite oxide–based photocatalyst can be utilized in the photodegradation of organic pollutants, water splitting, conversion of CO_2 to useful fuels, and so on. The unique characteristics of perovskite oxides have created an alternative pathway for fabricating solar cells that could replace conventional devices for energy generation. Hence, through this advanced nanotechnology of perovskite oxide photocatalysts, it has a great future and potential to be further developed and applied at industrial scale.

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Chapter 3
Biogenic Material With Iron Nanoparticles for As(V) Removal

G. García-Rosales, L. C. Longoria-Gándara, P. Avila-Pérez, D. O. Flores-Cruz, and C. López-Reyes

Contents

3.1 Introduction: Arsenic in the Water

Water is the most abundant chemical compound in the biosphere and essential for the sustenance of life on Earth (Domènech and Peral 2006). Although water is considered a renewable resource, it can be polluted by natural and anthropogenic sources, at such level that it can be harmful to biota and flora in ecosystems (Chena

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G. García-Rosales
Instituto Tecnológico de Toluca, Departamento de posgrado, Metepec, Mexico
e-mail: gegaromx@yahoo.com.mx

L. C. Longoria-Gándara
Division for Latin America/Department of Technical Cooperation International Atomic Energy Agency, Vienna, Austria
e-mail: L.Longoria-Gandara@iaea.org

P. Avila-Pérez (✉) · D. O. Flores Cruz
Instituto Tecnológico de Toluca, Departamento de Posgrado, Metepec, México

C. López-Reyes
Instituto Nacional de Investigaciones Nucleares, Ocoyoacac, Mexico

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and Wu 2018). An example is the presence of As in underground water, used for human consumption, a common problem in several countries in the world (Chakrabarti et al. 2018). The presence of As in underground water is due to contact of the water with mineral deposits or the volcanic and/or anthropogenic activity (IARC 2004; Kumar and Suzuki 2002). Arsenic in its organic and inorganic chemical form is a detrimental element to human health, even in low concentrations; it is persistent in the environment, and for this reason it has been integrated into the list of toxic substances by the US Environmental Protection Agency (USEPA) (EPA 2001). This pollutant tends to accumulate in the tissues of plants and animals, reaching harmful levels in the food chain.

At present, different methods are used to remove arsenic from underground drinking water; however, such methods have technical, economic, or efficiency limitations, so new technologies are investigated in order to obtain a competitive, efficient, and viable method to decrease the As from the water.

Recent researches have shown the effectiveness of the use of iron nanoparticles for the removal of heavy metals; however, due to the nanoparticle's tiny size, the recovery is difficult. This has motivated to investigate the use of new materials known as nanocomposites, consisting of a solid phase (matrix) and a nano-dimensional phase (or phases) dispersed into the matrix. The nanocomposites are effective and low-cost and can be used depending on the needs of remediation (Prathna et al. 2018; Khan and Malik 2018).

The nanoparticles are characterized by their large specific area and synthesized by various methods with relative ease, which do not need a large infrastructure for obtaining and providing high removal percentages of the metal ions (Sua et al. 2017; Gutiérrez-Muñiz et al. 2013; Zhang et al. 2018; Deng et al. 2013; Leusa et al. 2018; Boparai et al. 2011). Natural biomasses are one of the best alternatives for the removal of metal ions from the water due to their high potential as sorption materials, because of their porosity, low cost, and stability (Gul Kazi et al. 2018; Bilal Shakoor et al. 2018; Lu and Astruc 2018). Together, both materials are a viable alternative for obtaining carbons conditioned with nanoparticles.

3.1.1 Arsenic in Drinking Water for Human Consumption

The arsenic (As) is a metalloid which has an average concentration in the Earth's crust of 2 mg/kg. The trivalent (III) and pentavalent (V) forms are the predominant oxidation states of As. Inorganic arsenic compounds are generally more toxic than organic arsenic compounds (Xua et al. 2018; Huang et al. 2018).

The As concentration in natural water is controlled by three factors: the original source (atmosphere, rocks, minerals, etc.), the water-rock interaction processes (redox environment and pH), and the conditions of the underground flow. In contrast, its mobility in the environment is controlled mainly by chemical (oxidation-reduction reactions), biological (microbiological oxidation), and physicochemical (sorption/desorption and ionic exchange) processes (Bhatt and Tripathi 2011).

Arsenite or As(III) and arsenate or As(V) are two predominant soluble forms of inorganic arsenic. The formation and stability of these two species depend on the pH value. Under normal conditions, a reducing environment, characterized by low oxygen content, favors the presence of As(III), which occurs in lake sediments and groundwater (Choong et al. 2007; Litter et al. 2010).

Depending on the pH and the redox potential (Eh), the arsenic species can be adsorbed on the surfaces of Fe, Al, and Mn oxyhydroxides, as well as in calcite and clays from the surrounding soil, which is a natural control mechanism. The arsenate species form complexes on the surface of the iron oxyhydroxides and are strongly adsorbed in the pH values around neutrality, mainly, the oxyanions $H_2AsO_4^-$ and $HAsO_4^{2-}$. The arsenite apparently does not form complexes, and it is not strongly adsorbed by any pH value.

3.2 Methods for Arsenic Removal

The As pollution (Bundschuh et al. 2010; Baskan and Pala 2010) has motivated the development and application of different removal technologies, such as, coagulation-flocculation, electrodialysis, electrocoagulation, membrane technologies, biological methods, and sorption processes (adsorption and/or absorption) (Strathman 2010; Martínez-Villafañe et al. 2009; Sen et al. 2010), which have gained great relevance in recent years. The most recent researches have a nanotechnological approach, because the nanoscale gives the materials more effectiveness for the pollutant removal. The use of iron nanoparticles for the reduction and removal of As in an aqueous phase has significantly drawn attention.

3.2.1 Iron Nanoparticles

A nanoparticle is a structure of such a size that some of its three dimensions are less than 100 nanometers, which can confer new properties, allowing the design and procurement of new materials aimed to satisfying specific needs (Chen et al. 2008). In environmental matters, nanoparticles can be used in water treatment, air purification, and soil remediation (Kamal Koju et al. 2018; Araujo et al. 2015; Max Lu 2018).

Among the different types of nanoparticles used for the removal of As in the aqueous phase, protrude those of zerovalent iron and iron oxide (magnetite). These nanoparticles can be amorphous or crystalline with spherical or cubic geometry, and they have the advantage in responding to a magnetic field, which can help the material's recovery. The method most used for obtaining the iron nanoparticles is the chemical synthesis in which three precursors are required: (a) an iron salt, (b) a reducing agent, and (c) a surfactant substance.

Zerovalent iron nanoparticles are also effective in the removal of As(III), because they promote oxidation to As(V) (Ramos et al. 2009). However, their use in remediation is difficult to apply due to the tiny size and the complexity of manipulating and recovering the iron nanoparticles. An alternative to resolve this problem is the use of a support material to retain the nanoparticles and to facilitate the contact with the pollutant.

3.3 Material Synthesis

The different experimental stages for obtaining the carbonaceous material conditioned with iron nanoparticles coming from the pineapple peel are shown in Fig. 3.1. The pineapple (*Ananas comosus*) peel (PP) was washed with deionized water and was dried at 35 °C for 24 hours. After, the material was pulverized by means of an

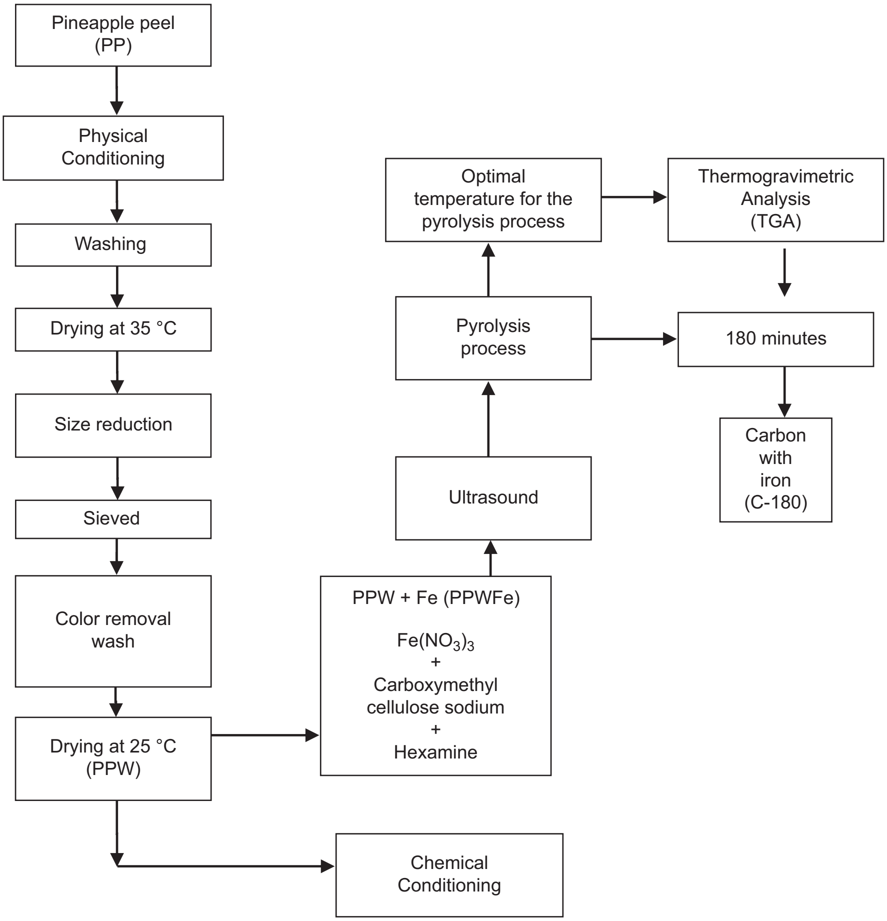

Fig. 3.1 Material synthesis process

agricultural mill trademark Mexicana de Suministros Agropecuario S.A. de C.V. and a food processor Osterizer® in order to decrease the particle size. The resulting material was sieved at 20 meshes (0.833 mm), washed with deionized water at 100 °C until the color and impurities elimination and dried in a stove at 25 °C for 48 hours to eliminate excess water (PPW). Later, $Fe(NO_3)_3{\cdot}9H_2O$ (Sigma-Aldrich, 98%), carboxymethylcellulose sodium (CMC) (Sigma-Aldrich) and 1 mL of $(CH_2)_6N_4$ (Sigma-Aldrich, 99.9%) were stoichiometrically mixed with 3 grams of pineapple peel under constant stirring at 600 rpm for 15 minutes in a reactor with an argon atmosphere. The reactor was sealed and placed in an ultrasound bath for 45 minutes, and then the material was subjected to a pyrolysis process. The chemically conditioned material was placed in a fused alumina crucible and then putted into a high-temperature quartz tube with an argon atmosphere, inside a Lindberg/Blue® Oven, Model CC58114A-1, at 650 °C. The 650 °C optimum temperature with 180 minutes time duration was the experimental condition in this study for obtaining the material C-180 by means of pyrolysis process.

The pyrolysis process involves the breaking up of the chemical bonds by heating (temperatures above 500 °C) with the absence of oxygen, which prevents combustion of the material (Alvarado et al. 2008). During this process, three types of products are obtained: solid (carbon and ashes), liquid (oil or tar), and a mixture of gases with a low molecular weight (H_2, CH_4, CO, CO_2) (Mohan and Pittman 2007). The pyrolysis time affects the composition as well as pore size and surface area of the carbonaceous material obtained from waste (Poole and Owens 2007).

3.3.1 Composition and Characterization of Pineapple Peel

The pineapple (*Ananas comosus*) is a fibrous peel fruit formed by about 150–200 individual fruits joined to a central axis (Fig. 3.2a). The pineapple contains mainly 80–85% water and 12–15% sugar, of which, two thirds are sucrose, glucose, and fructose. Maturation takes 5–6 months after the appearance of the flowers and it is available in Mexico from December to June as a seasonal fruit (D'Eeckenbrugge and Leal 2003). The pineapple production is mainly concentrated in the states of Tabasco, Jalisco, Nayarit, and Chiapas (SAGARPA 2011). The average organic composition of the waste pineapple corresponds to fiber (67.88%), carbohydrates (18.58%), and proteins (13.54%), and it is mainly composed of cellulose, hemicellulose, and lignin (Gutierrez et al. 2003), compounds that help to obtain a carbonaceous material of rigid structure through a process of pyrolysis.

The semiquantitative composition of the pineapple peel (Fig. 3.2b) obtained by energy dispersive X-ray spectroscopy (EDS) analysis shows the contents of C (54.55%), O (42.98%), Mg (0.11%), Al (0.71%), Si (0.21%), S (0.13%), Cl (0.10%), K (0.78%), and Ca (0.43%).

Figure 3.2c shows at 200× a rough area with folds that vary in size and depth from 100 to 200 μm. According to the EDS analysis (Fig. 3.2d), the elemental contents in the sample are C (54.55%), O (41.84%), Mg (0.27%), Al (0.11%), Si

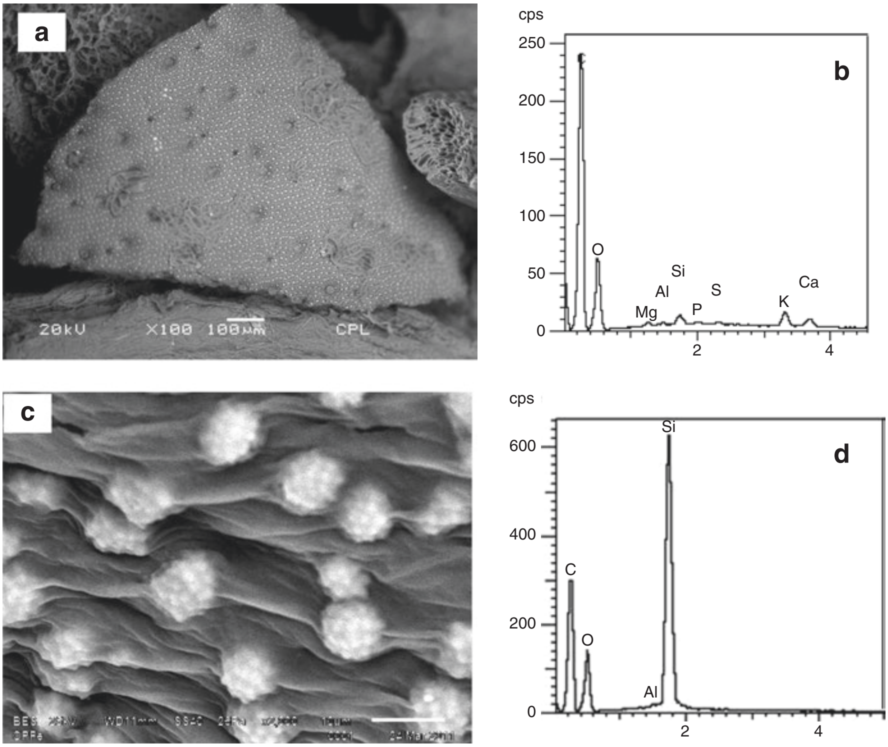

Fig. 3.2 (**a**) Micrographs of the pineapple (*Ananas comosus*) peel at 100×, obtained by a scanning electron microscope JEOL JSM 5900LV (low vacuum); (**b**) EDS analysis obtained with the OXFORD® 51-ADD0013 probe coupled with the microscope; (**c**) silicon nodules of the pineapple peel; (**d**) EDS analysis of a nodule

(0.58%), P (0.13%), S (0.21%), K (1.40%), and Ca (0.90%). The presence of trace elements in the pineapple peel is common to observe (López-Tellez et al. 2011).

In Fig. 3.3a an area of carbonaceous material obtained at 650 °C for 180 minutes is observed, where spheres of 6 μm in diameter as well as filaments of 107.77 in average width (σ = 14.56) (Fig. 3.3b) are observed. Both types of structures are formed at the top of the silicon nodules, so the above could be due to the interaction of Si with sodium carboxymethyl cellulose during the pyrolysis process.

The material C-180 contains C (24.60%), O (44.18%), Na (9.75%), Si (18.69%), K (2.15%), and Fe (0.62%), while the spheres contain C (66.86%), O (12.73%), Na (5.88%), Si (11.42%), K (0.54%), Ca (0.89%), and Fe (1.67%). In order to observe the iron nanoparticles in more detail, the surface of carbonaceous material was studied at 50,000× (Fig. 3.4a), where small spherical particles with an average diameter of 38.81 nm (σ = 9.93) (Fig. 3.4b) were observed. The elemental analysis (Fig. 3.4c) shows a content of C (75.57%), O (16.47%), Na (1.81%), Mg (0.24%), Al (0.27%), Si (0.95%), K (0.50%), Ca (1.58%), and Fe (2.61%). The mapping of the material C-180 (Fig. 3.4d) indicates that the iron dispersion on the surface of carbonaceous material is uniform.

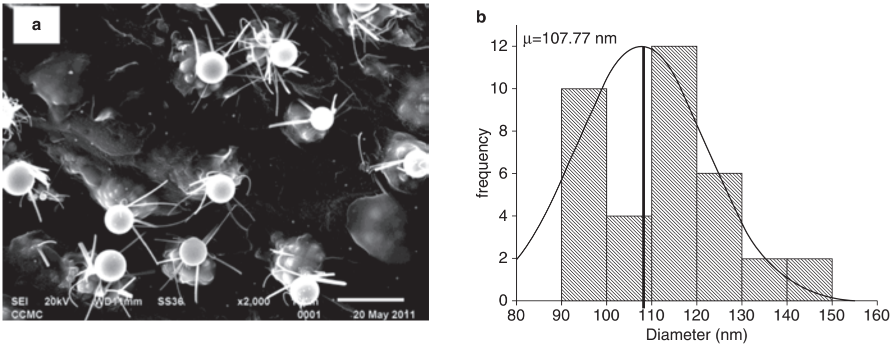

Fig. 3.3 (**a**) Micrograph of the material C-180, (**b**) size distribution of the filaments in the material C-180

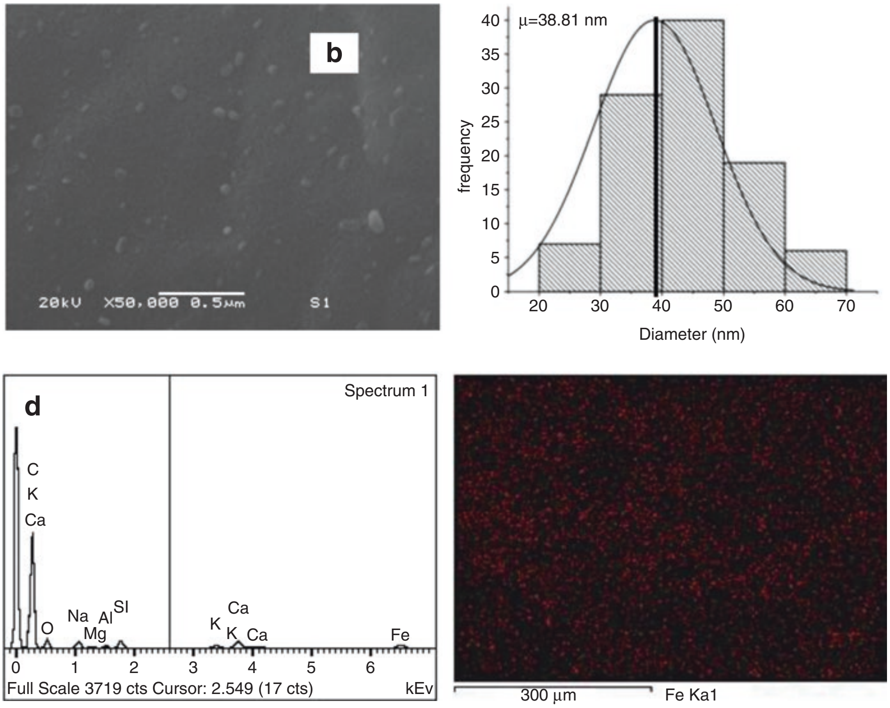

Fig. 3.4 (**a**) Morphology of particles in the material C-180, (**b**) size distribution of the spherical particles, (**c**) elemental analysis of the material, (**d**) distribution of iron on the material surface

The crystallographic phases present in the material C-180 were studied with a diffractometer SIEMENS® D5000, with a radiation source of copper Kα, with $\lambda = 1.54$: $2\theta_i$ angle = 4, $2\theta_f = 70$, size 0.03 and time of 1s, normal mode, interval time of 60 minutes, without rotation $\Theta_i = 2$, $\theta_f = 35$. The resulting diffractogram was

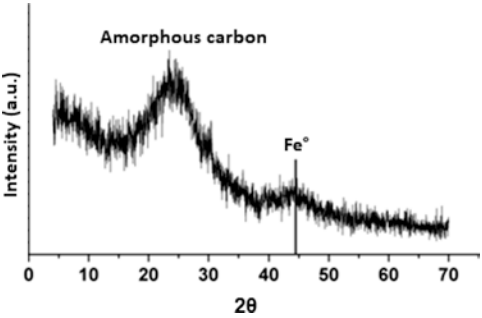

Fig. 3.5 Diffraction pattern of the material C-180

compared with the cards of the PDF 2007 database of the International Centre for Diffraction Data (ICDD).

In Fig. 3.5, the diffraction pattern of the material C-180 is presented. Two broad peaks are observed: one between 17° and 30° on the scale 2θ with centroid at 24° corresponding to amorphous carbon in accordance with card ICDDPDF2007 03-065-4899 and the other located between 40° and 50° with centroid at 44° that is due to the zerovalent iron (Fe°). The carbon obtained from organic waste presents an amorphous structure that makes it difficult to distinguish the diffraction peak of iron in the sample (Liu and Zhang 2010).

3.3.2 Neutron Activation Analysis (NAA)

The content of trace elements in the materials PP, PPW, and the carbon obtained through the pyrolysis process (C-180) was determined using the technique of neutron activation analysis. The quantification of elements was carried out by means of comparison with reference materials, using for this purpose, two reference materials: BCR-482 Lichen and IAEA Soil 7. Vials of polyethylene for short irradiation times (30 seconds to 5 minutes) and quartz ampoules for irradiation times of 20 hours were used in the analysis.

The samples were ground in an agate mortar to homogenize the material and then dried in an oven at 105 °C for 4 hours in order to remove the moisture. Approximately 0.020 grams were weighed for each one of the samples for the irradiation. The samples were irradiated with thermal neutrons in the Reactor TRIGA Mark III (National Institute for Nuclear Research, Mexico), for 30 seconds and 5 minutes in the SINCA position with a neutron flux of 1×10^{13} n/cm^2·s, while the irradiation of 20 hours took place in the SIFCA position with a neutron flux of 9×10^{12} n/cm^2·s. The sample activity was measured using a system of gamma spectrometry with a hyperpure (ORTEC®) germanium detector. The Nuclide Navigator (ORTEC®) software was used in the qualitative identification of isotopes taking into account the times of irradiation, decay, and half-life. The gamma spectra of samples and patterns were processed using the (HYPERMET-PC program 2008).

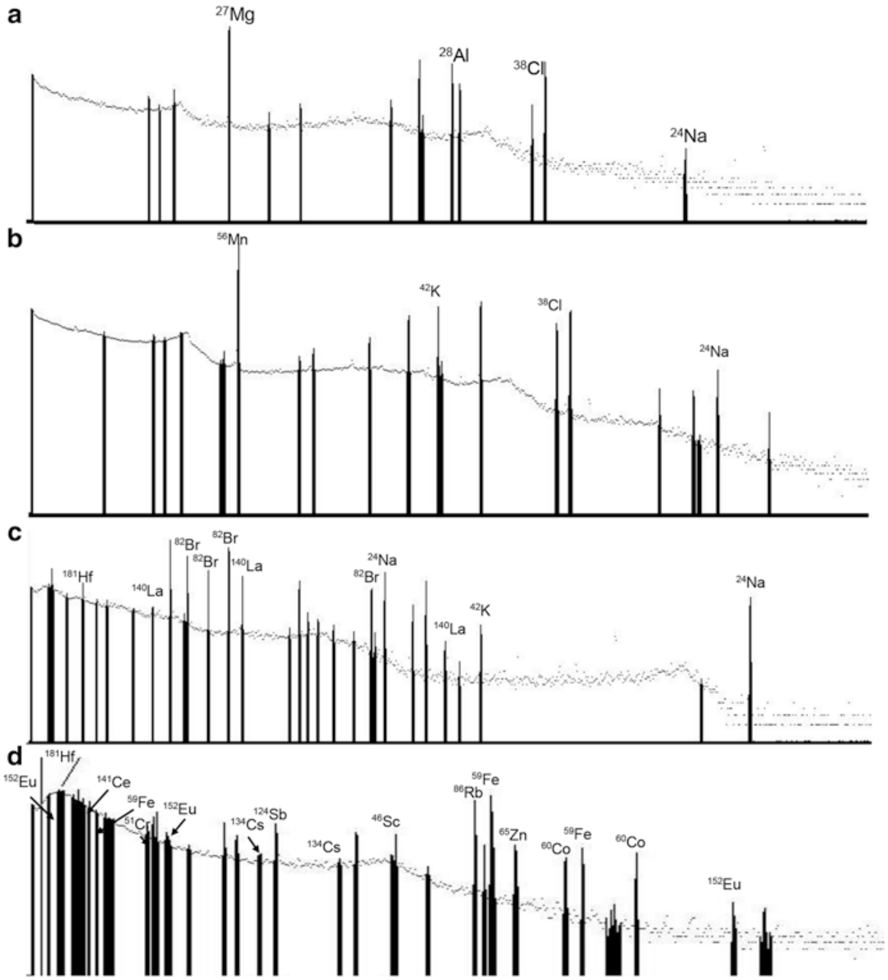

Fig. 3.6 Gamma spectrum of pineapple peel: (**a**) sample irradiated for 30 seconds; (**b**) sample irradiated for 5 minutes; (**c**) spectrum of the first measurement of the sample irradiated for 20 hours; (**d**) spectrum of the second measurement of the sample irradiated for 20 hours

The sample irradiated for 30 seconds (Fig. 3.6a) showed the presence of ^{27}Mg, ^{28}Al, ^{38}Cl, and ^{24}Na isotopes, while in the sample that was irradiated for 5 minutes (Fig. 3.6b), the isotopes corresponding to ^{56}Mn, ^{42}K, ^{38}Cl, and ^{24}Na were identified. In the irradiated sample for 20 hours (Fig. 3.6c, d), the isotopes of ^{152}Eu, ^{181}Hf, ^{140}La, ^{141}Ce, ^{59}Fe, ^{51}Cr, ^{82}Br, ^{134}Cs, ^{124}Sb, ^{46}Sc, ^{86}Rb, ^{65}Zn, ^{60}Co, ^{24}Na, and ^{42}K were identified.

The results of trace element concentration (Table 3.1) show the presence of the metals, Co, Cr, Cs, Fe, Hf, K, Mg, Mn, Na, Rb, Sc, and Zn; three elements of the lanthanides group, Ce, Eu, and La; nonmetallic element, Br; as well as the metalloid, Sb. Previous studies of the content of trace elements in pineapple peel have not been

Table 3.1 Results of trace element concentration in the materials

Isotope	Pineapple peel (mg/kg)	Pineapple peel washed (mg/kg)	Carbon with iron (C-180) (mg/kg)
Al	144 ± 14	60 ± 6	498 ± 14
Br	17 ± 0.9	1.5 ± 0.1	4.6 ± 0.2
Ce	0.122 ± 0.02	<0.001	0.139 ± 0.022
Co	0.287 ± 0.013	0.161 ± 0.007	0.288 ± 0.014
Cr	2.21 ± 0.07	0.938 ± 0.039	2.6 ± 0.08
Cs	0.074 ± 0.006	<0.01	0.074 ± 0.006
Eu	0.007 ± 0.001	0.003 ± 0.001	0.007 ± 0.001
Fe	4020 ± 77	36.7 ± 3.3	5196 ± 98
Hf	0.019 ± 0.003	0.001 ± 0.002	0.020 ± 0.004
K	28,341 ± 1063	361 ± 45	<0.001
La	0.159 ± 0.011	<0.001	<0.001
Mg	460 ± 60	193 ± 24	662 ± 78
Mn	92 ± 3	60 ± 2	152 ± 4
Na	<0.001	<0.001	30,499 ± 850
Rb	2.24 ± 0.28	0.904 ± 0.176	2.81 ± 0.39
Sb	0.78 ± 0.03	0.032 ± 0.004	0.842 ± 0.033
Sc	0.011 ± 0.001	0.005 ± 0.001	0.011 ± 0.001
Zn	132 ± 6	42 ± 2	136 ± 6

found in the scientific literature; however, the presence of trace elements in other vegetable foods has been reported (Kabata-Pendias 2011; Alhassan et al. 2011).

Eu, Sc, and Hf were the elements with the lowest concentration (0.001–0.02 mg/Kg) in the three materials, Hf being the one that presents the highest value. Cs, La, Co, and Ce are found in concentrations between <0.001 and 0.288 mg/Kg, while Sb, Cr, and Rb are in the range of 0.032–2.8 mg/Kg. Br, Mn, Zn, and Al are present in higher concentrations (1.5–498 mg/Kg), Mg and Fe are present among the 36.7 and 5196 mg/Kg, respectively, while K and Na are the elements with the highest concentrations, with a concentration range of <0.001 to 30,499 mg/Kg.

Comparing the concentrations of PP with PPW, it is possible to observe that Ce, Cs, and La are the most sensitive elements to the physical conditioning, since its concentrations were lower than the minimum detection limits of the analytic technique in the PPW material. The concentrations of Br, Fe, K, and Sb are also affected significantly, because they are reduced by 91.18%, 99.07%, 98.72%, and 95.91%, respectively, while the concentrations of Al, Cr, Eu, Mg, Rb, Sc, and Zn are reduced by 58.33%, 57.27%, 54.28%, 57.99%, 59.82%, 54.54%, and 68.18%, respectively. Co, Hf, and Mn were the least affected elements by the washing process with hot deionized water, because the reduction in the concentration were of 44.82%, 47.37%, and 34.78%, respectively. Sodium was found only in the material C-180 due to the use of sodium carboxymethyl cellulose during the chemical conditioning of the pineapple peel.

3.3.3 X-Ray Photoelectron Spectroscopy (XPS)

The elemental composition, chemical state, and electronic state of the elements within the PPW and C-180 materials were determined by means of a Thermo Scientific K-Alpha X-Ray Photoelectron Spectrometer®, using a photoelectron's source of Al (Kα). Ten scans per sample in conventional mode, 400 μm of aperture size and energy step size of 0.100 eV, were performed.

Figure 3.7a shows the XPS survey spectrum of the PPW material, with the following elemental composition: C (76.8%), O (19.85%), Ni (2.04%), and Si (1.32%). Figure 3.7b shows that carbon has seven chemical states: C-Si (283.6 eV), C-C (284.6 eV), C-H (285.2 eV), C-N (286.2 eV) (this chemical state was confirmed by the presence of a peak in the 400.1 eV energy of the N1 s survey spectrum), C-O (286.9 eV), C=O (287.9 eV), and O-C=O (288.9 eV). The material C-180 (Fig. 3.7c) shows the presence of C, O, Na, N, and Si, with an atomic percent of C1s 83.59%,

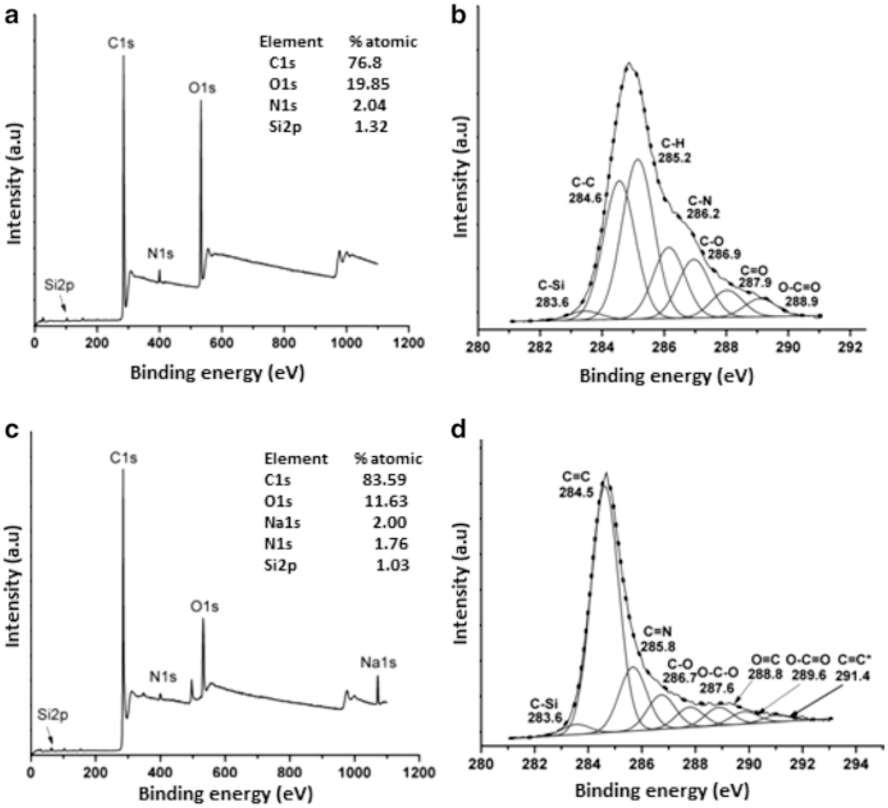

Fig. 3.7 (**a**) XPS survey spectrum from the PPW material; (**b**) deconvolution of C1s peak in the PPW material; (**c**) XPS survey spectrum from the material C-180; (**d**) deconvolution of C1s peak in the material C-180

Table 3.2 Chemical states of C1s peak in PPW and C-180 materials

PPW				C-180		
Chemical states	Binding energy (eV)	FWHM	Area (%)	Binding energy (eV)	FWHM	Area (%)
C-Si	283.6	1.2	1.83	283.6	1.2	2.44
C-C	284.6	1.2	28.76	284.5	1.2	59.78
C-H	285.2	1.2	33.16	–	–	–
C=C	–	–	–	284.5	1.2	59.78
C-N	286.2	1.2	14.72	–	–	–
C=N	–	–	–	285.8	1.2	15.49
C-O	286.9	1.2	12.16	286.7	1.2	8.33
C=O	287.9	1.2	5.61	–	–	–
O-C=O	288.9	1.2	3.76	289.6	1.2	2.99
O-C-O	–	–	–	287.6	1.2	4.89
O=C	–	–	–	288.8	1.2	4.39
C=C	–	–	–	291.4	1.2	1.69

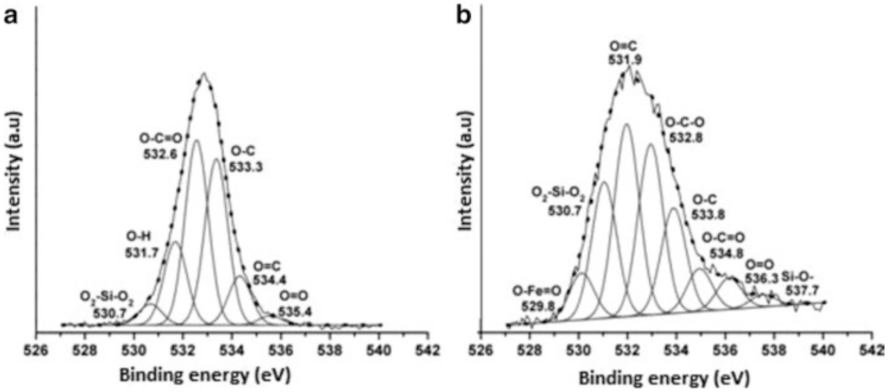

Fig. 3.8 Deconvolution of the O1s peak: (**a**) PPW material, (**b**) C-180 material

O1s 11.63%, Na1s 2.0%, N1 s 1.75%, and Si2p 1.03%. Iron was not detected due to the low concentration present in the surface of the material. The deconvolution of C1s peak in the material C-180 (Fig. 3.7d) shows eight chemical states, C-Si (283.6 eV), C=C (284.5 eV), C-H (285.0 eV), C=N (285.8 eV), C-O (286.7 eV), O-C-O (287.6 eV), C=O (288.8 eV), and O-C=O (289.6 eV), as well as π-π* interactions of the aromatic C=C bonds (291.4 eV). The presence of these last chemical states is frequent in carbons derived from organic waste. Table 3.2 summarizes chemical states of C1s peak in PPW and C-180 materials (Tamayo et al. 2018; Malitesta et al. 1987; Chenhall et al. 1985).

The deconvolution of the O1s peak for the PPW material is presented in Fig. 3.8a, and it is possible to observe the following chemical states: O_2-Si-O_2 (530.7 eV), O-H (531.7 eV), O-C=O (532.6), O-C (533.3 eV), O=C (534.4 eV), and O=O

Table 3.3 Chemical states of O1s peak in PPW and C-180 materials

PPW				C-180		
Energy states	Binding energy (eV)	FWHM	Area (%)	Binding energy (eV)	FWHM	Area (%)
O-Fe=O	529.8	–	–	529.8	1.2	6.33
O_2-Si-O_2	530.7	1.1	4.13	530.7	1.2	18.46
O-H	531.7	1.1	16.22	–	–	–
O-C=O	532.6	1.1	35.97	534.8	1.2	5.79
O-C	533.3	1.1	32.29	533.8	1.2	14.27
O=C	534.4	1.1	9.54	531.9	1.2	26.11
O=O	535.4	1.1	1.85	536.3	1.2	4.25
O-C-O	–	–	–	532.8	1.2	23.13
Si-O	–	–	–	537.7	1.2	1.66

(535.4 eV) (Barr 1991; Zhu et al. 2015; Lim et al. 2018; Singh et al. 2014; Taherymoosavi et al. 2017).

The deconvolution of O1s peak for the material C-180 is shown in Fig. 3.8b. The chemical states correspond to O-Fe = O (529.8 eV) (Onorevoli et al. 2018), O_2-Si-O_2 (530.7 eV) (Barr 1991), O=C (531.9 eV), O-C-O (532.8 eV), O-C (533.8 eV), O-C=O (534.8 eV), O=O (536.3 eV) (Ishimaru et al. 2007), and Si-O (537.7 eV) that corresponds to silicates. Table 3.3 summarizes the chemical states for both materials.

Results show that the chemical conditioning of the pineapple peel caused that iron to be incorporated to the carbonaceous material.

3.3.4 *Specific Surface Area and Isoelectric Point*

100 mg of the material C-180 was placed under a N_2 flow at 100 °C for 3 hours in an equipment BELPREP-flow® II (BEL JAPAN Inc.) in order to obtain the specific surface area of the material. After the pretreatment, the cell was placed in the equipment BELSORP-max® (BEL JAPAN Inc) in order to take the measurements at 77 K under environmental atmospheric pressure. In addition, 0.005, 0.05, 0.1, 0.15, 0.25, 0.35, and 0.50 g of the material C-180 were placed in polypropylene tubes with 5 mL of deionized water in order to determine the isoelectric point. 24 hours with continuous stirring was the contact time between the material and deionized water in order to guarantee full hydration of the material. After 24 hours, the pH was measured in each one of the mixtures using a Denver Instruments potentiometer.

Table 3.4 presents the results of specific surface area, volume, and pore diameter of the material C-180. These characteristics of the materials can affect the sorption process by limiting or favoring the amount of attracted and retained metal ions during the As(V) removal process.

Table 3.4 Specific surface area of the carbonaceous material

Material	Specific surface area (m^2/g)	Pore volume (cm^3/g)	Pore diameter (nm)
C-180	167.00	0.1053	2.52

The isoelectric point of the material C-180 is pH = 11, with a positive surface charge, which favors the negative ion retention of As(V), such as $H_2AsO_4^-$, $HAsO_4^{2-}$ y AsO_4^{3-}.

3.3.5 As(V) Sorption Studies

A standard of As_2O_5 (Titrisol, MERCK 1000 g ± 0.002 g) was used in the sorption experiments. The effect of the contact time between the material and As ions in aqueous phase was determined at ambient temperature. 30 mg of the material C-180 together with 10 mL of As(V) 30 mg/L solution was placed in polypropylene tubes and stirred at different interval times: 0.25, 0.5, 1, 3, 8, 24, and 48 hours. Additionally, 30 mg of the same material was placed in polypropylene tubes and mixed with 10 mL of a solution of 3, 5, 8, 10, 20, 30, and 40 mg/L of As(V) for 24 hours with constant stirring to obtain the adsorption isotherms. In both cases, after the previous process finished, the samples were centrifuged at 4000 rpm, the recovered solid material was rinsed with deionized water, it was dried at room temperature, and it was stored in polyethylene vials for the As quantification by NAA. The sample irradiation for As analysis was carried out for 2 hours in the SIRCA system with a neutron flux of 9×10^{12} n/cm^2·s. 20 mg of sample was weighed inside polyethylene vials, and 300 μL of As(V) standard reference solution was added. Finally, seven standards of As(V) were prepared in the Whatman 41 filter paper with a low ash content from a 1000 mg/L solution. The standards were irradiated under the same conditions as the samples. The peak in the gamma spectrum of the ^{76}As isotope at the energy of 559.10 kev was used for As quantification.

The experimental data of the As(V) sorption kinetics were adjusted to the kinetic models of pseudo-first order, pseudo-second order, and diffusion-chemisorption, while the adsorption isotherms data was adjusted to Freundlich and Langmuir models. ORIGIN® software was used in both cases.

In accordance with the results obtained previously from the sorption kinetics, the adsorption equilibrium can be reached in 8 hours. The adsorption kinetics experimental data of the C-180 material was adjusted to the kinetic models of pseudo-first order, pseudo-second order, and diffusion-chemisorption. Results show that models of pseudo-second order and diffusion-chemisorption are the ones that best adjust the experimental data. Figure 3.9a shows the data adjustment of the adsorption kinetics from the material C-180 to pseudo-second order model, where the coefficient of determination is $R^2 = 0.9998$. The good adjustment of data to this kinetic model indicates that the material sorption capacity is proportional to the active sites number on the surface, which favors a chemisorption process (Ho and McKay 1999).

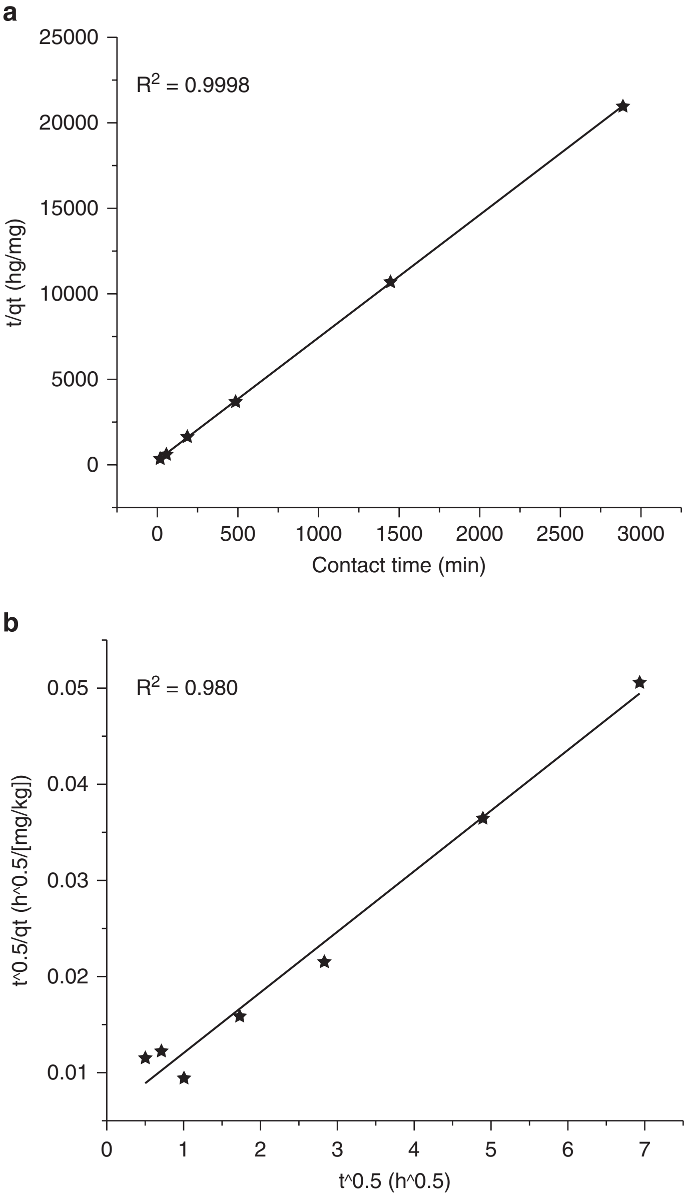

Fig. 3.9 (**a**) Data adjustment to the pseudo-second-order model; (**b**) data adjustment to the diffusion-chemisorption model

Table 3.5 Adjustment parameters of the three kinetic models

Parameter	Pseudo-first order	Pseudo-second order	Diffusion-chemisorption
R^2	0.750	0.999	0.980
q_e (mg/g)	0.099	0.138	0.159
K	9.99×10^{-4}	0.208	0.172

Figure 3.9b shows the data adjustment of the adsorption kinetics from the material C-180 to the diffusion-chemisorption model, where a coefficient of determination $R^2 = 0.980$ is obtained, which indicates that the kinetic data also adjusts properly to this model. Table 3.5 presents the adjustment parameters of the three kinetic models, where it is noted that the adsorption kinetics is best described by the pseudo-second-order model, with a theoretical mass of As(V) retained at equilibrium (qe) of 138.5 mg/kg for the material C-180.

In the scientific literature, some materials conditioned with iron nanoparticles have been found with the same kinetic behavior obtained in this work (Liu et al. 2010; Mostafa et al. 2011). The experimental data adjustment of the adsorption kinetics of the material C-180 to the pseudo-second-order model implies that removal occurs mainly as chemisorption in a monolayer and it is related to the specific active sites number occupied on the sorbent. The mechanism through which the chemisorption process of arsenic by zerovalent iron nanoparticles may occur is through the formation of iron hydroxide. First, zerovalent iron is oxidized to Fe(II), then, the Fe(II) is oxidized to Fe(III), and, immediately, iron hydroxide (III) is formed and takes place a ligands exchange, depending on the arsenic species present (Bang et al. 2005).

The results of sorption experiments show maximum percent removal of 77.39% with a maximum retention capacity of 5.73 mg of As/g. The experimental data was adjusted to the Freundlich and Langmuir isotherm models, as shown below. Figure 3.10 shows the experimental data fitting by Freundlich model, with a coefficient of determination $R^2 = 0.8797$.

The values of the parameters obtained for Langmuir and Freundlich isotherms are given in Table 3.6. It is possible to observe that the Freundlich model describes better the sorption data, which suggests the adsorption of As(V) on heterogeneous surface sites and formation of multilayer of the sorbate at saturation (Altundoğan et al. 2002). In accordance with the fit by Freundlich model, both capacity (K_f) and intensity ($1/n$) values show that the material C-180 is suitable for arsenic removal from aqueous phase.

A Fourier-transform infrared spectroscopy (FTIR) study was performed in the C-180 samples before and after the sorption process in order to identify functional groups involved in the sorption process. A FTIR spectrometer VARIAN® 640-IR was used. The spectra were recorded from 500 to 4000 cm^{-1} at 4 cm^{-1} resolution and ten scans.

Figure 3.11a shows the FTIR spectrum obtained before the sorption process, and Fig. 3.11b shows the FTIR spectrum obtained after the sorption process. In both spectra, it is possible to observe the bands corresponding to the NH, NH_2, C-H, N≡C, N=C=O, C=O, C=C, C-O, and C-C groups. The difference between both

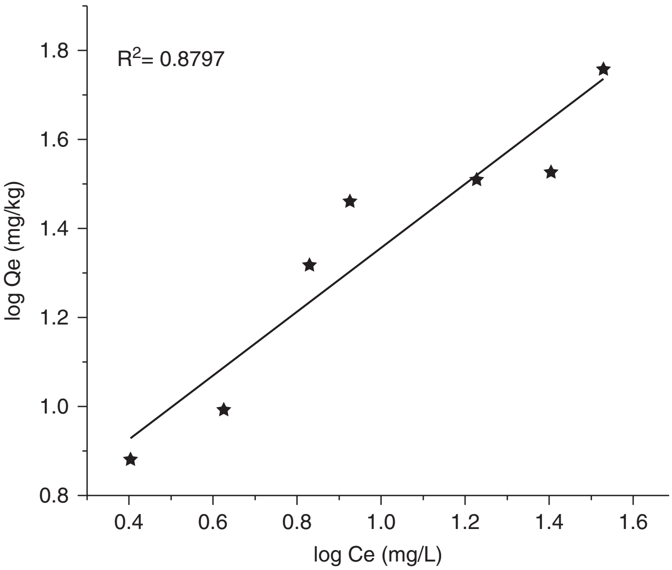

Fig. 3.10 Experimental data fitting by the Freundlich model

Table 3.6 Parameters of the fit by Freundlich and Langmuir isotherm

C-180	
Freundlich	Langmuir
$R^2 = 0.879$	$R^2 = 0.593$
$K_f = 4.332$	$1/Q_m K = 0.302$
$1/n = 0.718$	$1/Q_m = 0.011$

spectra is the bands' intensity at 2984–2895 cm^{-1}, 2362–2334 cm^{-1} and 1055 cm^{-1} after the sorption process. Figure 3.11b indicates that the groups N≡C, C-H and C-O increase in the aqueous phase, suggesting possible involvement in the sorption process of As(V).

3.4 Conclusions

In this research, a novel carbonaceous material with iron nanoparticles coming from pineapple (*Ananas comosus*) peel was obtained through a chemical conditioning with carboxymethylcellulose, hexamine, and ferric nitrate followed by a pyrolysis process to 650 °C for 180 minutes. The average diameter of the nanoparticles obtained was 38.81 nm.

Trace elements in the carbonaceous material were identified and quantified using the technique of neutron activation analysis. These trace elements come from the pineapple (*Ananas comosus*) peel used as raw material in the process, and its

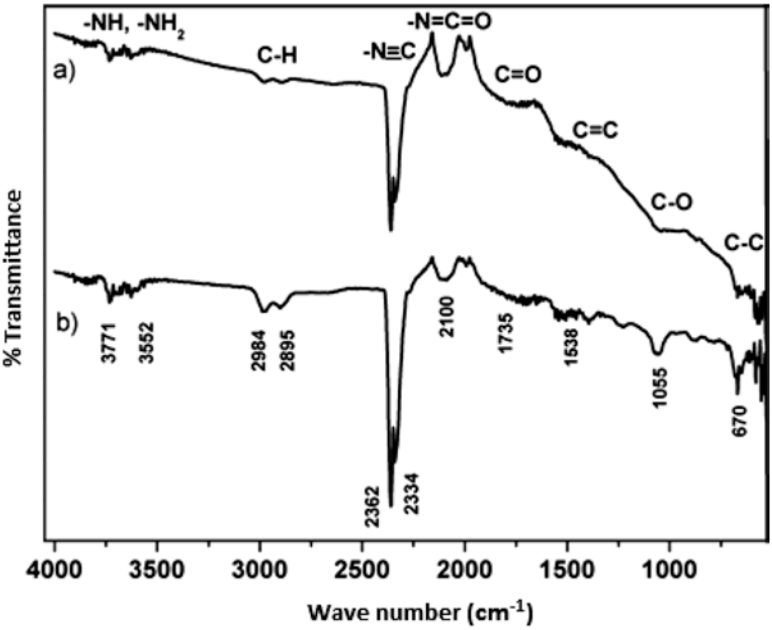

Fig. 3.11 FTIR spectra of the material C-180: (**a**) before the sorption process of As(V) and (**b**) after the sorption process of As(V), Ci = 30 mg/L

presence led to formation of the active sites on the surface, favoring the As(V) removal process. The FTIR results showed the presence of functional groups normally present in the biomass, as well as the isonitrilo and isocyanate groups, which are formed by the interaction of the carbonaceous matrix with the ammonium and hydroxyl radicals coming from the hexamine degradation during the pyrolysis process. XPS results demonstrate the presence of several chemical states of carbon and oxygen, as well as the chemical state O-Fe=O for Fe in the deconvolution of O1s peak. Carbonaceous material with iron nanoparticles presents a specific area of 167.00 m^2/g, site density of 7 ± 1 sites/nm^2, and isoelectric point of pH = 11; these surface features favor the sorption of anions in an aqueous phase.

Physical, chemical, and surface characteristics of the material C-180 subserve the sorption process of As(V), reaching equilibrium in the first 8 hours of contact and retaining 138.5 mg As/Kg. The pseudo-second-order kinetic model is the one that best describes this behavior, showing that the As(V) removal is due to a chemisorption process, which may be affected by changes in the pH solution. The Freundlich model best describes the sorption data for the material C-180, which suggests the adsorption of As(V) on heterogeneous surface sites and formation of multilayer of the sorbate at saturation. The FTIR spectra of the material C-180 before and after the sorption process proved an increase in the signal corresponding to the groups N≡C, C-O y C-H, which indicates possible involvement in the removal of As(V).

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Chapter 4
Potential of Biogenic Plant-Mediated Iron and Iron Oxide Nanoparticles and Their Utility

Ravindra Pratap Singh

Contents

4.1 Introduction

Nanotechnology is manipulation of matter to produce nanomaterials with distinctive properties. A nanoparticle (NP) is a microscopic particle with a minimum of one dimension less than 100 nm in size. They have unique mechanical, optical, thermal, electrical, chemical, and physical properties, which differ from those of bulk materials, and they have a variety of applications in the domains of health care, agriculture, environmental science, energy, information technology, mass communication, heavy industry, consumer goods, biosensor development, nanobiosensor development, biomedicine development, nanobiotechnology, bionanotechnology, diagnostic drugs, therapeutic drug delivery, development of treatments/cures for various infectious and noninfectious diseases and neurodegenerative disorders, drug

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R. P. Singh (✉)
Department of Biotechnology, Indira Gandhi National Tribal University (Central University), Amarkantak, Madhya Pradesh, India

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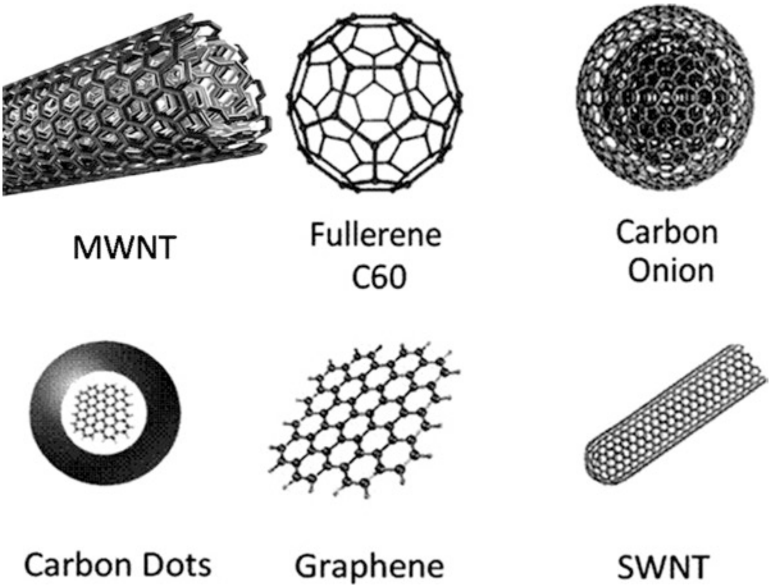

Fig. 4.1 Examples of nanomaterials

delivery using medical diagnostic tools, and cancer treatment agents (specifically, Au nanoparticles, Cu nanoparticles, Fe nanoparticles, etc.) (Singh and Choi 2010; Singh et al. 2010, 2012a, b, c, d, 2014) (Fig. 4.1).

Iron is employed in support railings and as structural beams in cars or buildings. It is also present in water, in blood to move chemical elements, and in magnets. Iron rust is iron oxide, formed from a combination of iron and oxygen. Nanoparticles of both iron and iron oxide are very useful. They are also magnetic in nature. Iron has four odd electrons, whereas the iron chemical compound has only two odd electrons. Fe^0 is black in color, whereas iron oxide is dark brown. In everyday life we are exposed to traces of iron nanoparticles or iron oxide nanoparticles (IONs), and in these trace concentrations they are nontoxic. Both types of iron are present in the environment. IONs are employed in the medical domain, e.g., as contrast agents in magnetic resonance imaging (MRI) or to improve delivery of drug treatments for neoplasms. Biological synthesis of nanoparticles can be a very challenging task and is also known as green synthesis.

Plant-mediated nanoparticle formation provides a lot of biocompatible nanoparticles in comparison with chemical synthesis of nanoparticles, and their application in the medical field can be attributed to the presence of non-toxic chemical species on the surfaces of the nanoparticles. Plant-mediated biological synthesis of nanoparticles has gained importance in recent years. With use of plants and concentrations of phytochemicals, nanoparticles can be synthesized within minutes or hours. IONs have numerous potential applications, and this has encouraged researchers to utilize them in cancer treatment, drug delivery, MRI, wastewater treatment, heat transfer

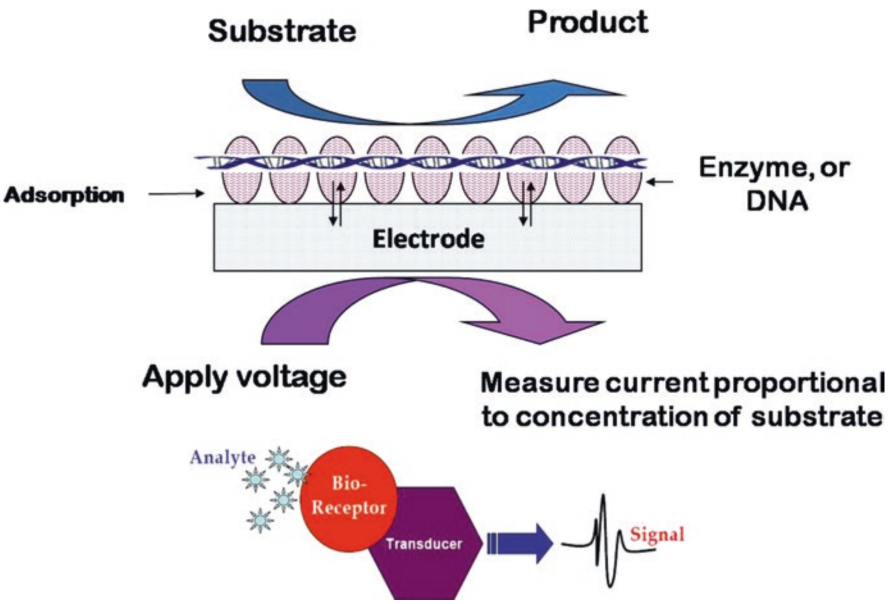

Fig. 4.2 Principle of biosensors

systems as super-robust materials, sensors, biosensors, nanosensors, nanobiosensors, antimicrobial agents, germicidal agents, catalysts, and photocatalysts (Singh et al. 2011; Shukla et al. 2010; Prasad 2014; Singh 2017, 2019) (Fig. 4.2).

Recent prospects in nanobiotechnology have increased utilization of nanomaterials, which could ultimately increase not just their benefits but also their biohazards to health and the environment. In this context, the goal is to develop environmentally benign methods for synthesis of metal and metal oxide nanoparticles to reduce their negative impacts in physicochemical ways. A green technology approach (i.e., a biological approach to synthesis of nanoparticles) has emerged and appears to be eco-friendly and efficient, being economical for very large-scale production of nanoparticles that are very valuable for use in health care, environmental, biotechnological, agricultural, and medical applications (Table 4.1).

Nanoparticles are particles with at least one dimension measuring 1–100 nm. Their properties are chiefly size dependent, with a high surface charge related to their high surface-to-volume ratio, and they have unique thermal, catalytic, optical, electrical, and magnetic properties with the potential for wide use in biological or medical applications such as treatment of metastatic tumors and antimicrobial, mosquitocidal, antiplasmodial, ovicidal, and larvicidal potential for use in the treatment of protozoal infections and infectious disease (Darezereshki et al. 2010; Shameli et al. 2012; Benelli 2016; Benelli et al. 2016; Dinesh et al. 2015; Prasad et al. 2016; Govindarajan and Benelli 2017; Vincent et al. 2017; Govindarajan et al. 2016; Murugan et al. 2015). Cancer is an international health issue. Surgery, chemotherapy, radiation, and immunotherapy are the most common regimens used

Table 4.1 Nanomaterials used in food products and packaging

Nanomaterials	Applications (in use)
Titanium nitride	Improvement of thermal properties, antimicrobial and deodorant agents, ultraviolet light filters, polyethylene terephthalate, refrigerators
Carbon black	Additives, rubbers, silicones, printing inks
Silicon dioxide	Antislipping agents, printing inks, paper and board, rubbers, silicones
Aluminum	Filler in polymers, scratch- and abrasion-resistant coatings, improvement of barrier properties, ultraviolet light filters
Silver	Antimicrobial, antibiotic, and antistatic agents; reusable food containers
Nanoclay	Improvement of barrier properties
Zinc oxide	Ultraviolet light filters, antimicrobial and fungistatic agents, deodorants, plastic glasses, plastic films

for treatment of cancer. They kill not only cancer cells but also normal cells (Tan et al. 2011; Kuppusamy et al. 2016).

Physicochemical methods for synthesis of IONs—such as sol–gel reactions, sonochemical methods, hydrothermal methods, microemulsion methods, flow injection synthesis, radiolysis, microwave methods, aerosol pyrolysis, and laser pyrolysis—have been established (Bagheri et al. 2013; Abdullah et al. 2017; Vijayakumar et al. 2000; Giri et al. 2005; Vidal-Vidal et al. 2006; Salazar-Alvarez et al. 2006; Abedini et al. 2014; Carenza et al. 2014; Tartaj et al. 2004; Bomati-Miguel et al. 2008). Nanoparticles synthesized by physicochemical methods not only lose their reactivity as a result of aggregation of air exposure, magnetism, and dispersibility but also cause contamination due to toxic solvents, by-products, and chemical precursors (Kim et al. 2008; Wu et al. 2008; Thakkar et al. 2010a).

In view of the aforementioned shortcomings, there is a growing trend toward use of clean, simple, inexpensive, and environmentally friendly approaches for synthesis of metal/metal oxide nanoparticles, using bacteria, fungi, algae, and plant extracts (Prasad et al. 2016, 2018). Plant-mediated nanoparticles are less expensive and simpler, less time consuming, much easier, and safer to use (Prasad 2014). Plant-mediated synthesis of nanoparticles is a green method for synthesis of iron and IONs, using aqueous plant extracts. Basavegowda et al. (2014a) reported green fabrication of ferromagnetic Fe_3O_4 nanoparticles and their novel catalytic application for synthesis of biologically interesting benzoxazinone and benzothioxazinone derivatives, using a fruit extract of *Artemisia annua*. Basavegowda et al. (2014b) reported use of sonochemically synthesized ferromagnetic Fe_3O_4 nanoparticles as a recyclable catalyst for preparation of pyrrolo[3,4-c]quinoline-1,3-dione derivatives, using a leaf extract of *Perilla frutescens*. Venkateswarlu et al. (2013) reported biogenic synthesis of Fe_3O_4 magnetic nanoparticles (MNPs) using a peel extract of plantain. Yew et al. (2016) reported green synthesis of magnetite (Fe_3O_4) nanoparticles using an extract of the seaweed *Kappaphycus alvarezii*.

Different parts of the *Juglans regia* tree—such as its kernels, leaves, tree bark, and green fruit husks—have been utilized in both the pharmaceutical industry and the cosmetic industry (Izadiyan et al. 2017; Stampar et al. 2006). Carvalho et al.

(2010) demonstrated antioxidant and antimicrobial activities of walnut leaves, seeds, and green husks, with use of low-cost natural materials to develop the same applications. Flavonoids, flavones, isoflavones, isothiocyanates, carotenoids, and polyphenols are also known natural resources for synthesis of metallic nanoparticles. Flavonoids have been identified to be responsible for the reduction of metal salts to synthesize IONs, along with polyhydroxy groups in santin, tannins, and saponins acting as capping agents. The presence of phenols, alkaloids, saponins, cardiac glycosides, steroids, carbohydrate, and proteins in plants has been reported to be responsible for reduction of ferric ions into nanoforms. Phenolic compounds, tannins, and alkaloids have been used for formation and stabilization of synthesized nanoparticles (Thakkar et al. 2010b).

This chapter describes synthesis of IONs with and without use of plant extracts to determine the role of these extract compounds in size control. Chang et al. (2012) reported preparation and characterization of a Fe_3O_4/graphene nanocomposite and investigation of its adsorption performance for aniline and p-chloroaniline. Chourpa et al. (2005) reported molecular composition of IONs for use as precursors for magnetic drug targeting, as characterized by confocal Raman microspectroscopy. Garcıa-Jimeno and Estelrich (2013) described a ferrofluid based on polyethylene glycol (PEG)–coated IONs, with its characterization and properties. Gholoobi et al. (2017) reported biopolymer-mediated synthesis of Fe_3O_4 nanoparticles and investigation of their in vitro cytotoxicity effects. Gupta and Gupta (2005) reported synthesis and surface engineering of IONs for biomedical applications. Hribernik et al. (2012) reported synthesis of magnetic iron oxide particles and development of an in situ coating procedure for fibrous materials. Karaoglu et al. (2011) reported synthesis and characterization of a dl-thioctic acid (DLTA)–Fe_3O_4 nanocomposite. Pardoe et al. (2003) reported an MRI-based method for measurement of tissue iron concentrations in liver arterially embolized with ferromagnetic particles designed for magnetic hyperthermia treatment of tumors. Shameli (2013) reported synthesis of talc/Fe_3O_4 magnetic nanocomposites using a chemical coprecipitation method. Zhao et al. (2010) reported magnetic and inductive heating properties of Fe_3O_4/PEG composite nanoparticles with a core–shell structure. Latha and Gowri (2014) reported ION synthesis using leaf extracts of *Carica papaya* and showed plate-like structures with coarsened grains and uniformly distributed small spherical particles. Senthil and Ramesh (2012) reported that carbohydrates containing *Tridax procumbens* plant extract were responsible for Fe_3O_4 nanoparticle synthesis at room temperature, and also revealed the presence of alkaloids, carotenoids, flavonoids, saponins, and tannins, reported to be responsible for the Fe_3O_4 nanoparticle synthesis.

Synthesis of metal and metal oxide nanoparticles by biological methods may lead to development of clean, environmentally acceptable, and nontoxic nanoparticles. Biosynthesis of safe and easily distributed IONs uses plant extracts with single and mixed iron salts.

4.2 Contrast Agents for Magnetic Resonance Imaging

MNPs are used as contrast agents for MRI because they have superparamagnetic properties, which permit them to be magnetized only under the influence of an externally applied magnetic flux, and to lose this magnetization once the field is deactivated. This property permits superparamagnetic IONs (SPIONs) to be employed in MRI as negative contrast agents. The pharmacokinetic properties of SPIONs permit them to accumulate, in a very nonspecific manner, in the mononucleate somatic cell system, which facilitates their use in MRI of organs such as the liver and spleen, lymph nodes, and bone marrow (Josephson et al. 1988; Park et al. 2009; Wang 2011; Hemmingsson et al. 1987; Weissleder et al. 1990; Seneterre et al. 1991). Arami et al. (2015) reported use of IONs either as effective bioimaging contrast agents or as carriers of biomolecules such as drugs, nucleic acids, and peptides for controlled delivery to specific organs and tissues. They noted that many vital criteria (e.g., size and size distribution, charge, coating molecules, and plasma supermolecule adsorption) may be effectively tuned to regulate the in vivo pharmacokinetics and biodistribution of the iron oxides. Skaat et al. (2013) described antibody-conjugated, dual-modal, near-infrared fluorescent IONs for antiamyloidgenic activity and specific detection of amyloid-β (Aβ) fibrils. The Aβ peptide is the main fibrillar component of plaque deposits found in brains affected by Alzheimer disease (AD) and is related to the pathogenesis of AD.

In a critical review, Ferguson et al. (2013) reported that magnetic particle imaging (MPI) is a promising new modality for imaging the distribution of ION tracers in vivo with high contrast, high sensitivity, and smart spatial resolution for clinical imaging in angiography and oncology. Ittrich et al. (2013) reported the use of SPIONs to image physiological processes and anatomical, cellular, and molecular changes in disease. The clinical applications range from imaging of tumors and metastases in the liver, spleen, and bone marrow to imaging of lymph nodes and the central nervous system (CNS), magnetic resonance angiography (MRA), perfusion imaging of atherosclerotic plaques, and thrombosis imaging. The authors described new experimental approaches in molecular imaging, using undirected superparamagnetic iron oxide (SPIO) trapping (passive targeting) in inflammation, tumors, and associated macrophages with directed accumulation of SPIO ligands (active targeting) in tumor endothelia and tumor cells, areas of programmed cell death, infarction, inflammation, and degeneration in cardiovascular and neurological diseases, and in atherosclerotic plaques or thrombi. They additionally reported the labeling of stem or immune cells to permit visualization of cell therapies or transplant rejection. Further, they reported coupling of SPIOs to ligands, radiotherapeutics, and/or chemotherapeutics, embedding in carrier systems or activatable smart device probes, and externally controlled focusing (physical targeting) to modify molecular tumor therapies or to image metabolic and catalyst processes. Finally, they speculated that monodispersed SPIOs with defined physicochemical and pharmacodynamic properties will improve SPIO-based MRI in the future, and use of SPIONs as targeted probes in diagnostic magnetic resonance (DMR) using chip-based micronuclear magnetic resonance (μNMR) may considerably expand the spectrum of in vitro analysis strategies for biomarkers, pathogens, and tumor cells.

As a brand new imaging modality, MPI offers new applications for SPIOs in cardiovascular, oncological, cellular, and molecular diagnostics and medical care. Bellusci et al. (2014) studied SPIONs as candidate contrast agents for MRI and targeted drug delivery. They stated that biodistribution and toxicity assessments are essential for the development of nanoparticle-based drugs, owing to nanoparticle-enhanced biological reactivity, and they investigated the in vitro and in vivo potential toxicity of metallic element solid solution ($MnFe_2O_4$) nanoparticles, using cultures of murine Balb/3T3 fibroblasts. Park et al. (2014) reported the effects of PEG molecular weight on the stability, T_2 contrast, cytotoxicity, and cellular uptake of SPIONs. The monodispersed SPIONs were synthesized and coated with PEG of variable molecular weights. They showed adequate stability and magnetic contrast, and exhibited minimal cytotoxicity and nonspecific cellular uptake. This work provided insights into the potential for safe clinical application of SPIONs.

The current research on SPIONs is opening up wide horizons for their use as diagnostic agents in resonance imaging and as drug delivery vehicles. Delivery of malignant neoplasm treatments to their target sites by coupling with functionalized SPIONs is one of the foremost areas of research in the development of cancer treatment strategies. In addition, SPIONs have incontestable potency as nonviral cistron vectors, which facilitate the introduction of plasmids into the nucleus at rates many times those of commonly available normal technologies. SPION-induced hyperthermia has additionally been utilized for localized killing of cancerous cells. Despite their potential medical specialty applications, alterations in gene expression profiles, disturbances in iron homeostasis, oxidative stress, and altered cellular responses are SPION-related toxicity aspects that need to be considered. A comprehensive understanding of SPIONs with regard to their preparation techniques, their utility as drug delivery vehicles, and a few other considerations is required before they can move from the benchtop to the bedside. Wahajuddin and Arora (2012) reported use of SPIONs as a magnetic nanoplatform for a targeted drug delivery system. SPIONs are small, synthetic γ-Fe_2O_3 (maghemite) or magnetic iron ore particles with a core ranging between 10 nm and 100 nm in diameter.

These magnetic particles are coated with certain biocompatible polymers, such as dextran or PEG, which provide chemical handles for conjugation of therapeutic agents and additionally improve the blood distribution profile. Tsuchiya et al. (2011) reported a histological study of the biodynamics of iron chemical compound nanoparticles with totally different diameters. Kucheryavy et al. (2013) reported synthesis of magnetic iron ore nanoparticles within a size range of 3.2–7.5 nm and in high yields under variable reaction conditions, using high-temperature hydrolysis of precursor iron(II) and iron(III) alkoxides in a diethylene glycol solution. The average sizes of the particles were adjusted by varying the reaction temperature and time, and by employing a consecutive growth technique. To obtain γ-iron(III) oxide particles within the same range of sizes, magnetite particles were oxidized with dry oxygen in diethylene glycol at room temperature. This resulted in an improved prospective imaging agent thanks to its chemical stability. Dadashzadeh et al. (2013)

reported that labeling of cells with SPIONs provided the flexibility to trace cells by MRI. Quantifying intracellular iron concentrations in SPIO-tagged cells would allow comparison of agents and techniques used to magnetically label cells. Kut et al. (2012) assessed the potential for injury to normal tissues in mice due to heating of systemically delivered MNPs in an alternating magnetic flux (AMF).

MNPs with even a modest heat output will cause harm, and even death, when sequestered in adequate concentrations. Dextran–SPIONs are deposited in the liver and spleen, making these sites of potential toxicity. Sun et al. (2012) reported in vitro labeling of endothelial progenitor cells (EPCs) isolated from peripheral blood with SPIONs. Transplantation of EPCs provides a completely unique methodology for treatment of human tumors or vascular diseases. MRI has been established to be effective in following transplanted stem cells through labeling of the cells with SPIONs. Rabbit peripheral blood EPCs were effectively labeled with home-synthesized SPIONs, with no influence on their main biological characteristics.

Kim et al. (2013) reported cerebral blood volume (CBV) MRI with intravascular SPIONs. The CBV could be a crucial physiological indicator of tissue viability and vascular reactivity. CBV-weighted functional MRI (fMRI) with ultrasmall SPIONs (USPIONs) provides increased sensitivity, a reduced large-vessel contribution, and improved spatial specificity relative to standard blood oxygenation level–dependent fMRI, and measures a single physiological parameter that is easily interpretable.

Toki et al. (2013) described a comprehensive analysis of transfection-assisted delivery of IONs to nerve fiber cells, with elaborated data on toxicity and the potency of polylysine (PL)–facilitated uptake of USPIONs by nerve fiber cells for cell-specific MRI. PL has been used to facilitate nerve fiber cell uptake of SPIONs to be used in MRI. The data suggested that utilization of PL to boost the labeling of dendritic cells (DCs) with SPIONs could be worthwhile. Acceptable standardization of the incubation time and concentrations of PL and SPIONs is crucial for the development of MRI technology for noninvasive imaging of DCs in vivo.

Starmans et al. (2013) reported ION micelles for sensitive (molecular) MPI and MRI. IONs are a promising nanoplatform for contrast-enhanced MRI as a brand new imaging modality that is able to directly visualize magnetic particles and provides a sensitive and quantitative alternative to MRI. The FibPep-ION-Micelle platform provides in vivo, noninvasive imaging of fibrin in diagnostic models of thrombus-related pathologies and coronary artery disease.

Schweiger et al. (2012) reported quantification of the internalization patterns of SPIONs with opposite charges. Shevtsov et al. (2014) reported a study of SPIONs conjugated with recombinant human epidermal growth factor (EGF) as a possible agent for MRI contrast enhancement for malignant brain tumors, using a C6 brain tumor cell culture. SPION–EGF conjugates offer targeted delivery and economical magnetic resonance contrast improvement of EGF receptor (EGFR)–overexpressing C6 gliomas.

Wei et al. (2012) reported use of compact zwitterion-coated IONs for biological applications. The potential of SPIONs in various medical specialty applications, together with MRI, sensing, and drug delivery, requires that their surface be derivatized to be hydrophilic and biocompatible. The authors reported synthesis of a compact and water-soluble zwitterionic dopamine sulfonate (ZDS) ligand with sturdy binding affinity for SPIONs. Simberg et al. (2009) reported a differential genetic analysis of the surface heterogeneity of dextran–IONs and also the implications for their in vivo clearance.

These data offer possibilities for a rational type of bioinert, long-circulating nanoparticles. Uchiyama et al. (2015) evaluated the use of cationic USPIONs as a nontoxic and economical MRI contrast agent and magnetic targeting tool. Cationic USPIONs provide a useful platform for the recent development of new materials for applications in theranostics.

Zaloga et al. (2015) reported that different storage conditions influence the biocompatibility and physicochemical properties of IONs. Their effectiveness of this therapy is dependent on the magnetic properties, stability, and biocompatibility of the particles. Ziv-Polat et al. (2012) described novel magnetic fibrin hydrogel scaffolds containing thrombin and growth factors conjugated with IONs for tissue engineering. Tomitaka et al. (2015) reported use of lactoferrin-conjugated IONs for targeting brain tumor cells in MPI. MPI could be a new real-time imaging modality, guaranteeing high tracer mass sensitivity and spatial resolution directly generated from IONs. Chao et al. (2012) reported recognition of dextran–SPION conjugates (Feridex) via macrophage scavenger receptor charged domains. Dextran-coated SPIONs (dextran–SPION conjugates) offer the chance to enhance MRI imaging sensitivity so that small or diffuse lesions can be detected. Juang et al. (2013) reported MRI of mouse islet grafts labeled with novel chitosan-coated SPIONs. They found that after syngeneic and allogeneic transplantation, islets labeled with these nanoparticles could be effectively and safely imaged by MRI. Gamarra et al. (2010) described use of MRI for quantification of SPIONs in biological materials. Ren et al. (2011) reported facile, high-potency immobilization of lipase enzyme on magnetic IONs via a biomimetic coating. Immobilization of lipase on suitable solid supports is a method to boost stability and activity, and may be reused for very large-scale applications.

The quest for a simple, cost-effective, and high-loading-capability technique continues to be challenging. Immobilization of enzymes onto magnetic IONs via polydopamine film is economical. Kolhatkar et al. (2015) reported primary in vitro enzymatic synthesis of paramagnetic and magnetic nanoparticles for magnetic enzyme-linked immunosorbent serological assay coverage. Enzymatic synthesis of magnetic labels reduced costs and avoided the diffusional mass transfer limitations associated with presynthesized magnetic reporter particles, while retaining the benefits of magnetic sensing.

Magnetic IONs are renowned for their applications in MRI, hyperthermia, targeted drug delivery, etc. Surface modification of those MNPs has been explored extensively to realize functionalized materials with potential applications in medicine, environmental science, and catalysis. Bhandari et al. (2016) reported a unique and versatile single-step methodology for developing curcumin-functionalized magnetic Fe_3O_4 nanoparticles with no further linkers, employing a straightforward coprecipitation technique. The MNPs were characterized using transmission microscopy, x-ray diffraction, Fourier transform infrared (FTIR) spectroscopy, and thermogravimetric analysis. The developed MNPs were utilized in a cellular application for protection against an inflammatory agent—a polychlorinated biphenyl (PCB) molecule. Beckers et al. (2013) reported improved effects of nanometer-sized metallic (Pd, Ag, and Cu) and metallic oxide (Fe_xO_y) nanoparticles, encapsulated in porous silicon dioxide, on fermentative biohydrogen production from glucose by *Clostridium butyricum* bacteria. They observed an improvement in electron transfer through combinations of enzymatic activity and inorganic materials. Granot and Shapiro (2011) reported release activation of IONs (REACTION)—a completely unique, environmentally sensitive MRI paradigm.

Smart contrast agents for MRI-based cell tracking would enable utilization of MRI methodologies to detect not just the location of cells but also gene expression. Muller et al. (2008) studied the effect of atorvastatin on uptake of USPIONs (ferumoxtran-10) in human monocyte macrophages and its implications for MRI. Ferumoxtran-10 is beneficial as a contrast material in MRI for diagnosis of inflammatory and degenerative disorders related to high scavenger cell activity. Atanasijevic et al. (2006) described use of calcium-sensitive MRI contrast agents based on SPIONs and calmodulin.

Roh et al. (2006) reported extracellular synthesis of magnetic iron ore and metal-substituted magnetite nanoparticles. They developed a novel microbial method that exploited the ability of Fe(III)-reducing microorganisms to supply copious amounts of extracellular magnetites and metal-substituted magnetite nanoparticles. The Fe(III)-reducing microorganisms (*Theroanaerobacter ethanolicus* and *Shewanella* sp.) had the ability to reduce Fe(III) and various metals in aqueous media and formed various-sized magnetic iron ore and metal-substituted magnetite nanocrystals. The Fe(III)-reducing microorganisms formed the metal-substituted magnetites using iron oxide and other metals (e.g., Co, Cr, Mn, and Ni) in conditions of a comparatively low temperature (<70 °C), ambient pressure, and neutral to slightly basic hydrogen ion concentrations (pH 6.5–9). Baumgartner et al. (2016) reported elongated magnetite nanoparticle formation from a solid metallic element precursor in a very magnetotactic microorganism. Magnetotactic microorganisms are aquatic microorganisms that intracellularly mineralize ferrimagnetic nanoparticles, enabling the cells to align with the geomagnetic field. The microorganisms produce a magnetic mineral of a species-specific phase (magnetite $Fe(II)Fe(III)_2O_4$ or greigite $Fe(II)Fe(III)_2S_4$), size, morphology, and particle assembly. The authors investigated the formation of such irregularly shaped nanomagnets in the species *Desulfovibrio magneticus* RS-1. Their findings represented a completely unique observation on the interconversion of iron (oxyhydr)oxide materials, and they recommended that solid-state growth processes might be needed to supply irregularly shaped, elongated magnetic iron ore nanocrystals.

Cheng and Hsu (2017) used a facile technique to organize SPIO- and hydrophobic drug–encapsulated perishable polyurethane nanoparticles for use in a variety of medical applications such as MRI, targeting, and hyperthermia therapy. Norouz Dizaji et al. (2016) described an environmentally friendly procedure for silver (Ag) or gold (Au) deposition onto magnetic iron ore nanoparticles, using plant extracts

(*Ligustrum vulgare*) as reducing and stabilizing agents. The magnetic iron ore nanoparticles (measuring ~6 nm) with superparamagnetic properties were synthesized by coprecipitation of Fe^{2+} and Fe^{3+} ions. Color changes indicated differing amounts of Au and conductor ions reduced and deposited onto the SPIONs when the plant extracts were used. Magnetic saturation decreased when the quantity of the metallic deposition was magnified, which was measured by vibrating-sample magnetometry (VSM). The Ag/Au–deposited SPIONs were stable, and virtually no agglomeration was discovered for months. The Ag/Au–carrying magnetite nanoparticles originated from the plant extracts.

Wang et al. (2016) reported in vitro assessment of physiological changes in watermelon (*Citrullus lanatus*) growth with exposure to IONs. Nanobased iron fertilizer is used in agricultural applications. The authors reported that γ-Fe_2O_3 nanoparticles seemed to display an intrinsic peroxidase-like activity and had the power to improve iron deficiency chlorosis and promote the expansion of the watermelon plants.

4.3 Wastewater Treatment

Water is a universal solvent and is essential for life on earth. Two thirds of the earth's surface is covered by water, and 97% of the world's water is found in the oceans. Only 2.5% of the world's water is nonsaline H_2O, 75% of which is bound up in glaciers and ice caps; the remaining 25% of it is found in lakes, ponds, and rivers. Water is an essential resource for living systems, industry, agriculture, and domestic use. An adequate supply of safe water is a prerequisite for a healthy life.

Pollution occurs when a product added to the natural environment adversely affects nature's ability to dispose of it. Waste products adversely interfere with the health, comfort, property, and life style of individuals. Most pollutants are introduced into the environment as biodegradable pollution, agricultural waste, domestic waste, industrial waste, accidental discharges, and compounds used for plant and animal protection. As a result of the increasing demand for water and the shortage of its supply, it is necessary to intensify the development of water resources in the world and to ensure that water is used efficiently by appropriate treatment and management of this resource (Itodo and Itodo 2010).

A brand new quaternary magnetic $Fe_3O_4/ZnO/Ag_3VO_4/AgI$ nanocomposite has been developed and was shown to be an excellent visible-light-driven photocatalyst, fabricated via preparation of a $Fe_3O_4/ZnO/Ag_3VO_4$ nanocomposite followed by coupling of it with silver iodide through ultrasonic irradiation. The magnetic properties of the nanocomposite offered a convenient way to separate the photocatalyst from the reaction mixture by use of an external magnet (Aziz and Gohari 2016).

Iron nanoparticles obtained from tea leaf extract have been shown to contain iron compounds and oxohydroxide. Shahwan et al. (2011) reported green synthesis of iron nanoparticles and the effectiveness of their application as a Fenton-like catalyst for removal of aqueous cationic and anionic dyes, such as methylene blue and methyl orange, over a large range of concentrations (10–200 mg L^{-1}).

Chromium is used in a variety of industries and plays specific roles in refractories, alloy production, electroplating, pigment production, catalyst generation, and animal skin tanning. It is found in the environment as trivalent and hexavalent ions. Trivalent chromium is employed as a necessary macronutrient for the regulation of lipid, supermolecule, and protein metabolism; however, excessive concentrations may cause toxicity due to disturbances of red blood cell membranes and may also cause skin irritation. Hexavalent chromium is even more toxic. It can penetrate the skin and kill cells, and it can damage polymers through generation of reactive oxygen species (ROS). The World Health Organization (WHO) has reported that chromium is genotoxic and is recognized as an individual group 1 carcinogen. Widespread ecosystem exposure to chromium poses an environmental threat; thus, removal of Cr(VI) from the environment is probably necessary. Remediation of soil, water, etc., to remove chromium is an urgent requirement.

The utility of nanoparticles for remediation of hexavalent chromium species has been demonstrated (Guertin et al. 2016; Mishra and Bharagava 2016; Owlad et al. 2009). Keller et al. (2012) reported toxicity of three commercial forms (uncoated, with an organic coating, and with an iron oxide coating) of nanoscale zero-valent iron (nZVI) to freshwater and marine organisms—specifically, three species of marine phytoplankton, one species of freshwater plant, and a freshwater zooplankton species (*Daphnia magna*). These organisms could be exposed downstream of wherever nZVI is applied to remediate contaminated soil. Zhu et al. (2008) reported uptake, translocation, and accumulation of factory-made IONs by pumpkin plants (*Cucurbita maxima*) grown in a liquid medium containing iron ore (Fe_3O_4) nanoparticles. Duan et al. (2014) described use of hierarchical hybrid peroxidase catalysts for remediation of phenol wastewater. Zhang et al. (2014) reported a straightforward solvothermal method for fabrication of a metal–organic framework with an iron oxide enclosure for determination of organophosphorus pesticides in biological samples. Cheng et al. (2015) reported removal of pentachlorophenol (PCP) from water with use of nZVI as a heterogeneous Fenton catalyst in an nZVI/H_2O_2 system; nZVI is an environmentally benign material and has been widely used as a reducing agent in treatment of environmental pollutants. The initial H_2O_2 concentration considerably influenced the phencyclidine removal rate, and nZVI performed better than commercial zero-valent iron (ZVI) as a catalyst. Moreover, iron ore (Fe_3O_4), which was the most abundant product of corrosion of the nZVI, was found to perform well as an adsorbent and catalyst; thus, it allowed the nZVI to be effectively reused. Wu et al. (2009) reported utilization of Fe^0 nanocomposites stabilized with extremely reactive iron ore (Fe_3O_4) nanoparticles for reduction and mitigation of hexavalent chromium(VI) species in liquid solutions. Zhou et al. (2016) reported utilization of Fe/Ni bimetallic particles to remove Cr(VI) from an aqueous solution in an ultrasound-assisted system across a pH range of 3–9.

Synthesis of iron nanoparticles through reduction of iron salt precursors with plant extracts has been widely established. What is more challenging is finding ways to control their properties—specifically, their size, shape, reactivity, monodispersity, oxidation potential, crystallinity, etc. (Valle et al. 2017). Wang et al. (2014) synthesized iron nanoparticles with green tea and eucalyptus leaves, which were able to remove nitrate. Luo et al. (2016) showed that grape leaf–mediated synthesis of Fe/Pd bimetallic nanoparticles removed orange II dye from a solution. Martinez-Cabanas et al. (2016) used eucalyptus-generated iron nanoparticles encapsulated in a chitosan matrix for removal of As(V) in column flow-through experiments.

Liu et al. (2008) evaluated oxidation of IONs, using humic acid and carbon as coating materials, for economical removal of heavy metals in water. Herrera-Becerra et al. (2007) reported that plant biomass not only provided an ample supply of carbon to coat as-synthesized nanoparticles with or without pretreatment but also served as a reducing agent when the hydrogen ion concentration was controlled. The hydrogen ion concentration was a size-limiting parameter. Ramasahayam et al. (2012) developed a protocol for microwave-assisted synthesis of a magnetic nanocomposite, using pinewood shavings and a spacer (saturated NaCl), and oven drying without microwaving and use of a spacer. Tannin played an important role in the production of reduced iron oxide using pinewood shavings and a spacer, while plastic materials were also used to synthesize and stabilize metal nanoparticles with oven drying without microwaving and use of a spacer. The reduced iron oxide nanocomposite size resulting from use of this protocol was used to remove phosphorus from water.

Lopez-Tellez et al. (2013) described use of ethanol-treated orange peel powder to synthesize iron oxide nanorods. The cellulose content of the orange peel functioned as a reducing agent for the metal ions, and the nanoparticles that were formed were stabilized on the surface of the orange peel by electrostatic and weak van der Waals interactions between the reduced form of the metal and the functional groups of the cellulose and hemicellulose components. The researchers found that iron was deposited on the surface of the biomass in the forms of iron, iron(II) oxide, and iron ore, and it was shown that this nanobiocomposite removed chromium from sewer water. Lunge et al. (2014) reported synthesis of inexpensive iron ore nanoparticles, using tea waste as a template, and identified a cuboid/pyramid-shaped crystal structure of magnetite nanoparticles with a size range of 5–25 nm. Additionally, they used as-synthesized nanoparticles for removal of arsenic (As(III) and As(V)) and demonstrated higher adsorption capability.

The use of IONs in medicine and environmental remediation has led to considerations concerning exposure of the general public to those nanoparticles. Few studies are available to gauge their effects on the environment, particularly on plants and food crops. Bombin et al. (2015) described the biological processes and reproductive effects of IONs in *Arabidopsis thaliana*. They investigated the consequences of positively charged (PC) and negatively charged (NC) Fe_2O_3 IONs on the physiology and reproductive capability of cress plants at concentrations of 3 and 25 mg/L. The plants treated with the 3-mg/L concentration failed to show evident effects on seeding and root length. The treated plants failed to show any discernible phenotypical changes in overall size or general natural characteristics, indicating that environmental nanoparticle contamination may be dangerously underestimated.

In agriculture, pesticides have became one of the key environmental pollutants. Fe_3O_4 IONs coated with catalysts, enzymes, or maybe even antibodies could be used as biosensors. Ali et al. (2013) described a potentiometric urea biosensor utilizing a chitosan–magnetic ION nanobiocomposite. Chauhan et al. (2016) prepared a nanobiocomposite from Fe_3O_4 and poly(indole-5-carboxylic acid) for detection of pesticides such as malathion and chlorpyrifos in a large range of concentrations (0.1–70 nm). Iron nanoparticles in the elemental state have additionally been utilized for purification of water and tested against reductive dehalogenation of organochlorine pesticides and insecticides, and chromium and arsenic. Modification of agglomeration of iron nanoparticles by use of surfactants not only reduces organochlorine pesticides but also prevents corrosion (Wang and Zhang 1997; Lien and Zhang 2001; Zhang 2003; Hu et al. 2004; Kanel et al. 2006). Mukherjee et al. (2015) reported utilization of ZVI particles made from steel industry waste for in situ remediation of groundwater contaminated with the organochlorine pesticide heptachlor.

Pesticides utilized in agriculture are somewhat harmful to animals and plants, and use of IONs for their removal could be very useful. Keum and Li (2004) reported reduction of nitroaromatic pesticides with ZVI and recommended its use for remediation, but this would release unhealthy residues into the environment.

4.4 Sensors/Biosensors/Nanosensors/Nanobiosensors

There are current trends and challenges associated with use of smart nanomaterials for various applications that pertain to biosensor development, engineering science, and nanobiotechnology. These growth areas can have a motivating influence on the manifestation of the latest ultrabiosensing devices (nanobiosensors) to resolve severe pollution issues in the future, which not only pose threats to human health but will also have adverse effects on other living entities (Singh 2016). These sensors could have various applications in the clinical, environmental, and agricultural fields (Prasad et al. 2014, 2017). Their ability to sense chemicals and biological agents that are present in air, foodstuffs, and water could be of interest. They will pioneer the ways in which the quality of air, food, and water is measured, because of their size and the speed and accuracy of their measurements (Fig. 4.3).

Top-down lithography, bottom-up assembly, and molecular self-assembly are the main strategies for producing nanosensors. These include chemical nanosensors (detecting very tiny amounts of chemical vapors), nanobiosensors (for cancer detection), nanoscale electrometers, deployable nanosensors, and multianalyte sensing element arrays (e.g., for chemical monitoring and disease detection). The particulars of the nanostructures (e.g., their size) and also the materials being used are essential in developing nanosensors such as nanoscale wires (with the capability for extreme detection sensitivity), carbon nanotubes (with very large surface areas), thin films, and nanoparticles.

The main advantage of nanosensors lies in their extraordinarily high surface-to-volume ratios, which permit high sensitivity and detection of as little as one molecule

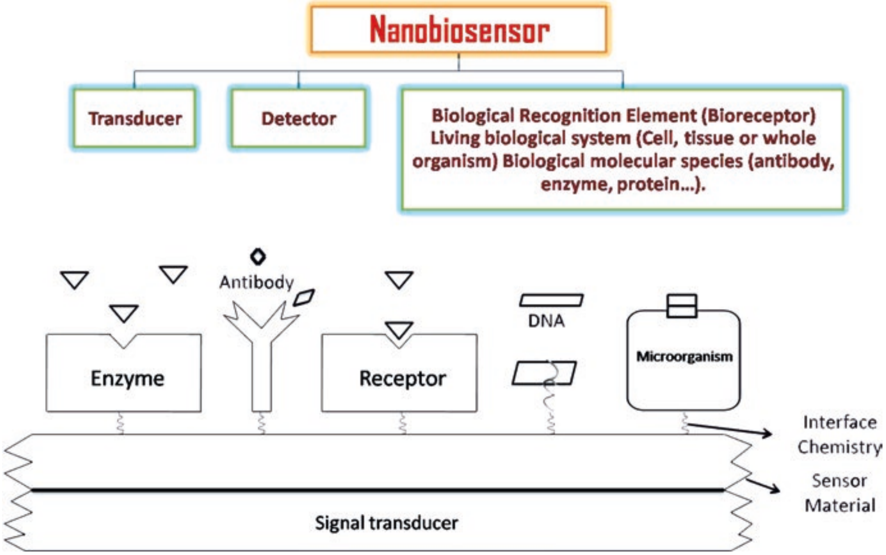

Fig. 4.3 Principle of nanobiosensors

or atom. MNPs have good potential for magnetic hyperthermia treatment, drug delivery, and cell sorting (Hilger et al. 2002; Li et al. 2015; Kocbek et al. 2013). Paramagnetic IONs can be used as contrast agents in MRI and photothermal therapy for cancer. Fe_3O_4 MNPs can be used for liver imaging, as a contrast agent for MRI, in immunochemical assays, for biosensing, and for drug delivery. Silica-coated iron oxide PEG-coated nanoparticles with a contrast component of gadolinium (Gd) have been used to access a particular area of the brain to find a neoplasm (Marcus et al. 2016; Yoo et al. 2008; Yu et al. 2008; Kamat et al. 2010, Singh 2016). IONs exhibit good biocompatibility and are regarded as stable. IONs labeled with antibodies can be used to detect carcinoma cells in vitro. Additionally, IONs conjugated with luteinizing hormone–releasing carcinoma cells can be used to find carcinoma in vivo (Artemov et al. 2003).

Karlsson et al. (2008) reported that copper oxide nanoparticles were extremely toxic in a comparison between metal oxide nanoparticles and carbon nanotubes. The manufacture and use of nanoparticles are increasing; humans are exposed to them occupationally or via merchandise and also via the environment. Different metal oxide (CuO, TiO_2, ZnO, $CuZnFe_2O_4$, Fe_3O_4, and Fe_2O_3) nanoparticles and nanotubes have been investigated and compared with regard to their cytotoxicity and ability to cause DNA injury and oxidative stress. Their toxicity was compared with that of carbon nanoparticles and multiwalled carbon nanotubes (MWCNTs), using the human respiratory organ epithelial cell line A549, which was exposed to the particles, and the cytotoxicity was analyzed using trypan blue staining. DNA injury and oxidative lesions were determined using a comet assay, and intracellular production of ROS was measured using the oxidation-sensitive fluoroprobe 2,7-dichlorofluorescin diacetate (DCFH-DA).

Shanmugam et al. (2011) reported an analysis of a sensitive, fast-response, enzymatic nanointerfaced biosensor for detection of putrescine. Putrescine (1,4-diaminobutane) is a biologically active diamine and a valuable analyte for clinical and analytical use. The enzyme diamine oxidase (DAO) was immobilized on IONs to quantify the amount of putrescine created by decarboxylation of ornithine, which was converted into hydrogen peroxide by the DAO. Rossi et al. (2004) reported an aldohexose oxidase–magnetite nanoparticle bioconjugate for glucose sensing. Immobilization of bioactive molecules on the surface of MNPs is done to enhance the delivery and recovery of biomolecules in medical specialty applications. The authors described the preparation and functionalization of magnetic iron-ore (Fe_3O_4) nanoparticles 20 nm in diameter and also the successful covalent conjugation of the enzyme glucose oxidase to the amino-modified nanoparticle surface. Functionalization of the MNP surface with amino groups greatly increased the amount and activity of the immobilized enzyme in comparison with immobilization procedures involving physical adsorption. Immobilization of glucose oxidase on the nanoparticles also improved the stability of the enzyme. Almeida et al. (2017) reported carbon disulfide–mediated self-assembly of laccase and IONs on gold surfaces for biosensing applications.

4.5 Antimicrobial/Bactericidal Agents

It has been speculated that application of a sufficient external magnetic flux to IONs can be used to destroy microorganism membranes. The germicidal effects of metal nanoparticles may additionally be attributed to their small size and high surface-to-volume ratio. Many synthetic antibiotics available on the market have the major disadvantage of multiple resistance of detrimental microorganisms to individual drugs. Recent developments and opportunities to explore the germicidal effects of metal nanoparticles could resolve this problem. It has been established that antibacterial activity increases with a decrease in nanoparticle size and is also related to its form and orientation. Therefore, the concentration of nanoparticles is a significant issue for antibacterial activity. Lee et al. (1996) reported that inactivation of *Escherichia coli* by ZVI nanoparticles could be due to penetration of its cell membranes by these tiny particles (ranging in size from 10 to 80 nm) and their reaction with intracellular oxygen—i.e., oxidative stress—which causes disruption of the semipermeable membrane. Lee et al. (1996) reported germicidal effects of ZVI nanoparticles on *E. coli*.

Utilization of plant extracts for synthesis of iron nanoparticles has been studied to identify plants with high inhibitor concentrations and different phytochemical compositions that can be used in antimicrobial and/or medical applications. It has been established that soluble phytochemical extracts derived from plants can be used to form iron salt precursors into iron nanoparticles with antimicrobial and medical properties (Vuong et al. 2014). Davenport et al. (2000) reported that iron nanoparticles were oxidized to FeO and Fe_2O_3, with a film being formed on the surface of the nanoparticles, which prevented corrosion of the deeper layer.

SPIONs are frequently used in magnetic drug targeting, MRI, tissue repair, etc. When a chelating agent such as PO_4^{3-} is used in an air-saturated system, the biocidal activity of iron nanoparticles is reduced as a result of Fe(III) forming an insoluble metal chelate with PO_4^{3-} particles, whereas once a salt ($C_2O_4^{2-}$) particle is used, the germicidal activity is increased as a result of it forming a soluble complex with the iron particle. This is often additionally shown and monitored by a change in color from black to yellow. Fe(II) is very prone to oxidation by air; it does not remain stable unless it is stabilized by an acid.

SPIONs are helpful in drug delivery because an external magnetic flux can be used to direct them to the desired target and keep them there until the magnetic flux is brought to a halt. The size and form of Fe_3O_4 nanoparticles can also be controlled by monitoring the hydrogen ion concentration, the temperature, and the concentration of the reacting elements. Coating with an appropriate wetting agent will forestall their agglomeration (Hafeli et al. 1997; Lian et al. 2004; Zaitsev et al. 1999; Kang et al. 1996; Wang et al. 2013).

Whereas the deformation of the cell increases with the concentration of SPIONs. Coating of nanoparticles additionally influences the toxicity of the nanoparticles. Dextran-coated SPIONs are approved by the US Food and Drug Administration (FDA). The toxicity of empty SPIONs and SPIONs coated with –COOH and $–NH_2$ has been evaluated using the human cell lines HCM (heart), BE-2C (brain), and 293 T (kidney). The toxicity of the empty SPIONs was found to be greater than that of those coated with organic molecules because of their greater affinity to soak up proteins, vitamins, amino acids, and ions, changing the hydrogen ion concentrations of the drugs. Since the human cell contains proteins, vitamins, and amino acids, affinity is needed for binding with SPIONs, whereas SPIONs already coated with these substances have no empty space for chelation with them. The toxicity of coated SPIONs is therefore lower than that of uncoated ones. The low toxicity of coated SPION is beneficial for detection of cancer cells; as a result, they do not harm normal cells. One variety of SPION is detrimental to bound sorts of cells, whereas other varieties have insignificant effects (Mahmoudi et al. 2009a, b, c; Mahmoudi et al. 2010). Arakha et al. (2015) described antimicrobial activity of IONs upon modulation of the nanoparticle–bacterium interface. Chitosan coating of IONs leads to an interface that enhances ROS production and hence their antimicrobial activity.

Metal oxide and gold nanoparticles represent a brand new category of vital materials that are progressively being developed for use in analysis and health-related activities. In view of the immense importance of the biological system, elemental understanding of the influence of inorganic nanoparticles on cellular growth and functions is vital. Chatterjee et al. (2011) reported the effects of iron oxide and gold nanoparticles on microorganism growth, with a view to biological applications. The Fe_3O_4 and Au nanoparticles were prepared and characterized, and it was found that the IONs inhibited *E. coli* in an exceedingly concentration-dependent manner, whereas the gold nanoparticles showed no such activity. The authors additionally noted a metal nanoparticle–bacterium interaction at the cellular level, which could be utilized for useful biological applications; however, it additionally poses the potential for ecotoxicity, challenging the eco-friendly nature of nanoparticles.

4.6 Cancer/Tumor Therapy

The most commonly used MNPs are primary solid-solution nanoparticles or IONs, which have potential uses in drug and gene delivery, particular medical specialties, and novel fields such as theranostic nanomedicine. In essence, three completely different approaches are often utilized in the treatment of tumors with SPIONs: magnetically evoked hyperthermia, drug targeting, and selective suppression of neoplasm growth (Yu and Sun 2010). Also, tumor identification is often greatly improved as a result of the capability of MNPs to supply far better contrast in MRI, significantly increasing its sensitivity (Li et al. 2013).

Another promising technique that is improved by the properties of SPIONs is MPI, which has extremely high temporal resolution with high acquisition rates, achieving much greater sensitivity than MRI (Weizenecker et al. 2009). Khan et al. (2012) studied exposure of cancer cells to iron compound nanoparticles and observed that. They noted that these nanoparticles could be safely utilized in the treatment of tumors without damaging healthy cells. Additionally, they examined ROS generation when A549 cancer cells were treated with IONs, which subsequently induced autophagy. Wu et al. (2011a) reported selective growth inhibition of oral cancer by iron core–gold shell nanoparticles through mitochondria–mediated autophagy and showed that the gold-coated iron nanoparticles suppressed neoplastic cell growth in oral and colorectal cancer cells in vivo and in vitro. Healthy cells were equally exposed to the iron nanoparticles but were not greatly affected; also, the replication of cancer cells was repressed. Toxicity was possible because of the magnetic properties of the nanoparticles; however, their oxidation was reduced by the gold coating. ROS scavengers did not defend cancer cells from nanoparticles with Fe@Au-induced toxicity. The oxidation of iron nanoparticles and generation of ROS were coincidental processes that caused consecutive autophagy and suppressed neoplastic cell growth (Wu et al. 2011b).

Nanoparticles that are geared toward targeting of cancer cells but spare healthy tissues offer an attractive platform of implementation for hyperthermia or as carriers of chemotherapeutics. Pottler et al. (2015) reported genotoxicity of SPIONs in granulosa cells. They demonstrated that use of different coatings on the SPIONs improved their biocompatibility, particularly in terms of genotoxicity to cells of the genital system. Cai et al. (2010) published the first report of synthesis of Fe_3O_4 SPIONs with a size of 8 nm at an ambient temperature and normal air pressure, using soybean sprouts as a biotemplate. The biotemplate served as the nucleation site and controlled the dimensions and morphology of the nanoparticles on the cuticular surface and the interior stem wall when the biotemplate was immersed in Fe^{2+} and Fe^{3+} solutions for 4 hours and treated with NaOH. The nanoparticles that were recovered from the biotemplate were precipitated using processes of milling, magnetic separation, washing, and drying. The nanoparticle formation was confirmed by FTIR analysis, and a possible role of soybean sprout proteins and other biomolecules in nanoparticle synthesis was demonstrated.

MPI permits high spatial resolution and sensitivity, and also offers the chance to create real-time images by determining the spatial distribution of magnetic particles. To assess a prospective biosafe application of University of Luebeck dextran-coated (UL-D) superparamagnetic nanoparticles, the biocompatibility of SPIONs, their impact on biological properties, and their cellular uptake were evaluated by Lindemann et al. (2014), using head and neck squamous cancer cells (HNSCCs). The concluded that UL-D SPIONs are a promising tracer material for use in innovative neoplasm cell analysis by MPI. Hoff et al. (2013) reported a comparative study of ferrofluid and powder ION permeation through the blood–brain barrier. They found that the ferrofluid formulations achieved statistically greater permeation than the ION powder formulations at the barrier, suggesting potential uses for in situ–synthesized ferrofluid formulations of polyvinyl alcohol, bovine albumen, collagen, glutaminic acid, graphene, and their mixtures as materials that could cross the barrier to deliver medicine or achieve other neurological therapeutic efficacy. The results showed that a formulation of IONs with collagen achieved the least permeation across the barrier, suggesting that this could be used as an MRI contrast agent while limiting ION passage across the blood–brain barrier.

Shen et al. (2012) reported that IONs attenuated antigen-specific humoral responses and T lymphocyte cytokine expression in ovalbumin-sensitized mice. They found that one dose of IONs attenuated delayed-type hypersensitivity (DTH) reactions by suppressing infiltration and activity of T helper 1 cells and macrophages in response to antigen stimulation.

The presence of multidrug resistance-associated protein (MRP) in cancer cells is understood to be responsible for various therapeutic failures in current oncological treatments. Franke et al. (2013) reported that exposure of cancer cells to different physiological condition, IONs, and mitomycin C influences membrane MRP expression levels. This concept could be used to develop new treatment options using inhibitory mechanisms that actively export drugs from the target cells, thereby improving therapeutic outcomes in oncology. Daldrup-Link et al. (2011) described use of MRI in tumor-associated macrophages with clinically applicable IONs. The growth improvement achieved with clinically applicable IONs could offer a brand new biomarker for long-term prognosis, relevant treatment choices, and thus analysis of new immune-targeted therapies. Sharma et al. (2014) reported that ION agglomeration influences dose rates and modulates oxidative stress–mediated dose–response profiles in vitro. Namvar et al. (2014) reported cytotoxic effects of magnetic IONs synthesized using a seaweed aqueous extract. The synthesis of Fe_3O_4 MNPs involved reduction of a ferric chloride solution, using a brown seaweed (*Sargassum muticum*) aqueous extract containing hydroxyl radicals, carboxyl, and amino functional groups mainly relevant to polysaccharides, which could act as a possible stabilizer and metal reductant agent, with multiple applications across a broad spectrum of medical specialties, together with identification and treatment of cancer. The researchers evaluated the in vitro cytotoxic activity and cellular effects of Fe_3O_4 MNPs in human cell lines for cancer of the blood (Jurkat cells), breast cancer (MCF-7 cells), cervical cancer (HeLa cells), and cancer of the liver (HepG2 cells).

The nature of the synthesis and therapeutic potential of Fe_3O_4 MNPs could pave the way for additional analysis on green synthesis of therapeutic agents, notably in nanomedicine, to help with cancer treatment. Jingting et al. (2011) reported preparation and characterization of MNPs containing Fe_3O_4–dextran–anti-β-human chorionic gonadotropin (a new-generation choriocarcinoma-specific gene vector) by chemical coprecipitation and confirmed that Fe_3O_4–dextran–anti-β-human chorionic gonadotropin nanoparticles have potential as a secure, effective, and choriocarcinoma-specific cistron vector. Wu et al. (2014) reviewed nanoiron metal and nanoiron oxides, which are among the most widely used engineered and naturally occurring nanostructures. The increasing incidence of biological exposure to those nanostructures has therefore raised concerns regarding their biotoxicity due to ROS-induced oxidative stress, which depends upon the chemical composition, particle size, and crystalline phase of the particles; the physiological pH range; biogenic reducing agents; and different organic substances.

Lee et al. (2013) studied theranostic nanoparticles with controlled release of gemcitabine for targeted medical care and MRI in pancreatic cancer. The tumor stroma in human cancers considerably limits the delivery of therapeutic agents into cancer cells. To develop a good therapeutic approach that would overcome the physical barrier of the stroma, the researchers engineered urokinase plasminogen activator receptor (uPAR)–targeted magnetic IONs carrying the chemotherapy drug gemcitabine (Gem) for targeted delivery into uPAR-expressing growth and stromal cells. They concluded that theranostic amino terminal fragment (ATF)–ION–Gem nanoparticles have good potential in the development of targeted therapeutic and imaging approaches that are capable of overcoming the tumor stromal barrier to enhance the therapeutic effects of nanoparticle drugs on pancreatic cancers. Wang and Cuschieri (2013) described tumor cell labeling by MNPs with determination of the intracellular iron content and the spatial distribution of the intracellular irons. Magnetically labeled cells are used for in vivo cell tracking by MRI in clinical translation of cell-base therapies. Dextran-coated SPIO ferumoxides are used clinically as contrast agents primarily for internal organ imaging. This material is also widely used for in vitro cell labeling, as are different SPIO-based particles. Findings on the uptake of ferumoxides by human neoplastic cell lines indicate that electroporation in the presence of protamine sulfate (PS) leads to rapid and high uptake of SPIONs by parenchymal growth cells without important impairment of cell viability, thus ensuring the potential of this system for clinical tumor cell detection and destruction. Hanini et al. (2011) reported an evaluation of the biocompatibility of polyol-produced maghemite γ-Fe_2O_3 nanoparticles and confirmed that they caused necrobiosis within 24 hours of exposure, possibly through oxidative stress, and led to toxicity in the liver, kidneys, and lungs but not in the brain or heart.

Since γ-Fe_2O_3 may exhibit harmful properties, surface coating, cellular targeting, and local exposure need to be considered before developing clinical applications are developed. Malvindi et al. (2014) described a toxicity assessment of silica/silicon oxide/silicon dioxide/oxide–coated IONs and biocompatibility improvement by surface engineering using A549 and HeLa cells. They used empty and surface-passivated Fe_3O_4/SiO_2 nanoparticles to gauge the effects of coating on the particle stability and toxicity. The results indicated that surface engineering of Fe_3O_4/SiO_2 nanoparticles played a key role in increasing particle stability in biological environments, reducing cytotoxic and genotoxic effects. Williams et al. (2013) reported application of flux hyperthermia and SPIONs to HIV-1-specific T cell cytotoxicity.

Theranostic nanoparticle-supported SPIOs hold excellent promise for tumor identification and gene therapy. Li et al. (2014) reported theranostic nanoparticles based on a bioreducible polyethylenimine-coated iron oxide for redox-triggered gene release and use in MRI. They demonstrated the utility of disulfide-containing cationic polymer–decorated SPIONs as an extremely potent and low-toxicity theranostic nanosystem for specific nucleic acid delivery within cancer cells. West et al. (2014) reported assessment and optimization of electroporation-assisted tumoral nanoparticle uptake in a mouse model of exocrine gland ductal adenocarcinoma. Pancreatic ductal adenocarcinoma (PDAC) is usually fatal. The authors assessed the in vitro and in vivo uptake of doxorubicin-loaded iron chemical compound nanoparticles as an function of the electroporation voltage and the timing of administration in pancreatic adenocarcinoma cells. They showed that addition of electroporation to administration of nanoparticles considerably increased ION uptake by a PANC-1 cell line in an athymic mouse model of PDAC. Zhang et al. (2015) described iron nanoparticles as promising biomedical agents requiring evaluation of nanotoxicity to ensure safe application.

Schutz et al. (2014) reported differential stress reactions of human colon cells to oleic acid–stabilized and nonstabilized ultrasmall IONs, since engineered therapeutic nanoparticles, including USPIONs, can accumulate in the lower alimentary canal following intake or injection. The reactions of human colon cells to USPIONs, nonstabilized USPIONs, oleic acid–stabilized USPIONs, and free oleic acid were compared in human HT29 and Caco-2 animal colon cancer cells. The stress responses of the cells were ascertained, together with markers of programmed cell death and DNA repair, oxidative stress and degradative/autophagic stress, induction of heat shock protein, and lipid metabolism. Barhoumi and Dewez described the toxic effects of SPIONs on the green alga *Chlorella vulgaris*. Ma et al. (2012) reported that intraperitoneal injection of magnetic Fe_3O_4 nanoparticles induced hepatic and renal tissue injury via oxidative stress in mice.

Because of their distinctive magnetic properties, Fe_3O_4 nanoparticles have been widely used, and their applications in numerous fields have promised major benefits. Horniblow et al. (2015) studied alginate–iron speciation and its effects on in vitro cellular iron metabolism. Alginates are a category of biopolymers with known iron-binding properties. Additionally, alginates influence iron absorption in humans. They are beneficial for chelation of excess iron, particularly in the context of inflammatory bowel disease and colorectal cancer, where excess unabsorbed luminal iron is believed to be a driver of disease. Alili et al. (2015) reported an effect of Fe_3O_4 nanoparticles on neoplasm cells and dermal fibroblasts. They examined the toxicity, production of ROS, and invasive capability during treatment of human dermal fibroblasts (HDFs) and cells from the squamous tumor cell line SCL-1 with Fe_3O_4 nanoparticles. Tseng et al. (2015) studied use of cetuximab (cet)–conjugated IONs for cancer imaging and medical care. They developed theranostic nanoparticles—cet-PEG-dexSPIONs—by conjugation of the anti-EGFR antibody cetuximab to dextran-coated SPIONs via periodate oxidation. They demonstrated that use of cet-PEG-dexSPIONs maintained the therapeutic effects of cetuximab in addition to offering a way to focus on and image EGFR-expressing tumors. Cet-PEG-dexSPIONs represent a promising targeted magnetic probe for early detection and treatment of EGFR-expressing tumor cells.

Foy and Labhasetwar (2011) reported that IONs facilitated cancer diagnosis through enhanced contrast, selective enhancement of tumor necrobiosis with magnetic hyperthermia, and improved drug delivery with magnetic drug targeting. They proposed that high doses of IONs can be used as a treatment for cancer by generating an oxidative assault against the cancer. This proposal might be met with resistance, considering the controversy regarding iron in the field of cancer. Iron generates ROS through the Fenton reaction, which can either cause or cure cancer; thus, iron deprivation or iron overdose could be potential cancer therapies. Sungsuwan et al. (2015) reported lipopeptide-coated IONs as potential glycoconjugate-based synthetic anticancer vaccines. Zhu et al. (2010) reported oxidative stress and programmed cell death induced by IONs in cultured human umbilical endothelial cells. Shen et al. (2015) reported core–shell structured Fe_3O_4@TiO_2–doxorubicin nanoparticles for targeted chemosonodynamic cancer treatment. The engineered nanoparticles were endowed with multiple functions permitting them to selectively deliver a combination therapy payload to the tumor with increased therapeutic effectiveness and minimal side effects. Zhang et al. (2016) reported that dietary IONs delayed aging and ameliorated neurodegeneration in a *Drosophila melanogaster* AD model. IONs can mimic catalase and may decompose ROS. This has potential uses in the treatment of aging, metabolic disorders, and neurodegenerative diseases in which increased production of ROS may occur.

4.7 Drug Delivery

SPIONs have important applications in drug delivery. The drugs are bound on the SPION surface or encapsulated in magnetic liposomes and microspheres—which may deliver peptides, DNA, chemotherapeutics, and radioactive and hyperthermic medicines—and are targeted to the required site using an external magnetic flux. This method can allow reductions in the drug dose, absorption time, and interaction with nontarget cells. The iron nanoparticles need to be magnetic and smaller than the target cells so they can simply diffuse into them. Since use of a large abundance of SPIONs can result in agglomeration, high concentrations of them could also be avoided. Guo et al. (2009) described use of monodisperse mesoporous superparamagnetic single-crystal magnetite nanoparticles for drug delivery of doxorubicin, and ascertained that these nanoparticles had a very high drug-loading capability and slow release. Butoescu et al. (2009) performed an efficacy study in which magnetically retainable microparticles were used for drug delivery to a joint in an antigen-induced inflammatory disease model in mice.

Drug release is controlled by porousness, temperature, sensitivity, pH, surface functionalization, and biodegradability of the nanoparticles. Zhang et al. (2002) reported surface modification of superparamagnetic magnetite nanoparticles to improve their intracellular uptake for drug delivery to a desired target without interaction with other living cells. In the case of breast cancer (BT20 cells), PEG-coated nanoparticles between 10 and 100 nm in size were found to penetrate the cells. It is believed that since PEG is relatively soluble in both polar and nonpolar solvents, it can release the MNPs into neoplasm cells.

Magnetic IONs are an excellent drug carrier utilized in chemotherapy and are selective for cancer cells. Wang et al. (2008) described use of a variety of bimetallic nanoparticles of the kind MFe_2O_4 (where M = bivalent Mg, Fe, Co, Ni, Cu, or Zn) containing two metal ions for medical specialty applications. Multifunctional MNPs can be prepared by coating them with gold, silica, zinc oxide, polymer, liposomes, etc., and can be additionally functionalized to make the MNPs stable and multifunctional. Xu and Sun (2013) reported new kinds of superparamagnetic nanoparticles for medical specialty applications such as delivery of cisplatin to a solid tumor, using Fe_3O_4 HMNPs. It was shown that the drug could be delivered via matter exchange.

To extend the target yield of SPIONs, they are typically coated with polymers and functionalized by attaching carboxyl groups, biotin, avidin, carbodiimide, or other biomolecules. Koneracka et al. (1999) reported immobilization of proteins and enzymes, using fine magnetic particles. Mehta et al. (1997) reported direct binding of protein to magnetic particles, and Koneracka et al. (2002) reported direct binding of proteins and enzymes to fine magnetic particles. Alexiou et al. (2000) reported that once the drug is carried to the target cell (tumor cell), it can be discharged either by application of an external magnetic force or by changes in the pH, force per unit area, or temperature. Widder et al. (1978) reported that the drug is then taken up by the neoplasm cells and penetrates them via diffusion.

SPIONs are stable at a neutral hydrogen ion concentration, and the stability of the colloidal suspension relies on the dimensions and form of the nanoparticles and whether aggregation occurs; this can be prevented by coating them with an applicable surface-active agent. Tartaj and Serna (2003) reported synthesis of monodisperse superparamagnetic Fe/silica nanospherical composites. Barratt et al. (2002) reported that larger particles (larger than 10 nm) cannot penetrate the endothelium under normal conditions, whereas Moghimi et al. (2001) reported that they can easily penetrate tumor cells and inflamed cells. Gupta et al. (2007) described recent advances in surface engineering of magnetic IONs and medical specialty applications for them. Once coated nanoparticles enter tumor cells, the coating is dissolved in the biological fluid and they are exposed to other cellular elements. Hong et al. (2007) compared different methods for preparing magnetic Fe_3O_4 nanoparticles. Once the concentration is raised, aggregation of nanoparticles can occur, resulting in a larger magnetic interaction, and it was suggested that agglomeration of nanoparticles in capillaries could block their passage. Douziech-Eyrolles et al. (2007) described nanovectors for antitumor agents, using SPIONs at a biological hydrogen ion concentration and therefore a SPION isoelectric point at a hydrogen ion concentration of 7.0 for colloidal stability of the SPIONs.

When normal cells are exposed to drug delivery, it is essential that the drug is nontoxic to them. Thomsen et al. (2013) reported uptake and transport of SPIONs through human brain capillary endothelial cells. Sun et al. (2013) described use of synthesized aminosilane-coated IONs (AmS-IONs) to construct complex and multifunctional drug delivery systems. They determined the impacts of the surface charge and magnetic flux on the toxicity and uptake of AmS-IONs in CNS-relevant cell types, i.e., a mouse brain microvessel endothelial cell line (bEnd.3) and cultivated mouse astrocytes and neurons. They found that the toxicity seemed to depend on the surface coating rather than on the number of IONs present in the cell. Mistry et al. (2014) reported that nitrite induces extravasation of IONs in hypoxic tumor tissue. Nitrate undergoes reconversion to nitric oxide under conditions that are characteristic of the tumor microenvironment, such as hypoxia and a low hydrogen ion concentration. This selective conversion of nitrite into nitric oxide in tumor tissue provides an opportunity to improve drug delivery and therefore the radiation response. Dani et al. (2014) reported the use of a temperature-tunable ION-based delivery system for remotely controlled drug release specifically aimed at cancer cells. This delivery system showed good potential for remotely triggered drug delivery and therefore destruction of cancer cells. Prosen et al. (2013) described magnetofection—a reproducible technique for gene delivery to malignant melanoma cells—as a nanoparticle-mediated approach for transfection of cells, tissues, and tumors.

SPIONs are attractive materials that are widely utilized in medicine for drug delivery, diagnostic imaging, and therapeutic applications. Akbarzadeh et al. (2012) reported preparation and in vitro analysis of doxorubicin-loaded Fe_3O_4 MNPs altered with biocompatible copolymers. Elbialy et al. (2015) described doxorubicin-loaded magnetic gold nanoparticles (MGNPs) for in vivo targeted drug delivery. Their work was focused on coming up with biocompatible MNPs for use as a nanocarrier in a magnetically targeted drug delivery regimen. MGNPs were prepared, functionalized with thiol-terminated PEG, and then loaded with the anticancer drug doxorubicin. Magnetically targeted drug delivery technology not only minimizes random distribution of the chemotherapeutic agents but also reduces their side effects on healthy tissues, which are the two primary drawbacks of typical cancer therapies.

4.8 Catalysts/Photocatalysts

Nanobiocatalysts are a combination of nanotechnology and biotechnology, and represent an exciting and promising therapeutic domain. Xin et al. (2010) reported protease immobilization on gamma-Fe_2O_3/Fe_3O_4 MNPs for synthesis of oligopeptides in organic solvents. The possibility of using magnetic IONs as enzyme immobilization carriers has drawn attention because of their distinctive properties such as their controllable particle size, large surface area, modifiable surface, and ease of recovery. These authors studied γ-Fe_2O_3/Fe_3O_4 MNPs with immobilized proteases that were successfully prepared by three totally different immobilization methods: (1) with direct binding, (2) with thiophene as a linker, and (3) with triazole as a linker. The oligopeptide syntheses catalyzed by these MNPs with immobilized proteases were systematically studied, and it was found that the γ-Fe_2O_3 MNPs were better for use as an immobilization matrix than the Fe_3O_4 MNPs because of their smaller particle size and larger surface area.

Wu et al. (2008) described iron compound nanoparticle disposition to oxidation with exposure to air and aggregation in an aqueous solution. Zhou et al. (2011) reported a guided synthesis technique in which a biotemplate was used as an internal or external structure for generation of a nanostructure. Biotemplates, or soft templates, have the advantages of being inexpensive, renewable, eco-friendly, and easily removable. When a biotemplate is used, the biomolecules typically aid nanoparticle synthesis. Mazumder et al. (2016) described use of a reusable magnetic nanobiocatalyst for easy synthesis of silver and gold nanoparticles by reduction of nitrate and auric chloride, employing a nanobiocatalyst. The nanobiocatalyst was prepared by covalent coupling of alpha amylase on (3-aminopropyl)triethoxysilane (APTES)–modified magnetic IONs.

4.9 Future Perspectives

There is an urgent need to further explore plant resources, which are commonly utilized in this field of research, to optimize experimental conditions for preparation of plant extracts—namely, the plant mass–to–solvent ratio, extraction temperature, incubation time, pH, and mixing ratio of the plant extract and salt precursor, i.e., the optimal metal salt solution. The monodispersity and polydispersity, along with the surface area of the biosynthesized nanoparticles, must be optimized. Finally, there is an urgent need to promote as-biosynthesized nanoparticle application in a variety of domains—specifically, health care, environmental science, and agriculture.

4.10 Conclusion

This chapter has highlighted the potentialities and development of iron and iron oxide nanoparticle synthesis mediated by plants in the form of aqueous extracts, which are eco-friendly and economically feasible. Physical and chemical methods for synthesis of these nanoparticles are becoming more common. As-synthesized nanoparticles have been successfully utilized in the fields of medicine and environmental remediation. Iron and iron oxide magnetic nanoparticles are synthesized using plant extracts and microbes, and are coated with water-soluble polymers for high solubility, which prevent aggregation and allow them to easily diffuse through semipermeable membranes in a living system. Their shapes and sizes can be controlled through control of the temperature, pH, and salt precursor concentration. Their cytotoxicity varies with the shape, size, and paramagnetic/diamagnetic nature of the particles. Superparamagnetic iron oxide nanoparticles have immense potential, due to their magnetic properties, for use in instruments and medical devices, and as drug carriers for the treatment of many diseases. Iron oxide nanoparticles can also be used for removal of dyes in the textile industry, for treatment of contamination in wastewater, and for purification of groundwater.

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Chapter 5
Potential of Biogenic Plant-Mediated Copper and Copper Oxide Nanostructured Nanoparticles and Their Utility

Ravindra Pratap Singh

Contents

5.1 Introduction

Nanotechnology is the technology to control matter at nanoscale and deals with the science and engineering to create functional materials or nanodevices (1–100 nm). Metal and metal oxide nanoparticles are of much interest due to their unique mechanical, electrical, optical, electronic, and magnetic properties and utilized as magnetic storage media, solar energy, bioelectronics, nanobiosensors, and catalyst. Metal nanoparticles are utilized in every sphere of science including medical fields which are still very interesting to the scientists to explore new dimensions due to their small sizes. The metal nanoparticles are synthesized by physicochemical methods using toxic chemicals as reducing agents and later on showed various biological risks when

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R. P. Singh (✉)
Department of Biotechnology, Indira Gandhi National Tribal University (Central University), Amarkantak, Anuppur, MP, India

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utilized. To solve this problem, biological approaches are utilized by using green syntheses, i.e., biological molecules which are derived from plant sources for the metal nanoparticle synthesis. The alkaloids, flavonoids, and proteins present in the plant extract are responsible for nanoparticle stabilization, non-agglomeration, and biologically active characteristics (Singh 2016; Singh et al. 2011, 2012; Prasad 2014; Prasad et al. 2018; Joshi et al. 2018).

The development of nanobionic plants is facilitated by the passive assembly of high-zeta-potential nanomaterials within the chloroplast photosynthetic machinery. Single-walled carbon nanotubes (SWNTs) have the potential for increasing chloroplast carbon capture by promoting chloroplast solar energy harnessing and electron transport rates. SWNT real-time sensing of nitric oxide (NO) in extracted chloroplasts and leaves could also be extended to detect a wide range of plant signaling molecules and exogenous compounds such as pesticides, herbicides, and environmental pollutants. Nanomaterials offer a promising way to engineer plant function, but the absorption, transport, and distribution of nanoparticles within photosynthetic organisms remain poorly understood. This nanobionic approach to engineer plant function will lead to a new research field at the interface of nanotechnology and plant biology. Giraldo et al. (2014) have reported the interactions of plant cell organelles and nanomaterials, i.e., non-biological nanostructure nanomaterials, which have potentialities to enhance functionality of chloroplast manyfolds. The single-walled carbon nanotubes (SWNTs) have capability to passively transport and irreversibly localize within the lipid membrane of extracted plant chloroplasts, which promote over three times higher photosynthetic activity than that of controls, and enhance maximum electron transport rates. Furthermore, they reported that the SWNT-chloroplast assemblies also enable higher rates of leaf electron transport *in vivo* and concentrations of reactive oxygen species (ROS) inside extracted chloroplasts are significantly suppressed by delivering poly(acrylic acid)-nanoceria or SWNT-nanoceria complexes. They demonstrated that plant can function as a photonic chemical sensor. Finally, they speculated that nanobionic engineering of plant function may contribute to the development of biomimetic materials for light harvesting and biochemical detection with regenerative properties and enhanced efficiency (Dhas et al. 1998).

Plant extracts (derived from herbs, shrubs, and trees) may act as biological system for the synthesis of metal and metal oxide nanoparticles, which have been emerged as new simple, eco-friendly, cost-effective, and robust or fast technique. This technique is also known as green chemistry methodology and could be much more efficient rather than using microorganisms and physicochemical methods for synthesis of the same. The plant parts from underground, i.e., root, to aerial, i.e., stem, leaves, flowers, fruits, and seeds, are having phytochemical entities or constituent types of plant resources which provide an efficient platform for metal and metal oxide nanoparticles with lack of toxic chemicals, i.e., nontoxic, and additionally provide natural reducing, stabilizing, chelating, and capping agents. Besides this it reduces the cost of timing of identification, isolation, and culture media preparation for microorganisms when compared with plant resources, i.e., cost competitive feasibility. Apart from these, plants are easily available and safely handled and consist of a wide variability of phytochemicals or biomolecules and secondary metabolites, namely, alkaloids, flavonoids, terpenes, sterols, saponins, glucose, fructose, ascorbic acid, alcohols, carboxylic acids, amino acids, proteins, enzymes, etc. All these are playing a crucial role for the synthesis of metal and metal oxide nanoparticles as reducing agents, stabilizing agents, and capping agents. However, plants show complex networks of antioxidants and enzymes, which together counter the oxidative stress or damage to cellular constituents. Coenzymes and cofactors could play an important role in the reduction of desired starting precursor for the nanoparticle formation, whereas enzyme and protein contents, i.e., reductases, are involved in the biological reduction of substrate, i.e., metal salts, into their corresponding nanoparticles. It had been established that few plants could uptake and bioreduce metal ions from soil containing corresponding salts or minerals or ores by detoxification process and ultimately converted into nanoparticles (Mittal et al. 2013; Singh and Choi 2010).

This chapter highlights the biogenic approach for the synthesis of Cu and CuO nanoparticles which are simple, cost-effective and eco-friendly, highly stable, and reproducible using different plant extracts as stabilizing, capping, and reducing agents. The biosynthesized Cu and CuO NPs have been used for various applications for the betterment of human health as anticancer, antimicrobial, and antioxidant activity, etc.

5.2 Biosensing

The synthesis of morphologically different metal oxide nanoparticles is made from iron, manganese, titanium, copper, zinc, zirconium, cobalt, nickel, tungsten, silver, and vanadium. It also covers respective composites and their function and application in the field of electrochemical and photoelectrochemical sensing of chemical and biochemical species. The proper incorporation of chemical functionalities into these nanomaterials warrants effective detection of target molecules including DNA hybridization and sensing of DNA or the formation of antigen/antibody complexes. Di Tocco et al. (2018) reported the development of an electrochemical biosensor for the determination of triglycerides in serum samples based on a lipase/magnetite-chitosan/copper oxide nanoparticles/multi-walled carbon nanotubes/pectin composite. Lavanya et al. (2018) reported an electrochemical determination of purine and pyrimidine bases using copper-doped cerium oxide nanoparticles. DNA is a primary unit of heredity in all living organisms. The abnormalities related to four bases will have significant influence on disease diagnosis, crime detection, and biocomputing applications. Identification and quantification of DNA bases are important for diagnosis of genetic diagnosis and disorders. The developed sensor had exhibited good repeatability, reproducibility, sufficient stability, and good anti-interference ability, and was applied for simultaneous detection of AD, GU, TY, and

CY in denatured DNA sample. Liu et al. (2018b) reported an ultrasensitive cathode photoelectrochemical immunoassay based on TiO_2 photoanode-enhanced three-dimensional (3D) Cu_2O nanowire array photocathode and signal amplification by biocatalytic precipitation. They showed a low limit of detection (0.037 pg mL^{-1}) with a wide linear range (from 0.1 pg mL^{-1} to 50 ng mL^{-1}) for carcinoembryonic antigen (CEA) detection. Li et al. (2018c) reported a novel electrochemiluminescence (ECL) signal-off strategy based on CuS in situ grown on reduced graphene oxide (CuS-RGO) quenching luminol/H_2O_2 system. Luminol was grafted on the surface of $Au@Fe_3O_4\text{-}Cu_3(PO_4)_2$ nanoflowers (Luminol-$Au@Fe_3O_4\text{-}Cu_3(PO_4)_2$) which exhibited catalytic effect toward the reduction of H_2O_2 to enhance the ECL intensity of luminol. Dai et al. (2018) reported morphology-dependent electrochemical behavior of 18-facet Cu_7S_4 nanocrystal-based electrochemical sensing platform for hydrogen peroxide and prostate-specific antigen (PSA), and Cu_7S_4 nanocrystal holds great promising application in electrochemical sensors. Wang et al. (2018a) reported DNA-hosted copper nanoclusters/graphene oxide-based fluorescent biosensor for protein kinase activity detection. Moreira et al. (2018) reported redox probe-free readings of a beta-amyloid-42 plastic antibody sensory material assembled on copper@carbon nanotubes. The carbon nanotubes were modified with copper nanoparticles (CNT-CuO) and casted on the carbon area and showed a unique potential for on-site application in medical research and clinical diagnosis. Wu et al. (2018a) reported an efficient capture, rapid killing, and ultrasensitive detection of bacteria by a nano-decorated multifunctional electrode sensor using Zn-CuO nanoparticles and graphene oxide (GO) nanosheets on a Ni porous electrode showing good bacterial capture efficiency toward the applications in portable medical devices for on-the-spot diagnosis and also for simultaneous therapy of diseases caused by bacterial infections. Wang et al. (2018b) reported an electrochemiluminescent competitive immunosensor based on polyethyleneimine-capped SiO_2 nanomaterials as labels to release $Ru(bpy)_3^{2+}$ fixed in 3D Cu/Ni oxalate for the detection of aflatoxin B1. They have proposed immunosensor to provide a promising approach for ultrasensitive detection of other mycotoxins. Bhat et al. (2018) reported the fully nozzle-jet printed nonenzymatic electrode for biosensing application like printing of silver (Ag) precursor and copper oxide nanoparticle (CuO NP) inks by nozzle-jet technique to glucose biosensor on flexible polyethylene terephthalate (PET) substrate, i.e., CuO NPs/Ag/PET electrodes. This electrode fabrication using nozzle-jet printing would be regarded as a potential technique, i.e., biochemical sensor devices. Li et al. (2018d) reported the synthesis of $MoS_2@Cu_2O$-Pt nanohybrid as enzyme-mimetic label for the detection of the hepatitis B surface antigen. The nanocomposites (molybdenum disulfide @ cuprous oxide-platinum)

Demonstrated uniform coral morphology having specific surface area for loading the secondary antibody and the number of catalytically active sites, which increased the electrical conductivity. These findings are promising toward clinical applications. Yang et al. (2018b) reported an ultrasensitive sandwich-type electrochemical immunosensor based on the signal amplification strategy of echinoidea-shaped $Au@Ag\text{-}Cu_2O$ nanoparticles for prostate-specific antigen detection to determine tumor markers which play an important role in early diagnosis of cancer.

The gold nanoparticles functionalized nitrogen-doped graphene quantum dots (Au@N-GQDs) was fabricated and has enhanced conductivity, specific electrode surface area, and quantity of immobilized primary antibodies (Ab1), and echinoidea-shaped nanocomposites (Au@Ag-Cu_2O) composed of Au@Ag core-shell nanoparticles and disordered cuprous oxide were prepared success fabricated to label the secondary antibodies (Ab2) with biocompatibility and high specific surface area. Due to the synergetic effect of Au, Ag, and Cu_2O, the nanocomposites exhibited excellent electrocatalytic activity toward the reduction of hydrogen peroxide (H_2O_2) for the amplified detection of PSA. Chen et al. (2018a) reported an electrochemical aptasensor for thrombin using co-catalysis of hemin/G-quadruplex DNAzyme and octahedral Cu_2O-Au nanocomposites for signal amplification. The proposed aptasensor exhibited good sensitivity, high specificity, and reproducibility and could be applied in bioassay analysis. Sheta et al. (2018) reported a simple synthesis of novel copper metal-organic framework nanoparticles for the biosensing and biological applications. Cu-MOF-NPs (C1) showed more enhanced biological activity against various pathogens (five strains of bacteria, Gram positive and Gram negative) when compared to an antibacterial agent, and the effectiveness of Cu-MOF-NPs increases with increasing particle dose. Tang et al. (2017a) reported copper oxide coated gold nanorods like a film for electrochemical application. The gold nanorod-copper oxide nanocomposites (Au NRs-CuO nanocomposites) were fabricated and showed excellent electrocatalytic activity toward the oxidation of glucose compared with CuO NPs. Au NRs-CuO nanocomposites are promising candidate for the preparation of modified electrodes and electrochemical sensors. Hu et al. (2017) reported the self-cascade reaction catalyzed by CuO nanoparticle-based dual-functional enzyme mimics. The cupric oxide nanoparticle as oxidase mimics for the aerobic oxidation of cysteine to cystine with the generation of hydrogen peroxide was proposed, coupling this property with the peroxidase-like activity of CuO nanoparticles. They constructed a self-organized cascade reaction system based on a single-component nanozyme, which includes the oxidation of cysteine to yield cystine and hydrogen peroxide and the hydrogen peroxide-mediated oxidation of terephthalic acid to produce a fluorescence change. This platform was utilized for the detection of cysteine in pharmaceutical products and human plasma, which opens up a new route and holds promise for the development and applications of multifunctional nanomaterials as enzyme mimics. Arvand and Sayyar Ardaki (2017) reported poly-L-cysteine/electrospun copper oxide nanofibers-zinc oxide nanoparticles nanocomposite as sensing element of an electrochemical sensor for simultaneous determination of adenine and guanine in biological samples and evaluation of damage to dsDNA and DNA purine bases by ultraviolet (UV) radiation. They have fabricated poly-L-cysteine/zinc oxide nanoparticle-electrospun copper oxide nanofibers (PLC/ZnO-NPs-CuO-NFs) on the surface of the graphite electrode (GE), which enhanced the anodic peak currents of the purine bases. The biosensing platform not only detects DNA damage but also determines DNA oxidative damage. Lan et al. (2017) reported the size-controlled copper(I) oxide nanoparticles influence sensitivity of glucose biosensor. Copper(I) oxide (Cu_2O) is a semiconducting oxide with applications in photovoltaics and biosensing. The precise control of size and shape of Cu_2O nanostructures is possible by the electrodeposition utilizing ethylenediamine (EDA) as a size controlling agent. The large surface area of the Cu_2O NPs is able to immobilizing glucose oxidase for glucose biosensing. Fang et al. (2017) reported flowerlike MoS_2 decorated with Cu_2O nanoparticles for nonenzymatic amperometric sensing of glucose. The flowerlike MoS_2 decorated with Cu_2O nanoparticles had been synthesized as Cu_2O/MoS_2 nanohybrid which showed superior electrocatalysis to the oxidation of glucose due to the synergistic effect of Cu_2O nanoparticles and MoS_2 nanosheets. Buk et al. (2017) reported alginate-copper oxide nano-biocomposite as a novel material for amperometric glucose biosensing. A alginate-CuO-GOD film-based biosensor exhibited good performance with long-term stability and specificity for glucose when compared to possible interfering molecules such as ascorbic acid, uric acid, and acetaminophen. Shabnam et al. (2017) reported the doped graphene/Cu nanocomposite for high sensitivity nonenzymatic glucose sensor in food. The nitrogen-doped graphene with dispersed copper nanoparticles (Cu-NGr) was fabricated on modified glassy carbon electrode for glucose detection. The Cu-NGr composite presented electrocatalytic activity due to the synergetic effect of Cu NPs and nitrogen-doped graphene to detect glucose in food as a complex food material. Fu et al. (2017) reported a dual-potential electrochemiluminescence ratiometric sensor for sensitive detection of dopamine based on graphene-CdTe quantum dots and self-enhanced Ru(II) complex. They have designed dual-potential ratiometric electrochemiluminescence (ECL) sensor for detecting dopamine (DA) based on graphene-CdTe quantum dots (G-CdTe QDs) as the cathodic emitter and self-enhanced Ru(II) composite (TAEA-Ru) as the anodic emitter to biological small molecules.

Li et al. (2017a) reported a sensitive electrochemiluminescence immunosensor based on Ru(bpy)32+ in 3D CuNi oxalate as luminophores and graphene oxide-polyethylenimine as released $Ru(bpy)_3^{2+}$ initiator. Wang et al. (2017) reported the mimicking horseradish peroxidase and NADH peroxidase by heterogeneous Cu^{2+}-modified graphene oxide nanoparticles. Zhao et al. (2017) reported a sub-picomolar assay for protein by using cubic Cu_2O nanocages loaded with Au nanoparticles as robust redox probes and efficient nonenzymatic electrocatalysts. An electrochemical aptasensor for protein (thrombin-TB) in human serum samples was developed using cubic Cu_2O nanocages (Cu_2O-NCs) loaded with Au nanoparticles (AuNPs@Cu_2O-NCs) as nonenzymatic electrocatalyst redox probes which showed an efficient electrocatalytic capability in the reduction of H_2O_2. This nonenzymatic detection platform would be potential and promising in clinical diagnostics and protein analysis techniques. Li et al. (2017b) reported an ultrasensitive amperometric immunosensor for PSA detection based on Cu_2O@CeO_2-Au nanocomposites as integrated triple signal amplification strategy. The amino functionalized cuprous oxide @ ceric dioxide (Cu_2O@CeO_2-NH_2) core-shell nanocomposites were prepared for the quantitative detection of prostate-specific antigen (PSA). AuNPs (Cu_2O@CeO_2-Au) show better electrocatalytic activity toward the reduction of hydrogen peroxide (H_2O_2). Pino et al. (2016) reported high-performance sensor based on copper oxide nanoparticles for dual detection of phenolic compounds and a pesticide. Liu et al. (2016) reported *in situ* immobilization of copper nanoparticles on polydopamine-coated graphene oxide for H_2O_2 determination. Ma et al. (2016) reported the cubic Cu_2O nanoframes with a unique edge-truncated structure and a good electrocatalytic activity for immunosensor application for the quantitative detection of prostate-specific antigen (PSA). Gold nanoparticles decorated 3-aminopropyltriethoxysilane functionalized graphene sheets (Au@APTES-GS) having a large specific surface area, good biocompatibility, and superior electron transfer ability were developed as the matrix to provide method for the clinical monitoring of tumor markers. Xie et al. (2016) reported a sensitive fluorescent sensor for quantification of alpha-fetoprotein (AFP) in the human serum samples based on immunosorbent assay and click chemistry. Qin et al. (2016) reported a novel signal amplification strategy of an electrochemical aptasensor for determination of kanamycin antibiotic, based on thionine functionalized graphene and hierarchical nanoporous PtCu. The aptasensor uses thionine functionalized graphene (GR-TH) and hierarchical nanoporous (HNP) PtCu alloy as biosensing substrates for the determination of kanamycin in animal-derived food. Uzunoglu and Stanciu (2016) reported novel CeO_2-CuO-decorated enzymatic lactate biosensors operating in low oxygen environments. The detection of the lactate level in blood is useful for the diagnosis of some pathological conditions including cardiogenic or endotoxic shocks, respiratory failure, liver disease, systemic disorders, renal failure, and tissue hypoxia. The CeO_2-CuO-decorated sensor was detecting lactate in human serum with good selectivity and reliability. Feng et al. (2016) reported graphene oxide-supported rhombic dodecahedral Cu_2O nanocrystals for the detection of carcinoembryonic antigen (CEA). The rCu_2O-GO-AuNPs electrode also presents a potential alternative for the diagnostic applications of GO-supported special morphology materials in biomedicine and biosensors. Jimenez-Hernandez et al. (2016) reported 3-mercaptopropionic acid surface modification of Cu-doped ZnO nanoparticles and their properties and peroxidase conjugation. Yin et al. (2016) reported a regular signal attenuation electrochemical aptasensor for highly sensitive detection of streptomycin antibiotic in milk and honey samples. This electrochemical aptasensor is of great practical importance in food safety. Mei et al. (2015) reported novel phenol biosensor based on laccase immobilized on reduced graphene oxide-supported palladium-copper alloyed nanocages. They have fabricated RGO-PdCu NC immobilized laccase for the detection of catechol. Chen et al. (2015) reported the constructing heterostructure on highly roughened caterpillar-like gold nanotubes with cuprous oxide grains for ultrasensitive and stable nonenzymatic glucose sensor. Li et al. (2015) reported selective and sensitive determination of dopamine by the novel molecularly imprinted poly (nicotinamide)/CuO nanoparticle-modified electrode. They have suggested that the proposed sensor exhibited significant promise as a reliable technique for the detection of DA in human serum samples. Sun et al. (2015) reported CuO-induced signal amplification strategy for multiplexed photoelectrochemical immunosensing using CdS-sensitized ZnO nanotube arrays as photoactive material and AuPd alloy nanoparticles as electron sink. They have used cancer antigen 125, prostate-specific antigen, and α-fetoprotein as model analytes for the proposed immunoassay which exhibits excellent precision and sensitivity for the multi-detection of tumor markers. Wen and Ju (2015) reported an ultrasensitive photoelectrochemical immunoassay through tag-induced exciton trapping for the detection of protein. Derkus et al. (2015) reported copper-zinc alloy nanoparticle-based enzyme-free superoxide radical sensing on a screen-printed electrode. They have suggested that the enzyme-free electrode showed good performance with respect to the enzyme containing electrode indicating the superior functionality of enzyme-free electrode for the detection of superoxide radicals. Guo et al. (2015) reported an electrochemical immunosensor for ultrasensitive detection of carbohydrate antigen 199 (CA199) based on Au@CuxOS yolk-shell nanostructures with porous shells as labels. They have proposed immunosensor-based method which provides a new promising platform of clinical immunoassay for other biomolecules. Gao et al. (2015) reported an ultrasensitive electrochemical immunoassay for carcinoembryonic antigen (CEA) through host-guest interaction of β-cyclodextrin functionalized graphene and Cu@Ag core-shell nanoparticles with adamantine-modified antibody. They have fabricated immunosensor which exhibits excellent analytical performance for the measurement of CEA and provides an enormous application prospect in clinical diagnostics. Bajaj et al. (2015) reported controllable one-step copper coating on carbon nanofibers (CNFs) for flexible cholesterol biosensor substrate biosensing applications. Siebman et al. (2015) reported the two-dimensional (2D) algal collection and assembly by combining alternative current (AC) dielectrophoresis with fluorescence detection for contaminant-induced oxidative stress sensing. They have developed an alternative current (AC) dielectrophoretic lab-on-chip setup as a rapid tool of capture and assembly of microalga *Chlamydomonas reinhardtii* in two-dimensional (2D) close-packed arrays and explored the reactive oxygen species (ROS) production and oxidative stress during short-term exposure to several environmental contaminants, including mercury, methylmercury, copper, copper oxide nanoparticles (CuO NPs), and diuron. Hu et al. (2014) reported the fluorescent hydrogen peroxide sensor based on cupric oxide nanoparticles and its application for glucose and l-lactate detection. Lavanya et al. (2014) reported the fabrication of folic acid (FA) sensor based on the Cu-doped SnO_2 nanoparticle-modified glassy carbon electrode. They have fabricated sensor for the determination of FA. Wang et al. (2014) reported the platinum porous nanoparticles hybrid with metal ions as probes for simultaneous detection of multiplex cancer biomarkers. They have developed an electrochemical immunosensor for simultaneous detection of carcinoembryonic antigen (CEA) and alpha-fetoprotein (AFP) and suggested that the proposed electrochemical immunoassay provides a potential application of clinical screening for early-stage cancers. Zhou et al. (2014) reported an ultrasensitive nonenzymatic glucose sensor based on three-dimensional network of ZnO-CuO hierarchical nanocomposites (HNCs) by electrospinning. They have revealed that the ZnO-CuO HNCs composed of the ZnO and CuO showed good synergetic effect in between CuO and ZnO. Song et al. (2013) reported the synthesis of graphene oxide-based CuO nanoparticles composite electrode for highly enhanced nonenzymatic glucose detection. They have showed and suggested an outstanding long-term stability, good reproducibility, excellent selectivity, and accurate measurement in real serum sample. Ahmad et al. (2013) reported a wide linear-range detecting nonenzymatic glucose biosensor based on CuO nanoparticles inkjet-printed on electrodes on silver electrodes. Finally, they have utilized proposed electrode for the determination of glucose in human serum samples. Ma et al. (2013) reported a sensitive and selective chemosensor for oxidized glutathione (GSSG) detection based on the recovered fluorescence of NDPA (naphthalimide-DPA) -Fe_3O_4 at SiO_2-Cu(II) nanomaterial. Wang et al. (2013) reported an electrochemical immunosensor with graphene quantum dots and apoferritin-encapsulated Cu nanoparticles double-assisted signal amplification for detection of avian leukosis virus subgroup J (ALVs-J). Liu et al. (2013) reported graphene-wrapped Cu_2O nanocubes for the nonenzymatic electrochemical sensors for the detection of glucose and hydrogen peroxide with enhanced stability. They have fabricated cubic Cu_2O nanocrystals/graphene hybrid with high sensitivity for the detection of glucose and H_2O_2. Hong et al. (2013) reported the chemiluminescent cholesterol sensor based on peroxidase-like activity of cupric oxide nanoparticles with good selectivity and enhanced sensitivity. They have suggested the applicability of proposed sensor for the determination of cholesterol in milk powder and human serum samples. Ge et al. (2013) reported a disposable immunosensor device for point-of-care test (POCT) of tumor marker based on copper-mediated amplification. They have fabricated a paper-based immunodevice for point-of-care test (POCT) for cancer screening and also suggested good applicability of the proposed multiplex immunoassay in clinical diagnosis. Meng et al. (2013) reported the nonenzymatic biosensor based on CuxO nanoparticles deposited on polypyrrole nanowires for detecting glucose (GLC). They have showed the electrocatalytic activity of CuxO/PPy/Au toward GLC in alkaline conditions and suggested that these excellent performances make CuxO/PPy/Au as a good nonenzymatic GLC sensor. Zhou et al. (2013) reported the sodium dodecyl benzene sulfonate functionalized graphene for confined electrochemical growth of metal oxide nanocomposites for fructose sensing application. They have revealed the sensing properties of (Sodium dodecyl benzene sulfate) SDBS/GR/CuOCu toward fructose and suggested that SDBS/GR/CuOCu electrode is one of the promising electrode materials for electrochemical detection of fructose. Won and Stanciu (2012) reported the Cu_2O and Au/Cu_2O particles for the surface properties and applications in glucose sensing. Peng et al. (2012) reported the functionalization of silver nanowire surfaces with copper oxide for surface-enhanced Raman spectroscopic biosensing. El Khatib and Abdel Hameed (2011) reported the development of Cu_2O/carbon Vulcan XC-72 as nonenzymatic sensor for glucose determination. Bedi and Singh (2010) reported the room-temperature ammonia sensor based on cationic surfactant-assisted nanocrystalline CuO. Jiang and Zhang (2010) reported a highly sensitive nonenzymatic glucose sensor based on CuO nanoparticles-modified carbon nanotube electrode. Wang et al. (2010) reported using flowerlike polymer-copper nanostructure composite and novel organic-inorganic hybrid material to construct an amperometric biosensor for hydrogen peroxide. Niu et al. (2009) reported the sensitive DNA biosensor improved by luteolin copper(II) as indicator based on silver nanoparticles and carbon nanotubes-modified electrode for the detection of DNA hybridization. The copper(II) complex of luteolin $C_{30}H_{18}CuO_{12}$ (CuL2) as an electroactive indicator based on silver nanoparticles and multi-walled carbon nanotubes (Ag/MWCNTs)-modified glassy carbon electrode (GCE) was quantified the target ssDNA of the human hepatitis B virus (HBV). Zhang et al. (2009) reported the fixture-reduced method for the synthesis of Cu_2O/MWCNT nanocomposites and its application as enzyme-free glucose sensor. Cu_2O/MWCNT (multi-walled carbon nanotube) nanocomposites-modified electrode was utilized toward glucose determination, i.e., enzyme-free glucose sensor. Shlyahovsky et al. (2005) reported the optical and electrochemical detection of NADH and of NAD^+-dependent biocatalyzed processes by the catalytic deposition of copper on gold nanoparticles for the sensing of ethanol by the NAD^+-dependent alcohol dehydrogenase.

5.3 Catalysts

Li et al. (2019) reported aBiOCl-CuO photocatalyst based on *p-n* heterojunction and its photocatalytic performance under visible light. They suggested that the CuO nanoparticles (NPs) with narrow bandgap and near-infrared (NIR) light response act as the co-catalyst and CuO NPs enhance the photocatalytic performance of BiOCl semiconductor. The heterojunction exhibited photocatalytic activity and photostability to decompose organic pollutants such as acid orange (AO) and bisphenol A (BPA). Duran et al. (2019) reported novel 3D copper nanoparticles/chitosan/nanoporous alumina (CCSA) membranes with catalytic activity to decompose methylene blue (MB). The CCSA membranes were tested in the reduction of methylene blue (MB). Wang et al. (2019a) reported layered copper-manganese oxide (LCMO) for the efficient catalytic carbon monoxide (CO) and volatile organic compound (VOC) oxidation. They suggested that LCMO showed an excellent resistance to H_2O, SO_2, CO_2, and other VOCs. Ghafuri et al. (2019) reported the synthesis and characterization of magnetic nanocomposite Fe_3O_4@TiO_2/Ag,Cu and investigation of photocatalytic activity by degradation of rhodamine B (RhB) under visible light irradiation. They investigated the photocatalytic activity in aqueous solution under visible light irradiation and suggested that the Ag- and Cu-doped nanoparticles have synergistic effect to increase the photocatalytic activity of as-synthesized nanocomposite. Khatibi et al. (2019) reported efficient surface design of reduced graphene oxide, carbon nanotube, and carbon active with copper nanocrystals for enhanced simulated-solar-light photocatalytic degradation of acid orange in water and suggested that photoactivity of Cu/RGO among Cu/MWCNT and Cu/AC is due to a synergistic effect between RGO and Cu nanoparticles. Wang et al. (2019b) reported honeycomb porous carbon (HPC) frameworks from wheat flour as supports for CuxO-CeO_2 monolithic catalysts. They have showed that the small-sized CeO_2 particles on HPC surface having oxygen vacancies, to participate in oxygen activation and oxidation of carbon monoxide and improve the redox reactivity of copper species and ceria. Su et al. (2019) reported for the first time a freestanding and flexible Cu@CuO nanowire (NW) mesh as Fenton-like catalyst and showed an excellent catalytic performance toward the degradation of organic dyes such as rhodamine B (RhB) crystal violet, methylene blue, and rhodamine 6G. Qin et al. (2019) reported the

CuO-ZnO heterojunctions decorated graphitic carbon nitride hybrid nanocomposite for ethanol gas sensing application. They suggested those graphitic carbon nitrides (g-C_3N_4) are used as metal-free catalyst in gas sensing field due to its unique chemical stability and excellent substrate characteristics. The CuO-ZnO/g-C_3N_4 ternary composite exhibited enhanced sensing properties to ethanol. Oh et al. (2019) reported Au/Cu_2O/TiO_2 core-shell nanorods using three-step chemical synthesis technique and suggested that the Au nanoparticles core of Au/Cu_2O performed as the catalytic activity enhancer and the Cu_2O shell acts as a co-catalyst. The Au/Cu_2O/TiO_2 nanorods showed photocatalytic performance, recyclability, and stability to degrade organic pollutants under solar light irradiation, whereas *p-n* junction at the interface of Cu_2O shell and the TiO_2 nanorods contributes to the enhanced catalytic activity. Padikkaparambil et al. (2019) reported a facile preparation of noble metal-free Cu-doped CeO_2 oxidation catalyst suitable for engine exhaust gas treatment and suggested carbon monoxide oxidation reaction without any stabilizing agents. The results indicated the formation of lattice-expanded CeO_2 solid solution as well as highly dispersed copper oxides as the active centers of the catalyst. Zhan (2019) reported a synthetic architecture of integrated nanocatalysts with controlled spatial distribution of metal nanoparticles. Tou et al. (2019) reported the room-temperature oxidation of CO using ozone-assisted catalysis (OAC) over monometallic or bimetallic catalysts supported on γ-Al_2O_3. They have demonstrated monometallic catalysts (Ag, Pd, Fe, Mn, and Cu). Naeimi et al. (2019) reported ultrasonic-assisted fabrication of first MoO_3/copper complex bio-nanocomposite based on *Sesbania sesban* plant for green oxidation of alcohols. They have also reported atom-efficient and selective oxidation of alcohols using hydrogen peroxide catalyzed by NMCS bio-nanocomposite under ultrasonic irradiation. Hu et al. (2019) reported catalytic decomposition of ammonium perchlorate (AP) on hollow mesoporous CuO microspheres. Hollow mesoporous CuO microspheres (CuO-HM) could be described as CuO micro-sized spheres composed of self-assembled nanoparticles, possessing hollow and mesoporous structure which improved catalytic efficiency in AP decomposition due to large surface area, easily accessible porous, and hollow structure. They have also demonstrated that hollow and mesoporous CuO was a promising catalyst for the application in solid-fuel rocket propellants. Duan et al. (2018a) reported the Z-scheme heterojunction between TiO_2 nanotubes and Cu_2O nanoparticles mediated by Ag nanoparticles for enhanced photocatalytic stability and activity under visible light. They have revealed the potential application of noble metal nanoparticles to enhance the Z-scheme heterojunction under visible light-driven photocatalysis and provide new insights to the transition from traditional *p-n* heterojunctions to Z-scheme heterojunctions. Gao and Hensen (2018) reported highly active and stable spinel oxide-supported gold catalyst for gas-phase selective aerobic oxidation of cyclohexanol to cyclohexanone. The Au/$MgCuCr_2O_4$ catalysts have demonstrated very efficient for gas-phase oxidation of cyclohexanol to cyclohexanone due to Au-Cu synergical effect. Fedorov et al. (2018) reported structure and chemistry of Cu-Fe-Al nanocomposite catalysts for CO oxidation. Khoshnamvand et al. (2018) reported response surface methodology (RSM) modeling to improve removal of ciprofloxacin from aqueous solutions in photocatalytic process using copper oxide nanoparticles (CuO/UV). Ciprofloxacin (CIP) is antibiotic and an emerging and biological resistant pollutant. The removal of CIP from synthetic aqueous solutions is needed by photocatalytic process through copper oxide nanoparticles as catalyst (CuO/UV). They have demonstrated that photocatalytic process using copper oxide nanoparticles decomposes CIP in aqueous solutions. Lai et al. (2018) reported copper oxide nanoparticles (CuO NPs) as catalysts or semiconductors and showed an adverse genotoxicity and cytotoxicity effects on various cells. CuONPs have aggravated pulmonary inflammation and apoptosis of epithelial cells due to increased reactive oxygen species (ROS) and promoted collagen accumulation and expression of the progressive fibrosis marker alpha-smooth muscle actin (alpha-SMA, plays an important role in fibrogenesis) in the lung tissues. They also alarm toward an urgent need to prevent the adverse effects of CuO NPs in the human respiratory system. Nirumand et al. (2018) reported copper ferrite nanoparticles supported on MIL-101/reduced graphene oxide as an efficient and recyclable sonocatalyst. The magnetic $CuFe_2O_4$/MIL-101/graphene (CMG) ternary nanocomposite decomposes some organic dyes, namely, methylene blue, rhodamine B, and methyl orange (MO) in water by using H_2O_2 as a green oxidant. Sartin et al. (2018) reported an effect of particle shape and electrolyte cation on CO adsorption to copper oxide nanoparticle electrocatalysts. Cu_2O-derived nanoparticles are efficient catalysts for the electrochemical conversion of CO and CO_2 to multicarbon products. Mahapatra et al. (2018) reported growth, structure, and catalytic properties of ZnO x grown on CuO x/Cu(111) surfaces. ZnO / Cu configuration as a catalyst plays an important role in the synthesis of methanol from CO_2 hydrogenation. Tabakova et al. (2018) reported promotional effect of gold on the (Water-gas shift (WGS) reaction, a well-known industrial process for the production of hydrogen) activity of alumina-supported copper-manganese mixed oxides. Velusamy et al. (2018) reported an electrochemical synthesis of copper oxide nanoparticles decorated graphene-β-cyclodextrin composite for trace-level detection of antibiotic drug metronidazole. The copper oxide nanoparticle (CuO NP) decorated graphene/β-cyclodextrin (GR-β-CD) composites exhibit an excellent catalytic activity and lower reduction potential toward the electrochemical detection of metronidazole (MTZ). Jafarirad et al. (2018) reported an innovative biocapped CuO nano-photocatalysts for a rapid and green method for photocatalytic degradation of 4-nitrophenol. Cobalt nanoparticles (CONPs) acts as nanophotocatalyst which could be photodegraded 4-nitrophenol as an environmental pollutant. The fabrication protocol opens the windows for a large-scale and green approach for generating other metal oxide that are useful as nano-photocatalyst. Gong et al. (2018a) reported *in situ* synthesis of highly dispersed Cu-Co bimetallic nanoparticles for tandem hydrogenation/rearrangement of bioderived furfural in aqueous phase. They reported a synergism between copper and cobalt. Pandas and Fazli (2018) reported nanoparticles (NPs) from lanthanum oxide (La_2O_3) and copper oxide (CuO) with spherical morphology which were synthesized through precursor calcinations of copper and lanthanum carbonate and then using a bioactive shell membrane of eggshell. Janmohammadi et al. (2018) reported copper nanoparticles supported on MoO_3 (Cu NPs/MoO_3) which were prepared by a green method using sun spurge leaf extract for the catalytic activity. Duan et al. (2018b) reported ionic liquid-assisted synthesis of reduced graphene oxide-supported hollow spherical PtCu alloy and its enhanced electrocatalytic activity toward methanol oxidation and suggested that the hollow spherical PtCu alloy supported on RGO will have great potential applications for direct methanol fuel cells. Amirzadeh et al. (2018) reported a nonenzymatic glucose sensor based on a pencil graphite electrode (PGE), a modifier suspension including the conducting polymer poly (3,4-ethylenedioxythiophene):poly(styrenesulfonate) (PEDOT:PSS) and CuO nanoparticles. The PEDOT:PSS/CuO/MWCNTs-PGE-based sensor exhibited better electrocatalytic activity toward glucose and showed excellent reproducibility, good long-term stability, and excellent anti-interference ability in the existence of common interfering species. Mardani and Ziari (2018) reported the synthesis and characterization of new nanomagnetic coordination composite from Fe_3O_4 and Cu(II) complex as an efficient catalyst in oxidation of benzyl alcohol. Kalimuthu et al. (2018) reported boron carbonitride sheet/Cu_2O composite for an efficient photocatalytic hydrogen evolution. The enhanced photocatalytic activity was due to the influence of Cu_2O on the Boron carbon nitride (BCN) surface and enhanced charge separation in the interface at Cu_2O with BCN. Xie et al. (2018b) reported monodisperse core-shell Cu/In_2O_3 nanoparticles (NPs) to boost efficient and tunable syngas formation via electrochemical CO_2 reduction for the first time. The efficiency and composition of syngas production on the developed carbon-supported Cu/In_2O_3 catalysts are highly dependent on the In_2O_3 shell thickness. Liu et al. (2018a) reported mesoporous CuO/MgO synthesized by a homogeneous-hydrothermal method and its catalytic performance for the ethynylation reaction of formaldehyde and exhibits excellent catalytic activity for the formaldehyde reaction of acetylene. Gong et al. (2018b) reported metal-organic-framework-derived controllable synthesis of mesoporous copper-cerium oxide composite catalysts for the preferential oxidation of carbon monoxide. The as-prepared CuO-CeO_2 catalysts display variable morphologies, crystal structures, and specific surface areas based on different ratios of Cu/Ce and calcination temperature. Rao et al. (2018) reported the hierarchical CuO microstructures' synthesis for visible light-driven photocatalytic degradation of Reactive Black-5 dye. Bao et al. (2018) reported a novel core-shell structured nanocatalyst (Fe_3O_4@SiO_2-NH_2-FeCu nanoparticles) with ultrafine FeCu alloy NPs magnetically immobilized in porous silica showed excellent activity and chemoselectivity for catalyzing the hydrogenation of nitroarenes to corresponding anilines using hydrazine hydrate as the hydrogen source, and the reaction could be carried out smoothly in water, which is an environmentally friendly solvent. The FeCu NPs are magnetically immobilized in the silica spheres (Fe_3O_4@SiO). Rani and Shanker (2018) reported the photocatalytic degradation of toxic phenols from water using bimetallic metal oxide nanostructures, namely, Ni-Cu oxide (NiCuO), Cu-Cr oxide ($CuCr_2O_4$), and Ni-Cr oxide ($NiCrO_3$) using *Aegle marmelos* leaf extract. Yousaf et al. (2018) reported an ultra-low Pt-decorated NiCu bimetallic alloy nanoparticles supported on reduced graphene oxide for electrooxidation of methanol. Zhang et al. (2018a) reported an embedded CuO nanoparticles@TiO_2-nanotube arrays for photoelectrocatalytic reduction of CO_2 to methanol. Yuan et al. (2018) reported copper stearate as a catalyst for improving the oxidation performance of heavy oil in *in situ* combustion process. Hosseini et al. (2018a) reported preparation, characterization, and catalytic behavior of copper oxide nanoparticles on thermal decomposition of ammonium perchlorate particles. Lykaki et al. (2018) reported ceria nanoparticles shape effects on the structural defects and surface chemistry and an implication in CO oxidation by Cu/CeO_2 catalysts. Taleb et al. (2018) reported alumina/graphene/Cu hybrids as highly selective sensor for simultaneous determination of epinephrine, acetaminophen, and tryptophan in human urine. The fabricated sensor is an appropriate candidate for the pharmaceutical applications and clinical investigations. Sati et al. (2018) reported a facile synthesis procedure for nanocomposites consisting of one-dimensional (1D) carbon nanotubes, 2D graphene, and metal oxide nanoparticles (CuO, ZnO) referred as metal oxide dispersed on graphene-wrapped carbon nanotubes (CuO/GC and ZnO/GC) nanocomposites. Hoseini et al. (2018) reported designing of some platinum- or palladium-based nanoalloys as effective electrocatalysts for methanol oxidation reaction. They concluded that these non-precious bi- and trimetallic alloy nanostructured thin films have better electrocatalytic performance than Pt monometallic thin films and other Pt nanostructures due to the geometric, electronic, and stabilizer effect. Gulati et al. (2018) reported a green approach for decarboxylative C(sp3)-H activation of proline amino acid which was accomplished by coupling with aldehydes and alkynes to afford α-alkynylated *N*-substituted pyrrolidines as value-added synthons using reduced graphene oxide-supported copper oxide (RGO@CuO) nanocatalysts. Pham et al. (2018) reported oxidative degradation of the antibiotic oxytetracycline by Cu@Fe_3O_4 core-shell nanoparticles. They demonstrated that Cu@Fe_3O_4 is a novel prospective candidate for the pharmaceutical and personal care products degradation in the aqueous phase. Hemmati et al. (2018) reported the biosynthesis of CuO nanoparticles using *Rosa canina* fruit extract as a recyclable and heterogeneous nanocatalyst for C-N Ullmann coupling reactions. Dong et al. (2018) reported an enhancing photocatalytic activity of titanium dioxide via well-dispersed copper nanoparticles and may provide a new strategy to improve photocatalytic efficiency of TiO_2 without using high-cost noble metals. Ibrahim et al. (2018) reported a novel heterobimetallic coordination polymer as a single source of highly dispersed Cu/Ni nanoparticles for efficient photocatalytic water splitting. They anticipated directing the future development of efficient, low-cost, and noble metal-free semiconductor photocatalysts for solar H_2 production.

Xu et al. (2018) reported design and fabrication of Ag-CuO nanoparticles on reduced graphene oxide for nonenzymatic detection of glucose. Imani et al. (2018) reported unraveling in situ formation of highly active mixed metal oxide $CuInO_2$ nanoparticles during CO_2 electroreduction. Anku et al. (2018) reported Graft Gum Ghatti caped Cu_2O nanocomposite for photocatalytic degradation of naphthol blue-black dye. Pattanayak et al. (2018) reported fabrication of cost-effective non-noble metal supported on conducting polymer composite such as copper/polypyrrole graphene oxide (Cu_2O/PPy-GO) as an anode catalyst for methanol oxidation in Direct methanol fuel cell (DMFC). Ling et al. (2018) reported versatile three-dimensional porous Cu@Cu_2O aerogel networks as electrocatalysts and mimicking peroxidases.

Kosmambetova et al. (2018) reported an effect of ultrasonic treatment of the mechanically mixed nanosized CuO-MgO solids on their catalytic properties in the CO oxidation. Zhang et al. (2018c) reported a facile and efficient one-pot method for the synthesis of well-dispersed hollow $CuFe_2O_4$ nanoparticles (H-$CuFe_2O_4$ NPs) in the presence of cellulose nanocrystals (CNC) as the support and suggested that the ferrite nanoparticles supported on CNC acted as a promising catalyst and exhibited potential applications in numerous ferrite-based catalytic reactions. Selvarajan et al. (2018) reported a novel highly selective and sensitive detection of serotonin based on Ag/polypyrrole/Cu_2O nanocomposite-modified glassy carbon electrode. They showed electrocatalytic activity, repeatability, stability, fast response, and good selectivity against potentially interfering species. Comelli et al. (2018) reported an influence of the synthetic conditions on the composition, morphology of CuMgAl hydrotalcites, and their use as catalytic precursor in diesel soot combustion reactions. Sharma and Dutta (2018) reported Se-doped CuO NPs/H_2O_2/UV as a highly efficient and sustainable photo-Fenton catalytic system for enhanced degradation of 4-bromophenol. Yisilamu et al. (2018) reported preparation of cuprous oxide nanoparticles coated with aminated cellulose for the photocatalytic reduction of carbon dioxide to methanol. Dobrucka (2018) reported antioxidant and catalytic activity of biosynthesized CuO nanoparticles using extract of *Galeopsidis herba* and showed catalytic activity in the reduction of malachite green. Naghdi et al. (2018) reported *Cuscuta reflexa* leaf extract-mediated green synthesis of the Cu nanoparticles on graphene oxide/manganese dioxide nanocomposite and its catalytic activity toward reduction of nitroarenes and organic dyes. Chen et al. (2018b) reported PdCu alloy flowerlike nanocages with high electrocatalytic performance for methanol oxidation and suggested the unique flowerlike nanocage structure with high surface area and the synergic effect of Pd and Cu. Li et al. (2018b) reported nanoporous CeO_2-Ag catalysts prepared by etching the CeO_2/CuO/Ag_2O mixed oxides for CO oxidation. They suggested that the catalytic activity was attributed to the enhancement of interfacial interaction between CeO_2 ligament and Ag particle. Tavella et al. (2018) reported the development of photoanodes for photoelectrocatalytic solar cells based on copper-based nanoparticles on titania thin films of vertically aligned nanotubes. They suggested that the main role of CuO nanoparticles is to act as co-catalyst to improve the H_2 photogeneration rate rather than to promote charge separation or other effects, which promote the photocurrent density. Aparna et al. (2018) reported an Au-Cu_2O/RGO nanocomposite-based electrochemical sensor for selective and simultaneous detection of dopamine and uric acid. Dean et al. (2018) reported design of copper-based bimetallic nanoparticles for carbon dioxide adsorption and activation. Soori and Nezamzadeh-Ejhieh (2018) reported synergistic effects of copper oxide-zeolite nanoparticles composite on photocatalytic degradation of 2,6-dimethylphenol aqueous solution. Hasanpour et al. (2018) reported an ultrasensitive electrochemical sensing of acetaminophen and codeine in biological fluids using CuO/$CuFe_2O_4$ nanoparticles as a novel electrocatalyst. Esmaeilpour et al. (2018) reported dendrimer-encapsulated Cu(Π) nanoparticles immobilized on superparamagnetic Fe_3O_4@SiO_2 nanoparticles as a novel recyclable catalyst for *N*-arylation of nitrogen heterocycles and green synthesis of 5-substituted

1H-tetrazoles. Fe_3O_4@SiO_2 nanoparticles as the magnetic catalyst can be separated by an external magnet bar and is recycled seven times without significant loss of its activity. Zhou et al. (2018) reported an efficient degradation of 2,4-dichlorophenol in aqueous solution by peroxymonosulfate activated with magnetic spinel $FeCo_2O_4$ nanoparticles. They showed that magnetic spinel $FeCo_2O_4$ nanoparticles (NPs) have proposed as a catalyst of peroxymonosulfate (PMS) for the degradation of 2,4-dichlorophenol (2,4-DCP) and revealed that the $FeCo_2O_4$/PMS system shows potential for degrading contaminants in the environment. Chen et al. (2018c) reported an enhanced catalyst activity by decorating of Au on Ag@Cu_2O nanoshell. They showed combination of Au, Ag, and Cu_2O which exhibited excellent catalytic properties. Ag@Cu_2O-Au nanocomposite was used to detect the organic, toxic pollutant, 4-nitrophenol (4-NP), which could be ascertained for water remediation. Cai et al. (2018) reported performance of preformed Au/Cu nanoclusters deposited on MgO powders in the catalytic reduction of 4-nitrophenol in solution. Ma et al. (2018) reported a magnetic hierarchical core-shell structured Fe_3O_4@PDA-Pd@[$Cu_3(btc)_2$] nanocomposite. The Fe_3O_4@PDA-Pd@[$Cu_3(btc)_2$] ($n = 5$) nanocomposite shows ultrahigh catalytic activity for the 4-nitrophenol reduction and also exhibits a synergistic effect in the catalytic system. Zhang et al. (2018b) reported catalytic ozonation of *N*,*N*-dimethylacetamide (DMAC) in aqueous solution using nanoscaled magnetic $CuFe_2O_4$. *N*,*N*-dimethylacetamide (DMAC) is used in chemical industry and could cause reproductive toxicity. The copper ferrite ($CuFe_2O_4$) magnetic nanoparticles (MNPs) were introduced for the degradation of DMAC by catalytic ozonation and showed high catalytic activity, stability, and recyclability. Tada et al. (2018) reported Cu species incorporated into amorphous ZrO_2 with high activity and selectivity in CO_2-to-methanol hydrogenation. Mandal et al. (2018) reported the role of copper oxide in electrochemical CO_2 reduction in real time. Gong et al. (2018c) reported in situ synthesis of Cu_2O/reduced graphene oxide composite as effective catalyst for ozone decomposition. The decomposition of ozone is still technologically challenging in humidity levels. Cu_2O/reduced graphene oxide composite (Cu_2O/RGO) is in situ synthesized by reducing a mixed solution of Cu^{2+} and GO. Tian et al. (2018) reported an ultrasensitive electrochemical detection method to detect MCF-7 circulating tumor cells (CTCs) in breast cancer by using reduced graphene oxide/gold nanoparticles composites (RGO/Au NP composites) as a support material with CuO nanozyme as a catalyst. MCF-7 cells were detected by an electrochemical cytosensor with effective surface recognition between specific mucin 1 protein (MUC-1) over-expressed on the MCF-7 cell membranes and MUC-1 aptamer. Xie et al. (2018a) reported CuO nanoparticles decorated 3D graphene nanocomposite as nonenzymatic electrochemical sensing platform for malathion detection. The CuO NPs/3DGR nanocomposite possesses high affinity toward malathion and showed good recovery, stability, and selectivity. Reddy et al. (2018) reported the catalytic activity of copper oxide nanoparticles dispersed on titanium dioxide in water for one-pot synthesis of a library of hydrazinyl-thiazoles via a three-component reaction of various aldehydes/ketones with thiosemicarbazide and different phenacyl bromides for large-scale applications in pharmaceutical industries and suggested that the reaction begins with the activation of the carbonyl group of both aldehyde/ketone and phenacyl bromide by copper oxide nanoparticles supported on titanium dioxide in water. Rezaei et al. (2018) reported heterogeneous magnetic nanocatalyst, Fe_3O_4@SiO_2-ligand-Cu(II) MNPs, revealed high catalytic performance within the synthesis of propargylamines using the multicomponent coupling reaction of aldehydes, phenylacetylene, and secondary amines in water as a solvent. Suwannapichat et al. (2018) reported the direct synthesis of dimethyl ether (DME) from CO_2 hydrogenation over novel hybrid catalysts containing a Cu-ZnO-ZrO_2 catalyst admixed with WOx/Al_2O_3 catalysts. The activity of the hybrid catalyst attributed a combination of coke deposition, sintering of Cu-based catalyst and WOx/Al_2O_3 catalyst, and strongly adsorbed water molecules. Gu et al. (2018) reported an ultrasound-assisted biosynthesis of CuO NPs using brown alga *Cystoseira trinodis* extracts as an eco-friendly and time-saving process. The photocatalytic studies revealed the activity of the prepared CuO NPs as an efficient catalyst for the degradation of methylene blue (MB) in the presence of UV and sunlight. Finally, they introduced a facile, green, and low-cost method for the synthesis of monoclinic CuO NPs with catalytic, antioxidant, and antibacterial properties. Soleimani and Moghaddami (2018) reported the synthesis, characterization, and thermal properties of poly(methyl methacrylate) (PMMA)/CuO polymeric nanocomposites. The photocatalytic activity of CuO NPs, modified NPs, and PMMA/CuO polymeric nanocomposites (PNCs) was investigated in the degradation of methyl orange (MO) under UV radiation. Pang et al. (2018) reported the direct growth of Cu_2ZnSnS_4 on three-dimensional porous reduced graphene oxide thin films as counter electrode with high conductivity and excellent catalytic activity for dye-sensitized solar cells. Chen et al. (2018d) reported the preparation of Cu_2O@Au yolk/shell structures for efficient photocatalytic activity with a self-generated acid etching method. Cu_2O@Au yolk/shell structures were prepared with self-generated acid etching method at room temperature. The photocatalytic property of Cu_2O@Au yolk/shell structures was studied by degrading MO under the irradiation of visible light at room temperature. Benefiting from the synergistic effect of cavity micro-reactor and electron transfer, the photocatalytic performance of the as-prepared Cu_2O@Au yolk/shell structures was much better than that of pure Cu_2O. They proposed the possible photocatalytic mechanism of the Cu_2O@Au yolk/shell catalysts and suggested that yolk/shell structures have potential applications in photocatalysis for its active sites on the large specific area. Olivo et al. (2018) reported sustainable carbon dioxide photoreduction by a cooperative effect of reactor design and titania metal promotion. They have developed an effective process based on the photocatalytic reduction of CO_2 to face, on the one hand, and the crucial problem of environmental pollution, on the other hand, to propose an efficient way to produce clean and sustainable energy sources. Copper (in the oxide CuO form) or gold (as nanoparticles) was employed as promoting metal. Basumatary et al. (2018) reported a novel Ni-Cu/ZnO@MWCNT anode employed in urea fuel cell to attain superior performances. NiCu alloy nanoparticles loaded onto ZnO-coated multi-walled carbon nanotubes (MWCNTs) were evaluated as anode catalysts in direct urea fuel cells. The Ni-Cu/ZnO@MWCNT catalyst was synthesized by a two-step hydrothermal process. Palomino et al. (2018) reported hydrogenation of CO_2 on ZnO/Cu

(100) and ZnO/Cu (111) catalysts and role of copper structure and metal oxide interface in methanol synthesis. Reaction with CO_2 oxidized the zinc, enhancing its stability over the copper substrates. Pielsticker et al. (2018) reported surface segregation, restructuring, and sintering phenomena in size-selected copper-nickel nanoparticles (NPs) supported on silicon dioxide substrates were systematically investigated as a function of temperature, chemical state, and reactive gas environment. Zedan et al. (2018) reported the tailoring reducibility and catalytic activity of CuO nanoparticles for low-temperature CO oxidation. Venkatesha and Ramesh (2018) reported citric acid-assisted synthesis of nanoparticle copper catalyst supported on an oxide system for the reduction of furfural to furfuryl alcohol in the vapor phase. Hassan et al. (2018) reported an exploiting copper-silica-zirconia cooperative interaction for the stabilization of tetragonal zirconia catalysts and enhancement of the visible light photodegradation of bisphenol A. Kim et al. (2018) reported the mesoporous SiO_2-supported Cu_2O nanoparticles as an eggshell-type catalyst. The obtained Cu_2O/SiO_2 eggshell nanocatalyst had a large surface area and narrow pore size distribution, and the catalytic performance can be attributed to the synergistic advantages of mesoporous structure and monodispersed Cu_2O nanoparticles. Jeong et al. (2018) reported copper catalysts for the electrochemical reduction of carbon dioxide. Cu is the only metallic electrode capable of electrochemically converting CO_2 into hydrocarbons and alcohols with significant faradaic efficiencies. Ghadari et al. (2018) reported the synthesis of graphene oxide-supported copper-cobalt ferrite material functionalized by arginine amino acid as a new high-performance catalyst. $Cu_{0.5}Co_{0.5}Fe_2O_4$@Arg-GO catalytic system was prepared in which ferrite moiety acts as an oxidation catalyst and arginine has the role of base catalyst. Also, arginine amino acid was used to modify the surface of graphene oxide nanosheets which the prepared support can improve dispersion and uniform loading of nanoparticles. The prepared $Cu_{0.5}Co_{0.5}Fe_2O_4$@Arg-GO nanocomposite was used as an efficient catalyst for one-pot tandem oxidative synthesis of 2-phenylbenzimidazole derivatives in good yields. Abbas et al. (2018) reported the shape- and size-controlled synthesis of Cu nanoparticles wrapped on RGO nanosheet catalyst and their outstanding stability and catalytic performance in the hydrogenation reaction of dimethyl oxalate. Hou et al. (2018) reported in situ characterization of Cu-Fe-Ox catalyst for water-gas shift reaction. Jiang et al. (2018) reported three-dimensional Mn-Cu-Ce ternary mixed oxide networks prepared by polymer-assisted deposition for formaldehyde (HCHO) catalytic oxidation. These ternary mixed oxide networks will have good potential to be applied in various catalytic reactions. The polymer-assisted deposition approach could be further employed to develop a remarkably broad range of composite metal oxide materials for technical applications. Mohd Zabidi et al. (2018) reported the synthesis and characterization of Cu/ZnO catalyst on carbon nanotubes and Al_2O_3 supports. Cu/ZnO catalyst was synthesized on multi-walled carbon nanotubes (MWCNTs) and Al_2O_3 supports via incipient wetness impregnation method. Products obtained from the CO_2 hydrogenation reaction in the presence of these catalysts were methanol, ethanol, methyl formate, and methane. Hasan et al. (2018) reported *in situ* formation of graphene stabilizes zero-valent copper nanoparticles and significantly enhances the efficiency

of photocatalytic water splitting and suggested a novel method for metallic copper stabilization which illustrates the effect of metallic copper as a catalyst for the *in situ* formation of RGO. Chen et al. (2018e) reported thermally stable and highly active Pt/CeO_2@SiO_2 catalysts with a porous/hollow structure. They were proposed an efficient way to acquire thermally stable and highly active Pt/CeO_2@SiO_2 catalysts with a porous/hollow structure which exhibit high catalytic activity and remarkable durability toward CO oxidation. Ahmed et al. (2018) reported molten salts-derived copper tungstate nanoparticles as bifunctional electrocatalysts for electrolysis of water and supercapacitor applications. They investigated the potential for industrial applications and stability of the electrodes. Hosseini et al. (2018b) reported the CuO nanoparticles supported on three-dimensional nitrogen-doped graphene as a promising catalyst for thermal decomposition of ammonium perchlorate. CuO@3D-(N)GF was used as a promising catalyst for thermal decomposition of ammonium perchlorate (AP) as one of the most common oxidizers in composite propellants. Gupta et al. (2018) reported the copper chalcogenide nanoparticles (Cu_7S_4) supported on graphene oxide (GO), synthesized for the first time from Cu_2S, and used as highly efficient heterogeneous catalysts for oxidative orthoselective C-H aminomethylation of phenols with *N*,*N*-dimethylbenzylamines. Shahrokhian and Rezaee (2018) reported vertically standing Cu_2O nanosheets promoted flower-like PtPd nanostructures supported on reduced graphene oxide for methanol electro-oxidation. The PtPd-NFs/Cu_2O-NSs/RGO exhibited an outstanding electrocatalytic activity, lower onset potential, and high level of poisoning tolerance toward methanol oxidation in acidic media ascribed to the synergetic effect between bimetallic PtPd, Cu_2O, and RGO. And finally, PtPd-NFs/Cu_2O-NSs/RGO can be considered as a promising anode catalyst in direct methanol fuel cells. Zanganeh et al. (2018) reported sinter-resistant and highly active sub-5 nm bimetallic Au-Cu nanoparticle catalysts encapsulated in silica for high-temperature carbon monoxide oxidation. The gold-copper-based silica-encapsulated mixed metal oxide (MMO) core-shell catalyst Au-Cu@SiO_2 is suitable for its application in automotive combustion engine exhausts. Sartin et al. (2018) reported an effect of particle shape and electrolyte cation on CO adsorption to copper oxide nanoparticle electrocatalysts. Qiu et al. (2018) reported yolk-shell structured Cu_2O as a high-performance cathode catalyst for the rechargeable Li-O_2 batteries with long cycling life and high rate capacity. Muthukumar et al. (2018) reported fabrication of strong bifunctional electrocatalytically active hybrid Cu-Cu_2O nanoparticles in a carbon matrix. Cu-Cu_2O NPs@C has been used as bifunctional electrocatalysts for the oxygen evolution reaction (OER) and hydrogen evolution reaction (HER) and has exhibited a strong bifunctional electrocatalytic response at a high current density with a low catalyst loading among the different Cu-based nanostructured catalysts explored for the water splitting reactions.

Saiadian and Khorshidi (2018) reported the catalytic activity of copper nanostructures in the condensation reaction of selected indoles and aldehydes or ketones. Sheng et al. (2018) reported octahedral Pd nanocages with porous shells converted from $Co(OH)_2$ nanocages with nanosheet surfaces as robust electrocatalysts for ethanol oxidation to boost their large-scale applications for direct ethanol fuel cells.

The catalysts are prepared from the second template of a nanosheet surface of amorphous $Co(OH)_2$ octahedral nanocages, which are prepared from the original template of octahedral Cu_2O. These Pd octahedral nanocages exhibit a porous rough surface, which consists of smaller Pd nanoparticles, endowing them with highly active surface area and many active sites. Lang et al. (2018) reported CO oxidation over MOx (M = Mn, Fe, Co, Ni, Cu) supported on $SmMn_2O_5$ composite catalysts. They demonstrated that the best catalytic performance of the CuOx/Samarium Manganese Oxygen (SMO) composite also stems from the additional CO adsorption on the CuOx sites. Sivaranjan et al. (2018) reported the synthesis of highly active RGO-supported mono- and bimetallic nanocomposites as catalysts for chemoselective hydrogenation of α,β-unsaturated ketone to alcohol. The catalytic activity performances of mono- and bimetallic NC catalysts were studied toward the chemoselective hydrogenation of an α,β-unsaturated ketone to an alcohol. They observed catalytic activity and revealed that the bimetallic Cu-Pd/RGO NC catalyst showed a higher conversion yield, reusability, and good selectivity than Cu-Au/RGO as well as monometallic (Pd/RGO, Au/RGO) NCs. Salabat et al. (2018) reported a microemulsion route to fabrication of mono- and bimetallic Cu/Zn/γ-Al_2O_3 nanocatalysts for hydrogenation reaction. Finally, γ-Al_2O_3 was added to the colloidal systems to make Cu/Al_2O_3 or Cu-Zn/Al_2O_3 nanocatalysts. The prepared nanocatalysts were tested for hydrogenation reaction of an unsaturated aldehyde in a batch reactor and mild condition. Huang et al. (2018) reported an *in situ* strategy to understand the photocatalytic performance of Cu_2O-Ag@RGO nanocomposites through interfacial photocatalysis on an optical microfiber. The photocatalysts were conjugated on the surface of an optical microfiber immersed in an organic solution, forming an interface consisting of photocatalysts and organic molecules between the silica microfiber and the solution, which was within the evanescent field of the optical microfiber. The photodegradation efficiency of Cu_2O-Ag@RGO was almost twice that of Cu_2O, while the degradation rate constant was more than five times larger, because the coupling between the silver nanoparticles and reduced graphene oxide (RGO) enhanced the photocatalytic performance of Cu_2O. Chandel et al. (2018) reported the synthesis of multifunctional $CuFe_2O_4$-reduced graphene oxide nanocomposite used as an efficient magnetically separable catalyst as well as high-performance supercapacitor and first-principle calculations of its electronic structures. $CuFe_2O_4$-RGO nanocomposites have shown the catalytic properties toward the reduction of 4-nitrophenol and the epoxidation reaction. Bouazizi et al. (2018) reported silver nanoparticle-embedded copper oxide as an efficient core-shell for the catalytic reduction of 4-nitrophenol and antibacterial activity improvement. They reported a microporous CuO@Ag^0 core-shell with high catalytic and antibacterial activities. CuO@Ag^0 also exhibited an antibacterial activity against *Staphylococcus aureus*. The antibacterial effects were found to strongly depend on the size, contact surface, morphology, and chemical composition of the catalyst particles. The Ag^0 NPs open promising prospects for their potential applications as a low-cost catalyst in wastewater treatment and antibacterial agent in cosmetics. Chen et al. (2018f) reported a Cu_2Se-Cu_2O film electrodeposited on titanium foil as a highly active and stable electrocatalyst for the oxygen evolution reaction. The hybrid catalyst film composed of Cu_2Se and Cu_2O nanoparticles directly grown on Ti foil (Cu_2Se-Cu_2O/TF) via a cathodic electrodeposition method and resulted in sustained catalytic oxidation of water. Abbasi et al. (2018a) reported a unique combination of deep eutectic solvent (the combination of urea with choline chloride) and magnetic CuO@γ-Fe_2O_3 nanoparticles as a green magnetic nanocatalyst that promotes the synthesis of *N*-acylureas from reaction of carbodiimides with carboxylic acids. Wu et al. (2018b) reported a highly selective conversion of toxic nitrobenzene to nontoxic aminobenzene by $Cu_2O/Bi/Bi_2MoO_6$, a ternary catalyst. They also reported the active interfacial contact between copper oxide/metallic Bi/Bismuth Molybdenum oxide (BM)(Cu_2O/Bi/BM) in the designed sandwich structure facilitated the production and maintained the balance of Bi^{3+}/Bi^0 pairs, contributing to the enhanced activity and excellent stability. Bordbar et al. (2018) reported *Melissa officinalis* L. leaf extract-assisted green synthesis of CuO/ZnO nanocomposite for the reduction of 4-nitrophenol and rhodamine B. They have showed excellent catalytic activity in the degradation of 4-nitrophenol (4-NP) and rhodamine B (RhB) in water at ambient temperature. Yang et al. (2018a) reported CO oxidation on inverse Ce_6O_{12}/Cu (111) catalyst and the role of copper-ceria interactions. Shah et al. (2018) reported catalytic activity analysis of copper nanoparticles (Cu NPs) supported on a zinc oxide-polythiophene (ZnO-PTh) nanocomposite. Cu NPs@ZnO-PTh was used as a heterogeneous catalyst for the synthesis of propargylamine, tetra-substituted propargylamine, and pyrrolo[1,2-a]quinoline using a microwave technique in ethylene glycol as a recyclable, green, and biodegradable solvent with 98% yield. The high catalytic activity of Cu NPs@ZnO-PTh was due to the high surface area and synergetic effect of both the Cu NPs and ZnO-PTh nanocomposites, which make it cost-effective and environmentally benign with high atom economy. Ji et al. (2018) reported a hydrothermal synthesis of Fe_3O_4@C hybrid nanoparticle and magnetic adsorptive performance to remove heavy metal ions in aqueous solution. Advanced core-shell material with a high specific area has been considered as an effective material to remove heavy metal from aqueous solutions. They provide an ideal mode to remove heavy metal ions using core-shell Fe_3O_4@C under the water treatment condition. A new approach is clarified that core-shell nano-/micro-functional materials can be synthesized well on large scales which are used in many fields such as environmental remediation, catalyst, and energy. Yi et al. (2018) reported that nano-metal binary oxides were prepared by the combined method of complexation and impregnation in ultrasonic intervention for low-temperature catalytic oxidation of toluene under microwave radiation. Activity differences of prepared samples were evaluated using the removal rate and the mineralization rate as assessment criteria. Khan et al. (2018) reported the green synthesis of ZnO and Cu-doped ZnO nanoparticles from leaf extracts of *Abutilon indicum, Clerodendrum infortunatum*, and *Clerodendrum inerme* and investigation of their biological and photocatalytic activities. They have showed good candidates for the future therapeutic applications. Tabatabaei et al. (2018) reported a novel visible light-driven Cu-based MOFs/Ag_2O composite photocatalysts with enhanced photocatalytic activity toward the degradation of orange G (OG) and their photocatalytic mechanism and optimization study. They synthesized two visible light-driven Cu-based metal organic frameworks (Cu-H_3-btc and Cu-H_2-bdc) composited with Ag_2O nanoparticles to form Cu-H3-btc-Ag_2O-NPs and Cu-H_2-bdc-Ag_2O-NPs, and these are applied for the photocatalytic degradation of orange G (OG) dye in the presence of a blue light-emitting diode (LED). These photocatalytic performances of the as-prepared photocatalysts remain almost constant after reuse or exposure under visible light. Gao et al. (2017) reported designed synthesis CuO hollow microboxes coated with Pd nanosheets and SnO_2 nanoparticles as a highly efficient Rochow reaction catalyst. They designed and synthesized CuO/SnO_2/Pd hollow microboxes for dimethyldichlorosilane synthesis via the Rochow reaction. Song et al. (2017) reported encapsulated NdCuOx bimetallic nanoparticles with nitrogen-doped carbon as an efficient electrocatalyst for oxygen reduction reaction (ORR) in alkaline medium. Zhan and Zeng (2017) reported synthetic protocol for preparation of binary multi-shelled hollow materials (MSHMs) and their enhanced oxidation application. The number of layers in binary CuO/ZnO could be controlled by adjusting copper loading, annealing temperature, or heating ramp rate, and binary CuO/ZnO MSHMs exhibited pronounced catalytic activity on the advanced oxidation process (AOP) toward dye wastewater treatment. Narasaiah et al. (2017) reported biosynthesis of copper oxide nanoparticles from *Drypetes sepiaria* leaf extract and their catalytic activity to dye degradation. They performed photocatalytic activity to examine the photocatalytic degradation efficiency of CuO NPs to Congo Red and colloidal solutions of CuO NPs showed good catalytic activity. Mu et al. (2017) reported the composite catalysts of Cu/CuxO nanoparticles supported on the carbon fibers were prepared for styrene oxidation reaction. Bae et al. (2017) reported colloidal zinc oxide-copper(I) oxide nanocatalysts for selective aqueous photocatalytic carbon dioxide conversion into methane. Gopiraman and Chung (2017) reported highly active and cost-effective CuO-based carbon nanocomposite with unique morphology for catalytic synthesis of imines under solvent-free conditions. Yan et al. (2017) reported in situ integration of ultrathin PtCu nanowires with reduced graphene oxide nanosheets for efficient electrocatalytic oxygen reduction. Clarizia et al. (2017) reported an effect of surface properties of copper-modified commercial titanium dioxide photocatalysts on hydrogen production through photoreforming of alcohols. Dai et al. (2017) reported hollow zeolite-encapsulated Fe-Cu bimetallic catalysts for phenol degradation. Dante et al. (2017) reported polymeric carbon nitride was synthesized from urea and doped with Cu and Fe to act as co-catalysts. The material doped with Fe was a new composite material composed of Fe(III) oxides (acting as a co-catalyst) wrapped by the polymer layers and amorphous carbon. Hsiao and Lin (2017) reported growth of a superhydrophobic multi-walled carbon nanotube forest on quartz using flow-vapor-deposited copper catalysts. Xie et al. (2017) reported recent advances in Cu-based nanocomposite photocatalysts for CO_2 conversion to solar fuels. Li et al. (2017c) reported preparation of ultrafine $Cu_{1.5}Mn_{1.5}O_4$ spinel nanoparticles and its application in *p*-nitrophenol reduction. Wu et al. (2017) reported one-pot method for the fabrication of reduced graphene oxide (RGO)/metal (oxide) (e.g., RGO/Au, RGO/Cu_2O, and RGO/Ag) composites using glucose as the reducing agent and the stabilizer. The glucose not only reduced GO effectively to RGO but also reduced the metal precursors to form metal (oxide) nanoparticles on the surface of RGO. These developed nanomaterials were utilized as an electrode catalyst to simultaneous electrochemical analysis of L-ascorbic acid, dopamine, and uric acid. Dong et al. (2017) reported synthesis, characterization, and application of CuO-modified TiO_2 electrode exemplified for ammonia electrooxidation. CuO-TiO_2 catalyst was synthesized using the coprecipitation method with $Cu(NO_3)_2$ as the active component for the electrochemical oxidation (ECO) of ammonia (NH_3). Mateo et al. (2017) reported photoassisted CO_2 methanation which can be carried out efficiently at 250 °C using Cu_2O nanoparticles supported on few layer graphene (Cu_2O/G) as a photocatalyst. Vimala Devi et al. (2017) reported the synthesis, defect characterization, and photocatalytic degradation efficiency of Tb-doped CuO nanoparticles. They have demonstrated the photocatalytic performance of undoped and Tb-doped CuO on degradation of methylene blue (MB) and methyl orange (MO). Ghosh et al. (2017) reported amberlite resin formate (ARF) with a polyionic polar environment is successfully utilized as a unique support for immobilization of stabilized Cu_2O nanoparticles (NPs). Elhamifar et al. (2017) reported magnetic iron oxide-supported copper/Schiff- base complex (Cu/SB-Fe_3O_4) as nanocatalyst for the synthesis of biologically active 3,4-dihydropyrimidinones.

Bondarenko et al. (2017) reported copper$^{(0)}$ nanoparticles supported on Al_2O_3 as catalyst for carboxylation of terminal alkynes for the first time used as heterogeneous catalyst. Ghasemi Estarki (2017) reported simple synthesis of $CuAl_2O_4$ nanoparticles by a new morphological control method and characterization of its photocatalytic activity. The synthesis of semiconducting copper aluminate ($CuAl_2O_4$) nanoparticles using aluminum nitrate and copper nitrate as the starting reagent in the presence of different natural polymers such as polyoxyethylene (80) sorbitan monooleate, ethyl cellulose, and starch through sol-gel methods was reported. The photocatalytic decomposition of methyl orange (MO) pollutant was reported under visible illumination. Shi et al. (2017a) reported phenol hydroxylation over cubic/monoclinic mixed phase CuO nanoparticles prepared by chemical vapor deposition (CVD). CuO/SiO_2 catalysts exhibit a much higher dispersion degree of CuO than those by impregnation and thus much better catalytic performances in phenol hydroxylation to catechol and hydroquinone. Shi et al. (2017b) reported phase-controlled growth of cubic phase CuO nanoparticles by chemical vapor deposition. Cupric oxide has monoclinic, tetragonal, and cubic phases. The cubic phase of CuO was deposited on alumina substrate using $Cu(acac)_2$ as precursor. As catalysts, the cubic CuO on alumina was found to be active and selective in the hydroxylation of phenol to catechol, hydroquinone, and benzoquinone. Zhang et al. (2017a) reported the composite films consisting of graphene and CuPW11 polyoxometalates $\{GN/CuPW11\}n$. The introduction of CuPW11 improves electrocatalytic activity, stability, and CO-tolerance ability of Pt/graphene composite catalysts toward methanol oxidation. Maham et al. (2017) reported biosynthesis of the CuO nanoparticles using Euphorbia *c*hamaesyce leaf extract and investigation of their catalytic activity for the reduction of 4-nitrophenol. Tang et al. (2017b) reported an effect of particle size and morphology on surface thermodynamics and photocatalytic thermodynamics of nano-Cu_2O. They found that nano-Cu_2O with low surface energy exhibited a high photocatalytic activity. Liu et al. (2017) reported Cu_2O nanoparticles supported on carbon nanofibers as a cost-effective and efficient catalyst for RhB and phenol degradation. Due to the synergistic effect between photocatalytic activity of Cu_2O and excellent adsorption capacity of CNFs, the obtained Cu_2O/CNFs exhibited excellent photocatalytic activity for degradation of rhodamine B (RhB) and phenol. The hybrid composite Cu_2O/CNFs could be applied as catalytic materials for application in the future. Paulose et al. (2017) reported copper oxide alumina composite via template-assisted sol-gel method for ammonium perchlorate decomposition. Ye et al. (2017) reported PdCu alloy nanoparticles supported on reduced graphene oxide as active catalyst for electroless copper plating. PdCu bimetallic alloy nanoparticles on reduced graphene oxide could be used as active agent for electroless copper plating on epoxy board and paper. The as-prepared nanocatalyst was promising for the future development of interconnect technologies in electronic packaging. Ji et al. (2017) reported 3D porous Cu@Cu_2O films supported Pd nanoparticles for glucose electrocatalytic oxidation. They have found enhanced activity of the porous Cu@Cu_2O-Pd nanostructures which might be attributed to the unique hierarchical porous structures with highly exposed active sites and synergetic effect from metal oxide semiconductor Cu_2O and noble metal Pd. Vats et al. (2017) reported pristine graphene-copper(II) oxide nanocatalyst, a novel and green approach in CuAAC reactions. They have introduced a quick and green route to synthesize CuO nanocomposites using pristine graphene as a support material by microwave-assisted hydrothermal reaction. The pristine graphene in the nanocomposite increases the catalytic activity due to its better conductivity and ability to adsorb reactants through π-π interaction than RGO. The pristine graphene-CuO nanocomposite showed good recyclability. The CuAAC reactions were using water as a green solvent with pristine graphene-CuO nanocomposite as catalyst and sodium ascorbate as co-catalyst. Abbasi et al. (2017) reported copper oxide supported on magnetic nanoparticles (CuO@γ-Fe_2O_3), an efficient and magnetically separable nanocatalyst for addition of amines to carbodiimides toward synthesis of substituted guanidines.

5.4 Optoelectronics

Zhang et al. (2018d) reported preparation of bilayer graphene utilizing CuO as nucleation sites by CVD method. Graphene is an attractive 2D material for optoelectronics applications. Litvin et al. (2017) reported colloidal quantum dots for optoelectronic devices, photovoltaic cells, photodetectors, and LEDs. In addition, we analyze recent advances in charge transport layers, blocking layers, nanostructured photoanode fabrication, and the importance of QD surface treatments. Throughout, we emphasize the use of hybrid composite materials including combinations of QDs with metal oxides, plasmonic nanoparticles, graphene, and others. Finally, this review provides an analysis of prospects of these important selected quantum dot-based optoelectronic devices. Park et al. (2016b) reported transversally extended laser plasmonic welding for oxidation-free copper fabrication toward high-fidelity optoelectronics. They have reported physical/chemical properties of fabricated Cu conductors and showed durability in terms of bending and adhesion. They have also demonstrated a single-layer Cu-mesh-based touch screen panel (TSP) on thermally sensitive polymer film. Bian et al. (2014) reported a nanocomposite superstructure of metal oxides with effective charge transfer interfaces. Metal oxide mesocrystals have potentially tunable electronic, optical, and magnetic properties useful for applications to catalysis to optoelectronics and sensing to energy storage and conversion. Zhang et al. (2013) reported the deterministic growth of AgTCNQ and CuTCNQ nanowires on large-area reduced graphene oxide films for flexible optoelectronics. They were showed measurements of the optoelectronic properties of RGO/metal-TCNQ hybrid films which exhibit substantial photoconductivity and highly reproducible photoswitching behaviors, and this approach may open the door to the versatile and deterministic integration of functional nanostructures into flexible conducting substrates and producing low-cost and high-performance soft electronic and optoelectronic devices. Heusing et al. (2008) reported the development of printed indium tin oxide (ITO) coatings on PET and polyethylene naphthalate (PEN) foil for flexible organic photodiodes. They have demonstrated the performance of the photodiodes with printed ITO on plastic substrates by the deposition of a PEDOT/PSS layer (Baytron® P) on the ITO-coated foils.

5.5 Wastewater Removal and Its Purification

Wan et al. (2018) reported that manganese oxide nanoparticles impregnated graphene oxide aggregates for cadmium and copper remediation. Kostic et al. (2018) reported the synthesis of mesoporous triple-metal nanosorbent from layered double hydroxide as an efficient new sorbent for removal of dye from water and wastewater. They have carried out coprecipitation synthesis of the mesoporous triple-metal nanosorbent from Fe, Cu, Ni layered double hydroxide (FeCuNi-LDH). Obtained FeCuNi-280 material showed the ability for efficient removal of dye Reactive Blue 19 (RB19) from wastewater of textile industry in wide range of pH. Zhang et al. (2018e) reported the green and size-specific synthesis of stable Fe-Cu oxides as earth-abundant adsorbents for malachite green removal. A green and sustainable pathway is described using Virginia creeper (*Parthenocissus quinquefolia*) leaf extract in the presence of oxalic acid for the synthesis of earth-abundant Fe- and Cu-based nanoparticle adsorbents. This optimized green method could produce Fe- and Cu-based nanoparticles with a remarkably high maximum adsorptive capacity for aqueous malachite green (MG) removal. They were suggested that not only promotes the use of natural, earth-abundant, and renewable resources in synthesizing novel and efficient absorbents but also provides a simple, convenient, and cost-effective strategy for the purification of dye-laden wastewater. Hosseinzadeh and Ramin (2018) reported an effective removal of copper from aqueous solutions by modified magnetic chitosan/graphene oxide nanocomposites. Ursino et al. (2018)

reported the progress of nanocomposite membranes for water treatment. The nanocomposite membranes for water treatment applications such as wastewater treatment, water purification, and removal of microorganisms, chemical compounds, heavy metals, etc., have been established. The different nanofillers, such as carbon nanotubes, zinc oxide, graphene oxide, silver and copper nanoparticles, and titanium dioxide, have provided great advances for water treatment applications. Zhang et al. (2017b) reported comparison and distribution of copper oxide nanoparticles and copper ions in activated sludge reactors. Under equal Cu concentration, copper ions were more toxic toward microorganisms compared to CuO NPs. CuO NPs were removed effectively from wastewater due to a greater biosorption capacity of CuO NPs onto activated sludge, when compared to the copper ions. The decrease in live/dead ratio after 5 h of exposure of CuO NPs and Cu^{2+} indicated the loss of cell viability in sludge flocs. Piplai et al. (2017) reported the removal of mixture of ZnO and CuO nanoparticles (NPs) from water using activated carbon in batch kinetic studies. They were suggested that as there is a need for removing NPs from wastewater, removal of NPs using an AC-based adsorptive-filter might become a promising method. Zhang et al. (2017c) reported the combined impacts of nanoparticles on anammox granules and the roles of ethylenediaminetetraacetic acid (EDTA). Previous studies investigating the risk of engineered nanoparticles (NPs) to biological wastewater treatment have tested NPs individually, but limited data are available on the impact of NPs on the anaerobic ammonium oxidation (anammox) process. They were suggested that the toxicity of NPs was dependent on the amount of active metal reaching the anammox cells and provided insights into the combined toxicity of NPs on anammox biomass. Miao et al. (2016) reported aggregation and removal of copper oxide (CuO) nanoparticles in wastewater environment and their effects on the microbial activities of wastewater biofilms. The have investigated the transport behaviors of copper oxide (CuO) NPs in wastewater matrix and their possible impacts on microbial activities of stable wastewater biofilms cultivated in a lab scale rotating biological contactor (RBC). Extracellular polymeric substance (EPS)-adsorbed copper accounted for a large proportion of the total copper accumulated in biofilms. Biofilms secreted more EPS in response to the nano-CuO stress, with higher production of proteins when compared to polysaccharides. Swain et al. (2016) reported the sustainable valorization processes for selective recovery of pure copper nanopowder from indium tin oxide (ITO) etching wastewater by various wet chemical reduction processes. Phul et al. (2018) reported ascorbic acid-assisted synthesis, characterization, and catalytic application of copper nanoparticles showed degradation of RhB in the dark and light. They found enhancement in the catalytic efficiency of Cu nanoparticles.

5.6 Anticancer Activity

Abbasi et al. (2018b) reported the three new mononuclear Schiff-base complexes which were synthesized, characterized, and used as a precursor for preparation of metal oxide nanoparticles. In vitro cell proliferation via (3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide) (MTT) assay was studied to calculate the cytotoxicity of complexes and metal oxide nanoparticles against gastric cancer cell line (MKN-45) and suggested that all three compounds have anticancer activity with dose-response dependency. Muzammil et al. (2018) reported nanoantibiotics for the future nanotechnologies to combat antibiotic resistance. Metal and metal oxide nanoparticles have been established as better alternatives but the combination of antibiotics and metal oxide nanoparticles decrease the toxicity and enhance the antibacterial, antiviral, and anticancer efficacy. Kalaiarasi et al. (2018) reported copper oxide nanoparticles induce anticancer activity in A549 lung cancer cells by inhibition of histone deacetylase (HDACs). They have copper oxide nanoparticles (CuO NPs) promoting anticancer activity. A549 cells treated with CuO NPs downregulated oncogenes and upregulated tumor suppressor protein expression. Sulaiman et al. (2018) reported biogenic synthesis of copper oxide nanoparticles using *Olea europaea* leaf extract and evaluation of their toxicity activities and findings suggest that Cu NPs may have the potential to be anticancer agents. Afzali et al. (2018) reported square wave voltammetric determination of anticancer drug flutamide using carbon paste electrode modified by CuO/GO/PANI nanocomposite. The electrochemical behavior of flutamide was investigated using a carbon paste electrode (CPE) modified by CuO nanoparticles/graphene oxide/polyaniline (CuO/GO/PANI) nanocomposite. The modified electrode was applied for the determination of flutamide in human urine and pharmaceutical samples with satisfying results. Dey et al. (2018) reported *Azadirachta indica* leaves-mediated green-synthesized copper oxide nanoparticles induce apoptosis through activation of TNF-α and caspases signaling pathway against cancer cells. They were suggested that green synthesized CuO NPs might be beneficial for its application as an anticancer drug in in vivo and in vitro mice model. Khan et al. (2018) reported green synthesis of ZnO and Cu-doped ZnO nanoparticles from leaf extracts of *Abutilon indicum*, *Clerodendrum infortunatum*, and *C. inerme* and investigation of their biological and photocatalytic activities. They have carried out green synthesis and determination of the antioxidant, antibacterial, antifungal, anticancer, and photocatalytic properties of the resultant Cu-doped zinc oxide nanoparticles (NPs). Cu-doped ZnO NPs showed antimicrobial, antioxidant, and antifungal potential, and they are good candidates for therapeutic applications. Sriram et al. (2017) reported CuO-loaded hydrophobically modified chitosan as hybrid carrier for curcumin delivery and anticancer activity. The drug-loaded chitosan-phendione and chitosan with CuO nanoparticles were used for anticancer activities toward the cell lines M19-MEL, MCF-7, and HeLa. Gnanavel et al. (2017) reported biosynthesis and characterization of copper oxide nanoparticles and its anticancer activity on human colon cancer cell lines (HCT-116). They have biosynthesized the stable copper oxide nanoparticles (CuO NPs) from the leaves of *Ormocarpum cochinchinense* to demonstrate anticancer cytotoxicity on human colon cancer cell lines (HCT-116). Rehana et al. (2017) reported an evaluation of antioxidant and anticancer activity of copper oxide nanoparticles synthesized using medicinally important plant extracts, i.e., using different plant extracts obtained from the leaves of *Azadirachta indica, Hibiscus rosa-sinensis, Murraya koenigii, Moringa oleifera*, and *Tamarindus indica*. The leaf extracts showed the presence of carbohydrates, flavonoids, glycosides, phenolic compounds, saponins, tannins, proteins, and amino acids. They have evaluated the cytotoxicity of copper oxide nanoparticles against four cancer cell lines such as human breast (MCF-7), cervical (HeLa), epithelioma (Hep-2) and lung (A549), and one normal human dermal fibroblast (NHDF) cell line. Alishah et al. (2017) reported the green synthesis of starch-mediated CuO nanoparticles using starch extracted from *Solanum tuberosum* and its preparation, characterization, antimicrobial activities, and in vitro MTT assay against MCF-7 cell line. They have evaluated antibacterial activity of copper oxide nanoparticles tested against Gram-positive and Gram-negative bacteria. Peng et al. (2017) reported biocompatible CuS-based nanoplatforms for efficient photothermal therapy and chemotherapy. CuS nanoparticles were coated with mesoporous silicon dioxide (SiO_2) and further loaded with anticancer drug doxorubicin (DOX), i.e., CuS@MSN-DOX. The infrared thermal imaging of CuS@MSN-DOX exploited as a multifunctional platform for combined photothermal therapy (PTT) and chemotherapy at the cell level and in a mice model and also demonstrated that synergistic effect of chemo-photothermal therapy, i.e., combined therapy of cancer. Nagajyothi et al. (2017) reported copper oxide nanoparticles (CuO NPs) which were synthesized by a green route using an aqueous black bean extract and showed anticancer activity of copper oxide nanoparticles against human cervical carcinoma cells. They have showed that the CuO NPs can induce apoptosis and suppress the proliferation of HeLa cells. Giannousi et al. (2016) reported the synthesis and biological evaluation of PEGylated CuO nanoparticles against tumor formation, development, and progression. They have evaluated anticancer activity of the NPs on human cervical carcinoma HeLa cells by using human immortalized embryonic kidney 293 FT cells as a control. Ramaswamy et al. (2016) reported the potentiating effect of eco-friendly synthesis of copper oxide nanoparticles using brown alga for antimicrobial and anticancer activities. The anticancer activity of brown algae-mediated copper oxide nanoparticles was determined against the cell line (MCF-7). Gopinath et al. (2016) reported *in vitro* toxicity, apoptosis, and antimicrobial effects of phyto-mediated copper oxide nanoparticles. The synthesis CuO NPs use the aqueous dried fruit extract of *Tribulus terrestris* and assess their potential in vitro cytotoxicity and antibacterial activity for pharmaceutical applications. Baskar et al. (2016) reported *in vitro* cytotoxicity of copper oxide nanobiocomposites synthesized by *Catharanthus roseus* flower extract against breast cancer cell line. The anticancer activity of copper oxide *nanobiocomposite* against MCF-7 cancer cell lines was reported. Sankar et al. (2014) reported anticancer activity of *Ficus religiosa* engineered copper oxide nanoparticles. Sivaraj et al. (2014) reported biosynthesis and characterization of *Acalypha indica*-mediated copper oxide nanoparticles and evaluation of its antimicrobial and anticancer activity. Copper oxide nanoparticles showed antibacterial and antifungal effect against *Escherichia coli, Pseudomonas fluorescens*, and *Candida albicans*. The cytotoxicity activity of *A. indica*-mediated copper nanoparticles was evaluated against MCF-7 breast cancer cell lines and confirmed that copper oxide nanoparticles have cytotoxicity activity. Germi et al. (2014) reported the copper oxide nanoparticles which showed excellent antitumor activity against two kinds of cancer cells that are AGS (human gastric carcinoma) cells and HeLa (human cervix carcinoma) cells. Hou et al. (2013) reported a facile synthesis of water-dispersible Cu_2O nanocrystal-reduced graphene oxide hybrid as a promising cancer therapeutic agent. They have also reported a Cu_2O nanocrystal-reduced graphene oxide hybrid has anticancer activity and showed safe and applicable cancer therapy agents.

5.7 Antimicrobial/Antibacterial Activity

Bhushan et al. (2019) reported thedevelopment of inorganic nanoparticles-based novel antibiotic. Inorganic nanoparticles have the potential of being used as bactericidal agent due to their effective antimicrobial activity, colloidal aqueous stability, and comparatively low toxic profile. The antibacterial activities of the samples were established against pathogenic strains of bacteria such as *E. coli, B. subtilis, S. aureus*, and *S. typhi*. Wang et al. (2019c) reported photovoltaic and antimicrobial potentials of electrodeposited copper nanoparticle. They were fabricated ITO/CuNP/CuI/Cu (indium tin oxide/copper nanoparticle/copper iodide/copper) substrate solid-state photovoltaic cell by CuNP electrodeposition on the CuI substrate. Kumar et al. (2018) reported efficacious fungicidal potential of composite derived from nano-aggregates of Cu-diclofenac complexes and ZnO nanoparticles. They have reported the synergistically enhanced antifungal activity of the composite developed from self-assembled nano-aggregates of copper complexes of nonsteroidal anti-inflammatory drug, diclofenac (Cu-Dc) in combination with zinc oxide (ZnO) nanoparticles. They have showed increased zones of inhibition in agar well-diffusion method against a human pathogenic fungus (*Candida albicans*) and three plant pathogenic fungi (*Penicillium funiculosum*, *Aspergillus niger*, and *Fusarium oxysporum*). Hong et al. (2018) reported antibacterial activity of Cu_2O and Ag comodified rice grains like ZnO nanocomposites. Cu_2O-Ag/ZnO, Cu_2O/ZnO, and Ag/ZnO nanocomposites showed a synergistic effect on antibacterial activity and antimicrobial activity against *Escherichia coli* and *Staphylococcus aureus*. Markovic et al. (2018) reported antibacterial activity of Cu-based nanoparticles synthesized on the cotton fabrics modified with polycarboxylic acids. The fabrication of antimicrobial textile nanocomposite has provided maximum reduction of Gram-negative bacterium *E. coli* and Gram-positive bacterium *S. aureus*. Singh et al. (2018) reported green synthesis of metals and their oxide nanoparticles for the applications in environmental remediation. The green synthesis is regarded as an important tool to reduce the destructive effects associated with the traditional methods of synthesis for nanoparticles commonly utilized in laboratory and industry. Metal and metal oxide [e.g., gold (Au), silver (Ag), copper oxide (CuO), and zinc oxide (ZnO)] nanoparticles use natural extracts containing phytochemicals (e.g., flavonoids, alkaloids, terpenoids, amides, and aldehydes) as reducing agents and solvent systems.

Duffy et al. (2018) reported investigation into the antibacterial activity of silver, zinc oxide, and copper oxide nanoparticles against poultry-relevant isolates of *Salmonella* and *Campylobacter*. Ebrahim-Saraie et al. (2018) reported promising antibacterial effect of copper oxide nanoparticles against several multidrug-resistant uropathogens. Pugazhendhi et al. (2018) reported photocatalytic properties and antimicrobial efficacy of Fe-doped CuO nanoparticles against the pathogenic bacteria and fungi. They have reported for the first time showing both antibiofilm and antibacterial activities of Fe-doped CuO NPs against bacterial and fungal pathogens. El-Nahhal et al. (2018) reported the efficacy of surfactants in stabilizing coating of nanostructured CuO particles onto the surface of cotton fibers and their antimicrobial activity. The CuO NPs-coated cotton materials have also showed an excellent inhibition for the growth of the medically relevant *Staphylococcus aureus* and *Escherichia coli*. Chung et al. (2018) reported production of bioactive compounds and gene expression alterations in hairy root cultures (HRCs) of Chinese cabbage elicited by copper oxide nanoparticles. Chinese cabbage is an important vegetable and rich source of phytochemicals such as glucosinolates (GSLs) and phenolic compounds (PCs) that are used in pharmaceutical industries. CuO NPs-elicited HRCs offered an efficient and promising in vitro technique to induce secondary metabolites (GSLs and PCs) for possible nutraceutical and pharmaceutical uses. Zare Khafri et al. (2018) reported synthesis of CuS and ZnO/Zn$(OH)_2$ nanoparticles and their evaluation for in vitro antibacterial and antifungal activities. The antimicrobial activity of the CuS NPs and the ZnO/Zn$(OH)_2$ NPs against *Klebsiella pneumonia* (ATCC 1827), *Acinetobacter baumannii* (ATCC 150504), *Escherichia coli* (ATCC 33218), and *Staphylococcus aureus* (ATCC 25293) has been reported. Almasi et al. (2018) reported fabrication of novel nanohybrids by impregnation of CuO nanoparticles into bacterial cellulose and chitosan nanofibers . They have observed a synergistic effect between CuO and CHNF on the antimicrobial activity of CuO-CHNF nanohybrid, and also they have demonstrated the potential of fabricated nanohybrids in water purification and food packaging applications. Ruey Ong et al. (2018) reported an influence of CuO nanoparticle on palm oil-based alkyd resin preparation and its antimicrobial activity. They have found that the CuO speeded up the reaction rate and played antimicrobial role. Vaseghi et al. (2018) reported rapid biosynthesis of novel Cu/Cr/Ni trimetallic oxide nanoparticles with antimicrobial activity. The trimetallic oxide Cu/Cr/Ni nanoparticles (NPs) have been developed using the aqueous leaf extracts of *Eryngium campestre* (*E. campestre*) and *Froriepia subpinnata* (*F. subpinnata*) as bioreducing and capping agents. Safaei and Taran (2018) reported optimized synthesis, characterization, and antibacterial activity of an alginate-cupric oxide bio-nanocomposite. They have showed the alginate-CuO nanocomposite fabrication and ability to act as an antimicrobial agent against Gram-negative and Gram-positive bacteria. Gajalakshmi et al. (2018) reported guar gum (GG)-stabilized copper oxide nanoparticles with enhanced thermal and antimicrobial properties. Alzahrani et al. (2018) reported antibacterial activity of trimetal (CuZnFe) oxide nanoparticles. They have showed that the antibacterial activity of the trimetal oxide NPs was greater against *E. coli* than against *E. faecalis*. Zhang et al. (2018f) reported the effects of copper nanoparticles in porous TiO_2 coatings on bacterial resistance and cytocompatibility of osteoblasts and endothelial cells. Copper (Cu) has showed excellent antimicrobial activity and playing roles in human metabolism. Tran et al. (2017) reported biocompatible copper oxide nanoparticle composites from cellulose and chitosan as antimicrobial activity also known to have bactericidal activity. The composites exhibited antimicrobial activity against bacteria and fungi, including methicillin-resistant

Staphylococcus aureus; vancomycin-resistant Enterococcus; and highly resistant *Escherichia coli, Streptococcus agalactiae, Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, and *Candida albicans*. Shobha et al. (2017) reported plant pathovar inhibition from copper-based nanoparticles synthesized from leaf extract of *Flacourtia montana*. The Cu_2O showed remarkable antibacterial activity against *Xanthomonas vesicatoria* and antifungal activity against *Alternaria solani.* Babaei et al. (2017) reported the bactericidal effect of copper oxide nanoparticles on *Shigella sonnei* and *Salmonella typhimurium*. Manyasree et al. (2017) reported CuO nanoparticles' synthesis, characterization, and their bactericidal efficacy against *Escherichia coli, Proteus vulgaris*, *Staphylococcus aureus*, and *Streptococcus mutans*. The copper oxide is a good antibacterial agent against both Gram-positive and Gram-negative organisms. Pourbeyram et al. (2017) reported green synthesis and characterization of ultrafine copper oxide/reduced graphene oxide (CuO/RGO) nanocomposite. Hosseinzadeh et al. (2017) reported the green synthesis of copper oxide nanoparticles using aqueous extract of *Convolvulus persicus* L. as reusable catalysts in cross-coupling reactions and their antibacterial activity. Pansambal et al. (2017) reported phytosynthesis and biological activities of fluorescent CuO nanoparticles using *Acanthospermum hispidum* L. extract. Oun and Rhim (2017) reported carrageenan-based hydrogels and films: effect of ZnO and CuO nanoparticles on the physical, mechanical, and antimicrobial properties. Giannousi et al. (2017) reported copper-based nanoparticles as antimicrobials. El-Batal et al. (2017) reported melanin production by *Streptomyces cyaneus* and synthesis of copper oxide nanoparticles using gamma radiation. Melanin pigment is used in medicine, food, and cosmetic. *Streptomyces cyaneus* is utilized for the synthesis of melanin. Copper oxide nanoparticles (CuO NPs) exhibited antimicrobial activity against foodborne Gram-positive and Gram-negative bacteria and fungi; they can find potential applications for the food packaging approach. Ijaz et al. (2017) reported the green synthesis of copper oxide nanoparticles using *Abutilon indicum* leaf extract as antimicrobial, antioxidant, and photocatalytic dye degradation activities and also indicate that they are good candidates for future therapeutic applications. Muthulakshmi et al. (2017) reported preparation and properties of cellulose nanocomposite films with in situ generated copper nanoparticles using *Terminalia catappa* leaf extract. They have shown that the cellulose/CuNP composite films exhibited good antibacterial activity against *E. coli* bacteria. Albalawi et al. (2017) reported an effect of Ag, Cu, and ZnO nanoparticle suspensions on the antimicrobial activity of *Tribulus terrestris* herbal extracts against *E. coli, Proteus sp.*, *Morganella sp.*, *Entrococcus faecalis, Staphylococcus aureus*, and *Candida albicans*. Peszke et al. (2017) reported a unique property of silver and copper-silica-based nanocomposites as antimicrobial agents. The metallic silica-based nanostructure (Ag/SiO_2, Cu/SiO_2) has revealed inhibition of growth of Gram-positive and Gram-negative bacteria as well as microscopic fungi. Altikatoglu et al. (2017) reported the green synthesis of copper oxide nanoparticles using *Ocimum basilicum* extract which is found to have antibacterial activity against pathogenic bacterial strains *E. coli* and *S. aureus.* Syame et al. (2017) reported the synthesis of copper-chitosan nanocomposites and their applications in treatment of local pathogenic isolate bacteria.

Ong et al. (2016) reported the influence of CuO nanoparticle on non-edible rubber seed oil-based alkyd resin preparation and its antimicrobial activity. Moshalagae Motlatle et al. (2016) reported chemical synthesis, characterization, and evaluation of antimicrobial properties of Cu and its oxide nanoparticles. They have showed excellent antimicrobial activity of Cu_2O/CuO nanoparticles against a mixture of bacterial strains (*S. aureus, E. coli*, and *P. aeruginosa*), indicating that the size as well as oxidation state of Cu contributes to the antibacterial efficacy. Shaffiey and Shaffiey (2016) reported silver oxide-copper oxide nanocomposite preparation and antimicrobial activity as a source for the treatment of fish diseases. The antimicrobial activities of Ag_2O/CuO nanoparticles (NPs) provide application of Ag_2O/CuO nanoparticles as disinfectant and/or antibiotic in the fishery industry. Jayandran et al. (2016a) reported the green synthesis, characterization, and antimicrobial activity studies of salicylalchitosan biofunctionalized copper oxide nanoparticles. They observed that antimicrobial activities of biofunctionalized copper oxide nanoparticles have higher inhibition activity than the non-functionalized nanoparticles and salicylalchitosan against standard microbial species. Park et al. (2016a) reported copper oxide nanoparticles aggravate airway inflammation and mucus production in asthmatic mice via mitogen-activated protein kinase (MAPK) signaling. CuO NPs markedly increased inflammatory cell infiltration into the lung and mucus secretions and exhibited toxicity on the respiratory system. CuO NPs' exposure has a potential toxicity in humans with respiratory disease. Ramaswamy et al. (2016) reported potentiating effect of eco-friendly synthesis of copper oxide nanoparticles using brown alga as antimicrobial and anticancer activities. Jayandran et al. (2016b) reported the green synthesis, characterization, and antimicrobial activity studies of curcuminaniline biofunctionalized copper oxide nanoparticles. Biofunctionalization of nanoparticles is the recent and advanced technology in the fields of nanoscience and biotechnology which produces the environmentally benign and more efficient antimicrobial agents. Baskar et al. (2016) reported *in vitro* cytotoxicity of copper oxide nanobiocomposites synthesized by *Catharanthus roseus* flower extract against breast cancer cell line. The anticancer activity of synthesized copper oxide nanobiocomposite against MCF-7 cancer cell lines was established. Pathania et al. (2016) reported the fabrication, characterization, and cytotoxicity of guar gum/copper oxide nanocomposite and efficient removal of organic pollutant. The GG/CuO nanocomposite was nontoxic for the CHO-K1 cells, oral cancer cells KB, and rat glioma C6 cells. Katwal et al. (2015) reported electrochemical synthesized copper oxide nanoparticles for enhanced photocatalytic and antimicrobial activity. The CuO NPs were used as excellent photocatalyst for the degradation of different organic dyes like methylene blue. The antimicrobial efficiency of CuO NPs was investigated against bacterial strains (*E. coli* and *S. aureus*) and fungal strains (*Aspergillus niger* and *Candida albicans*). Singh et al. (2015) reported antibiofilm and membrane-damaging potential of cuprous oxide nanoparticles against *Staphylococcus aureus* with reduced susceptibility to vancomycin. Cu_2O NPs exert their action by disruption of the bacterial cell membrane and can be used as effective antistaphylococcal and antibiofilm agents in diverse medical devices. Thampi et al. (2015) reported functionalization of fabrics with PANI/CuO nanoparticles by precipitation route for antibacterial applications. Malka et al. (2013) reported the eradication of multidrug-resistant bacteria by a novel Zn-doped CuO nanocomposite. Melegari et al. (2013) reported evaluation of toxicity and oxidative stress induced by copper oxide nanoparticles in the green alga *Chlamydomonas reinhardtii*. Karthik and Geetha (2013) reported the synthesis of copper precursor, copper and its oxide nanoparticles by green chemical reduction method and its antimicrobial activity. The antimicrobial properties of copper nanoparticles were investigated using *Streptococcus pyogenes*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Staphylococcus aureus*. Perreault et al. (2012) reported polymer coating of copper oxide nanoparticles increases nanoparticles uptake and toxicity in the green alga *Chlamydomonas reinhardtii*. Mallick et al. (2012) reported iodine-stabilized Cu nanoparticle chitosan composite for antibacterial applications. Liang et al. (2012) reported the polyaniline/$Cu_{0.05}Zn_{0.95}O$ (PANI/CZO) nanocomposites which were prepared by in situ inverse microemulsion method and used against *Staphylococcus aureus*, *Escherichia coli*, and *Candida albicans* and exhibited excellent antibacterial activity against the growth of microorganisms. Delgado et al. (2011) reported polypropylene (PP) with embedded copper metal or copper oxide nanoparticles as a novel plastic antimicrobial agent.

Yang et al. (2019) reported long-term antibacterial stable reduced graphene oxide nanocomposites loaded with cuprous oxide nanoparticles. Bashiri Rezaie et al. (2018) reported environmentally friendly low-cost approach for nano-copper oxide functionalization of cotton designed for antibacterial and photocatalytic applications. Arun et al. (2018) reported influence of transition metal ion Ni^{2+} on optical, electrical, magnetic, and antibacterial properties of phyto-synthesized CuO nanostructure. Ghadi et al. (2018) reported phytochemical fabrication, characterization, and antioxidant application of copper and cobalt oxide nanoparticles using *Sesbania sesban* plant. Mersian et al. (2018) reported synthesis of zirconium-doped copper oxide (CuO) nanoparticles by the Pechini route and investigation of their structural and antibacterial properties. Sathiyavimal et al. (2018) reported biogenesis of copper oxide nanoparticles (CuO NPs) using *Sida acuta* and their incorporation over cotton fabrics to prevent the pathogenicity of Gram-negative and Gram-positive bacteria. Sharmila et al. (2018) reported biogenic synthesis of CuO nanoparticles using *Bauhinia tomentosa* leaf extract and showed antibacterial application. Vaidehi et al. (2018) reported antibacterial and photocatalytic activity of copper oxide nanoparticles synthesized using *Solanum lycopersicum* leaf extract. Gu et al. (2018) reported ultrasound-assisted biosynthesis of CuO NPs using brown alga *Cystoseira trinodis*. Jadhav et al. (2018) reported green biosynthesis of CuO and Ag-CuO nanoparticles from *Malus domestica* leaf extract and evaluation of antibacterial, antioxidant, and DNA cleavage activities.

5.8 Antioxidant Activity

Alavi and Karimi (2018) reported antibacterial, total antioxidant, scavenging, reducing power, and ion chelating activities of green synthesized silver, copper, and titanium dioxide nanoparticles using *Artemisia haussknechtii* leaf extract. Mahjouri et al. (2018) reported toxicity impacts of chemically and biologically synthesized CuO nanoparticles on cell suspension cultures of *Nicotiana tabacum*. Koca et al. (2018) reported phytotoxic effects of biosynthesized copper oxide nanoparticle and ionic copper on *Elodea canadensis*. Dobrucka (2018) reported antioxidant and catalytic activity of biosynthesized CuO nanoparticles using extract of *Galeopsidis herba*. The synthesized CuO nanoparticles showed very good catalytic activity in the reduction of malachite green. Kaur et al. (2018) reported DNA interaction and antiproliferative effect of copper oxide nanocolloids prepared from metallosurfactant-based microemulsions acting as precursor, template, and reducing agent. Jadhav et al. (2018) reported green biosynthesis of CuO and Ag-CuO nanoparticles from *Malus domestica* leaf extract and evaluation of antibacterial, antioxidant, and DNA cleavage activities. Pradhan et al. (2016) reported enzymatic biomarkers can portray nanoCuO-induced oxidative and neuronal stress in freshwater shredders. Mohamadifard et al. (2016) reported the effects of copper oxide nanoparticles and hydroalcoholic extracts of *Berberis vulgaris*, *Descurainia sophia*, and *Silybum marianum* on catalase, glutathione peroxidase, and malondialdehyde concentration in male diabetic rats. Antioxidants reduce the occurrence of damages caused by free radicals. They showed that the studied herbal extracts could be used for moderating the effects of oxidative stress, induced by copper oxide nanoparticles. Duman et al. (2016) reported chamomile flower extract (*Matricaria chamomilla*)-directed CuO nanoparticle formation for its antioxidant and DNA cleavage properties. Guin et al. (2015) reported synthesis of copper oxide nanoparticles using *Desmodium gangeticum* aqueous root extract. Udayabhanu et al. (2015) reported *Tinospora cordifolia*-mediated facile green synthesis of cupric oxide nanoparticles and their photocatalytic, antioxidant, and antibacterial properties. CuO NPs exhibit significant bactericidal activity against *Klebsiella aerogenes, Pseudomonas aeruginosa, Escherichia coli*, and *Staphylococcus aureus*. The study reveals robust method for the synthesis of multifunctional CuO nanoparticle employing underutilized medicinal plants. Shaw et al. (2014) reported nano-CuO stress-induced modulation of antioxidative defense and photosynthetic performance of Syrian barley (*Hordeum vulgare* L.). Das et al. (2013) reported synthesis and evaluation of antioxidant and antibacterial behavior of CuO nanoparticles. Vellora et al. (2013) reported the antimicrobial effect of copper oxide nanoparticles using Gum karaya leaves act as reducing agent and phytochemicals reduce copper hydroxide into copper oxide nanoparticles, and they showed antimicrobial activity tested with different Gram-positive and Gram-negative bacterial strains. Awwad et al. (2015) reported using leaves of *Malva sylvestris* to synthesized copper oxide nanoparticles treated with copper chloride dehydrate and finally showed as antimicrobial agents.

5.9 Imaging Agents

Wang et al. (2018c) reported Se atom-induced synthesis of concave spherical $Fe_3O_4@Cu_2O$ nanocrystals for highly efficient magnetic resonance imaging-surface-enhanced Raman scattering (MRI-SERS) imaging-guided NIR photothermal therapy. They have developed multifunctional nanoplatform, which integrates multimodality imaging and therapeutic functions into a single nanocarrier used in biomedicine and nanoscience. Fe_3O_4@Cu_2O nanocrystal (NC) is first reported as a multifunctional diagnostic agent for in vitro magnetic resonance imaging (MRI) and surface-enhanced Raman scattering (SERS) imaging-guided photothermal therapy (PTT) based on Se atom-induced transformation of core-shell Fe_3O_4@Cu_2O NCs. MRI-SERS imaging-guided PTT has great potential for precision theranostic nanomedicines. Shi and Shen (2018) reported integrin αvβ3 receptor targeting PET/MRI dual-modal imaging probe based on the ^{64}Cu labeled manganese ferrite nanoparticles. PET/MRI dual-modal imaging plays more and more important role in the diagnosis of cancers and dreaded diseases. Li et al. (2018a) reported selective growth synthesis of ternary Janus nanoparticles (JNPs) for imaging-guided synergistic chemo- and photothermal therapies in the second NIR window. Multifunctional therapeutic agents in the second near-infrared (NIR-II) window have synergetic properties for cancer therapy. PEG-CuS-Au-MnO_2 ternary JNPs can be regarded as a prospective therapeutic nanoplatform for dual-modal imaging-guided synergistic chemo-photothermal cancer therapy in the NIR-II window. Karimi et al. (2018) reported ^{64}Cu is one of the most beneficial radionuclides that can be used as a theranostic agent in positron emission tomography (PET) imaging. Feng et al. (2018) reported multifunctional nanotheranostic agent with high performance for tumor site-specific generation of singlet oxygen ($1O^2$) as well as imaging guidance is crucial to laser-mediated photodynamic therapy. Copper sulfide-loaded Fe-doped tantalum oxide (Fe-mTa_2O_5@CuS) nanoparticles produced heat and toxic $1O^2$ which can kill tumor cells *in vitro* and *in vivo* effectively. Perlman et al. (2018) reported copper oxide-loaded poly(lactic-co-glycolic acid) (PLGA) nanospheres toward a multifunctional nanoscale platform for ultrasound-based imaging and therapy. CuO-loaded PLGA nanospheres (CuO-PLGA-NS) were prepared by a double emulsion (W/O/W) method with subsequent solvent evaporation. CuO-PLGA-NS constitute a versatile platform useful for combined imaging and therapeutic ultrasound-based procedures. Tan et al. (2018) reported an ultrasmall Cu_2ZnSnS_4 (CZTS) nanocrystal with high near-infrared (NIR) photothermal conversion abilities and peroxidase-mimic properties are synthesized and functionalized with bovine serum albumin (BSA) for rapid clearance multifunctional theranostic platform. Antonoglou et al. (2017) reported elucidation of one-step synthesis of PEGylated CuFe bimetallic nanoparticles and showed antimicrobial activity of CuFe@PEG vs Cu@PEG. Huang et al. (2017) reported design and functionalization of the NIR-responsive photothermal semiconductor nanomaterials for cancer theranostics. Copper chalcogenide semiconductors have emerged as a promising photothermal agent attributed to strong absorbance in the near-infrared (NIR) region and high photothermal conversion efficiency. They have been formulated by integrating the photothermal agents with antitumor drugs, photosensitizers, or radiosensitizers, resulting in a synergistic effect. Fe_3O_4@Cu_2-xS and Cu_9S_5@mSiO_2 have showed integration of photothermal agents with contrast agents or other anticancer medicines, achieving cancer theranostic and synergistic treatment. They believe that the photothermal technology from the NIR-responsive photothermal semiconductor nanomaterials would be promoted cancer theranostics. Peng et al. (2017) reported biocompatible CuS-based nanoplatforms for efficient photothermal therapy and chemotherapy. Near-infrared (NIR) photothermal therapy (PTT) is a new approach to ablate cancer without affecting normal tissues. The potential of CuS@MSN-DOX utilized as a multifunctional platform for combined PTT and chemotherapy. Ben-Sasson et al. (2016) reported *in situ* surface functionalization of reverse osmosis membranes with biocidal copper nanoparticles. They have demonstrated that *in situ* grafting of Cu NPs on reverse osmosis membranes is a potential alternative to reduce biofouling. Ahir et al. (2016) reported tailored-CuO-nanowire decorated with folic acid-mediated coupling of the mitochondrial-ROS generation and miR425-PTEN axis in furnishing potent anticancer activity in human triple-negative breast carcinoma cells. Gao et al. (2016) reported Fe_3O_4@mSiO_2-FA-CuS-PEG nanocomposites for magnetic resonance imaging and targeted chemo-photothermal synergistic therapy of cancer cells. Fe_3O_4@mSiO_2-FA-CuS-PEG nanocomposite for magnetic resonance imaging (MRI) and targeted chemo-photothermal therapy was fabricated. It has synergistic effect of chemotherapy and photothermal therapy against HeLa cells under irradiation with a 915 nm laser and has a great potential in image-guided therapy of cancers. Perlman et al. (2015b) reported copper oxide nanoparticles as contrast agents for MRI and ultrasound dual-modality imaging. They have offered radiation-free high spatial resolution scans by MRI and cost-effective high temporal resolution scans by ultrasound. Wang et al. (2015) reported electrospray formation and combustion characteristics of iodine-containing Al/CuO nanothermite microparticles. Perlman et al. (2015a) reported preliminary study of copper oxide nanoparticles acoustic and magnetic properties for medical imaging. Zolata et al. (2014) reported radio-immunoconjugated, Dox-loaded, surface-modified superparamagnetic iron oxide nanoparticles (SPIONs) as a bioprobe for breast cancer tumor theranostics. Tian et al. (2013) reported sub-10 nm Fe_3O_4@Cu_2-xS core-shell nanoparticles for dual-modal imaging and photothermal therapy. Barreto et al. (2011) reported synthesis, colloidal stability, and ^{64}Cu labeling of iron oxide nanoparticles bearing different macrocyclic ligands. Glaus et al. (2010) reported in vivo evaluation of ^{64}Cu-labeled magnetic nanoparticles as a dual-modality PET/MR imaging agent. Patel et al. (2010) reported Cu^{2+}-labeled, SPION-loaded porous silica nanoparticles for cell labeling and multifunctional imaging probes. Jarrett et al. (2008) reported synthesis of ^{64}Cu-labeled magnetic nanoparticles for multimodal imaging.

5.10 Drug Delivery Agents

Bhushan et al. (2019) reported the study of synthesis and structural, optical, and magnetic characterizations of iron/copper oxide nanocomposites. They have been used as the potential antibiotic to counter the diseases caused by normal and multidrug-resistant pathogenic bacterial strains. Velusamy et al. (2018) reported novel electrochemical synthesis of copper oxide nanoparticles decorated graphene-β-cyclodextrin composite for trace-level detection of antibiotic drug metronidazole. Bakravi et al. (2018) reported synthesis of gelatin-based biodegradable hydrogel nanocomposite and their application as drug delivery agent. Xue et al. (2018) reported phyto-mediated synthesized multifunctional Zn/CuO NPs hybrid nanoparticles for enhanced activity for kidney cancer therapy: A complete physical and biological analysis. Zhen et al. (2018) reported reduced graphene oxide coated Cu_2-xSe nanoparticles for targeted chemo-photothermal therapy.

Ahmadian et al. (2018) reported synthesis of polyvinyl alcohol/CuO nanocomposite hydrogel and its application as drug delivery agent. Han et al. (2017) reported hollow copper sulfide nanosphere-doxorubicin/graphene oxide core-shell nanocomposite for photothermo-chemotherapy. Giannousi et al. (2016) reported synthesis and biological evaluation of PEGylated CuO nanoparticles. Jha et al. (2016) reported comparative nanoscale interaction of TiO_2/ZnO/Cu with human spermatozoa for biomedical application. Farhoudian et al. (2016) reported a facile synthesis of antibacterial chitosan/CuO bio-nanocomposite hydrogel beads. Delgado et al. (2011) reported polypropylene with embedded copper metal or copper oxide nanoparticles as a novel plastic antimicrobial agent. Yang et al. (2011) reported peptide conjugated Arginylglycylaspartic acid (cRGD)-functionalized, doxorubicin (DOX) an antibiotic-conjugated, and ^{64}Cu-labeled superparamagnetic iron oxide nanoparticles for targeted anticancer drug delivery and PET/MR imaging.

5.11 Diagnosis and Therapeutic Agents

Perlman et al. (2018) reported copper oxide-loaded PLGA nanospheres toward a multifunctional nanoscale platform for ultrasound-based imaging and therapy. Wu et al. (2015) reported rattle-type Fe_3O_4@CuS developed to conduct magnetically guided photoinduced hyperthermia at first and second NIR biological windows. Yugandhar et al. (2018) reported cost-effective green synthesis of copper oxide nanoparticles using fruit extract of *Syzygium alternifolium* (Wt.) Walp. Logpriya et al. (2018) reported the preparation and characterization of ascorbic acid-mediated chitosan-copper oxide nanocomposite for antimicrobial, sporicidal, and biofilm inhibitory activity. Jadhav et al. (2018) reported green biosynthesis of CuO and Ag-CuO nanoparticles from *Malus domestica* leaf extract which acts as a good stabilizing agent and evaluation of antibacterial, antioxidant, and DNA cleavage activities. The synthesized CuO and Ag-CuO nanoparticles using *Malus domestica* leaf-capped nanoparticles have exhibited interesting antibacterial activity with both Gram-positive and Gram-negative bacteria at microgram concentrations, and these greenly synthesized NPs act as a potent therapeutic agent. Bhuvaneshwari et al. (2018) reported green synthesis of copper oxide nanoparticles for biological applications. The nanometer-sized materials known as nanomaterials have unique physical, chemical, and biological properties. Among them nano-copper oxide has potential applications in many fields like heterogeneous catalysts, photocatalysts, antimicrobial agent, antioxidants, imaging agents, and drug delivery agents. A nanoparticle (NP) with biomolecules is useful in diagnosis and therapeutic. Sundaramurthy and Parthiban (2015) reported that CuO NPs have glorious potency to degrade methylene blue below solar irradiation. The green-synthesized CuO NPs were confirmed as economical catalysts with increased rates of textile dye decolourization. The CuO NPs can also suppress cell viability using several mechanisms, such as apoptosis and necrosis. Cell suicide mechanism which controls cell numbers is apoptosis. Two types of pathway are involved in apoptosis. Finally, CuO NPs have been used as photocatalyst, antimicrobial agent, and better anticancer compound with minimal side effects. CuO NPs can also act as efficient antibacterial agent when incorporated in coatings, plastics, and textiles (Yallappa et al. 2013; Kwak and Chongyoup 2005; Manoranjan and Gitisudha 2016). Nagajyothi et al. (2017) reported copper oxide nanoparticles (CuO NPs) were synthesized by a green route using an aqueous black bean extract and the cytotoxic effect of the CuO NPs was determined by sulforhodamine-B assay. They showed that the CuO NPs can induce apoptosis and suppress the proliferation of HeLa cells. Kumar et al. (2017) reported biofabrication of copper oxide nanoparticles (CuO NPs) using Andean blackberry fruit (ABF) and leaf (ABL) which showed antioxidant activity. They also suggested that green CuO NPs could be used in future biomedical application. Sangeetha et al. (2012) reported the synthesis of nanostructured copper oxide particles by green chemistry approach and aloe extract.

Ghidan et al. (2016) reported copper oxide nanoparticle (CuO NP) synthesis by green method using *Punica granatum* peel extract. Rajeshwari et al. (2014a) reported biogenic copper oxide nanoparticle synthesis using *Tabernaemontana divaricata* leaf extract and its antibacterial activity against urinary tract pathogen. Rajeshwari et al. (2014b) reported biosynthesis and characterization of *Acalypha indica*-mediated copper oxide nanoparticles and evaluation of its antimicrobial and anticancer activity. Sharma et al. (2015) reported green synthesized copper oxide (CuO) nanoparticles (NPs) as electrocatalytic materials for the fabrication of counter electrode in dye-sensitized solar cells (DSSCs) using the leaves extract of *Calotropis gigantea* plant in aqueous medium through green synthesis. Gnanavel et al. (2017) reported biosynthesis and characterization of copper oxide nanoparticles and its anticancer activity on human colon cancer cell lines (HCT-116). Shrikant et al. (2012) reported a novel route for rapid biosynthesis of copper nanoparticles using aqueous extract of *Calotropis procera* L. latex and their cytotoxicity on tumor cells. The progresses of green chemistry in the synthesis of nanoparticles with the use of plants have a great attention. Yallappa et al. (2013) reported microwave-assisted rapid synthesis and biological evaluation of stable copper nanoparticles using *T. arjuna* bark extract, and Cu NPs show very good antioxidant property. Udayabhanu et al. (2015) reported the green synthesis of copper oxide nanoparticles (CuO NPs) by a solution combustion method using *Tinospora cordifolia* water extract and found nanoparticles have spongelike structure and sizes which were found to be ~6–8 nm. These CuO NPs showed photocatalytic activity to degrade methylene blue (MB) in the presence of UV and sunlight and also reported significant bactericidal activity against *Klebsiella aerogenes*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Staphylococcus aureus*.

Green synthesis by using plant resources has been a simple and effective approach for the synthesis of various forms of nanoparticles. They possess strong biological activities in terms of antioxidant, anti-inflammatory, antidiabetic, and antibacterial potentialities which could be utilized in various biological applications by the cosmetic, food, and biomedical industries. Nanoparticles with antimicrobial activity, especially as a new class of biomedical materials for use in increasing the level of public health in daily life, have emerged.

Biological methods for nanoparticle synthesis using microorganisms, enzymes, and plants or plant extracts have been suggested as possible eco-friendly alternatives to chemical and physical methods. The nature acts like a large "bio-laboratory" comprising plants, algae, fungi, yeast, etc. which are composed of biomolecules. These naturally occurring biomolecules have been identified to play an active role in the formation of nanoparticles with distinct shapes and sizes, thereby acting as a driving force for the designing of greener, safe, and environmentally benign protocols for the synthesis of nanoparticles. The present review targets the comparative biogenic synthesis and mechanisms of nanoparticles using algae and waste materials (agro-waste in the presence of biomolecules). The use of waste materials not only reduces the cost of synthesis but also minimizes the need of using hazardous chemicals and stimulates "green synthesis." It also focuses on the computational aspects of binding of biomolecules to nanoparticles and some of the applications of the biosynthesized nanoparticles in biomedical, catalysis, and biosensor fields (Kuppusamy and Mashitah 2016).

The field of nanotechnology mainly encompasses with biology, physics, chemistry, and material sciences, and it develops novel therapeutic nanosized materials for biomedical and pharmaceutical applications. The biological syntheses of nanoparticles are being carried out by different macro-microscopic organisms such as plant, bacteria, fungi, seaweeds, and microalgae. The biosynthesized nanomaterials have been effectively controlling the various endemic diseases with less adverse effect. Plant contains abundant natural compounds such as alkaloids, flavonoids, saponins, steroids, tannins, and other nutritional compounds. These natural products are derived from various parts of plant such as leaves, stems, roots, shoots, flowers, barks, and seeds. Recently, many studies have proved that the plant extracts act as a potential precursor for the synthesis of nanomaterial in non-hazardous ways. Since the plant extract contains various secondary metabolites, it acts as reducing and stabilizing agents for the bioreduction reaction to synthesized novel metallic nanoparticles. The non-biological methods (chemical and physical) are used in the synthesis of nanoparticles, which has a serious hazardous and high toxicity for living organisms. In addition, the biological synthesis of metallic nanoparticles is an inexpensive, single-step, and eco-friendly methods. The plants are used successfully in the synthesis of various greener nanoparticles such as cobalt, copper, silver, gold, palladium, platinum, zinc oxide, and magnetite. Also, the plant-mediated nanoparticles are potential remedy for various diseases such as malaria, cancer, HIV, hepatitis, and other acute diseases. The biofabricated silver nanoparticles are extensively used in environmental, biotechnological, and biomedical applications. The synthesis of SNPs has been carried out by using the filtrate extract of novel fungal strain *Penicillium atramentosum* KM. The synthesized SNPs showed antimicrobial activity against bacterial strains (Narayanan and Sakthivel 2011).

The size, shape, and controlled dispersity of nanoparticles play a vital role in determining the physical, chemical, optical, and electronic properties attributing its applications in environmental, biotechnological, and biomedical fields. Various physical and chemical processes have been exploited in the synthesis of several inorganic metal nanoparticles by wet and dry approaches, viz., ultraviolet irradiation, aerosol technologies, lithography, laser ablation, ultrasonic fields, and photochemical reduction techniques. However, these methodologies remain expensive and involve the use of hazardous chemicals. Therefore, there is a growing concern for the development of alternative environment-friendly and sustainable methods. Increasing awareness toward green chemistry and biological processes has led to a necessity to develop simple, cost-effective, and eco-friendly procedures. Phototrophic eukaryotes such as plants, algae, and diatoms and heterotrophic human cell lines and some biocompatible agents have been reported to synthesize greener nanoparticles like cobalt, copper, silver, gold, bimetallic alloys, silica, palladium, platinum, iridium, magnetite, and quantum dots. Owing to the diversity and sustainability, the use of phototrophic and heterotrophic eukaryotes and biocompatible agents for the synthesis of nanomaterials is yet to be fully explored. This review describes the recent advancements in the green synthesis and applications of metal nanoparticles by plants, aquatic autotrophs, human cell lines, biocompatible agents, and biomolecules.

5.12 Future Perspectives

Metal and metal oxide NPs have been widely utilized in various biomedical applications, such as detection, diagnosis, imaging, and therapy and provide a perspective for future evolution of this field. CO_2 conversion via photocatalysis is a solution to address global warming and energy shortage. Photocatalysis can directly utilize the inexhaustible sunlight as an energy source to catalyze the reduction of CO_2 to useful solar fuels such as CO, CH_4, CH_3OH, and C_2H_5OH. Cu-based photocatalysts are the most attractive for CO_2 conversion. Cu-based photocatalysts for CO_2 conversion, which includes metallic copper, copper alloy nanoparticles (NPs), copper oxides, and copper sulfide photocatalysts, provide insight into the nature of potential active sites for the catalysts with much-enhanced energy conversion efficiency and production rates. Microbial infectious diseases are a global threat to human health and excess and improper use of antibiotics has created antimicrobial-resistant microbes that can resist clinical treatment. The metal oxide nanoparticles have fight against microbes resistant to use of various classes of antibiotics. The mechanisms of action of MO NPs against microorganisms, safety concerns, challenges, and future perspectives are potentially important. The challenges and perspective on nanomaterials toward drug delivery, imaging, and photothermal agents for diagnosis and therapy of diseases are alarming and potentially important to tackle. The size, size distribution, morphology, polymorphic nature, crystallinity, biocompatibility, biodegradability, drug elution profiles, and aggregation propensity are important issues for the future development of MNPs that address the present challenges and lead to new opportunities in nanomedicine and nanobiotechnology (Tseng et al. 2015; Sun and Yang 2014; Raghunath and Perumal 2017; Xie et al. 2017; George et al. 2018).

5.13 Conclusions

Copper and copper oxide nanoparticles can be fabricated by plant extracts. The shape and size may be controlled by maintaining the temperature, pH, and concentration of the reacting components. Their cytotoxicity varies with shape such as spherical, beads, and rods and has great potential for use in instruments and medical devices, as drug carrier, and in the treatment of many diseases. The plant extracts containing alkaloids, flavonoids, saponins, ketones, aldehydes, and phenols or reducing acids like citric acid and ascorbic acids can be used for nanoparticle synthesis. CuONPs can be used for removal of dyes, in wastewater treatment, purification of ground water and also used as a catalyst, biosensing, antibacterial, antimicrobial, anticancer activity and as an antioxidant.

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Chapter 6
Applications of Nanomaterials and Future Prospects for Nanobionics

Manoj Kumar Enamala, Bhulakshmi Kolapalli, P. Divya Sruthi, Silpi Sarkar, Chandrasekhar Kuppam, and Murthy Chavali

Contents

M. K. Enamala
Bioserve Biotechnologies (India) Private Limited, Hyderabad,
Telangana, India

B. Kolapalli
Prathista Industries Limited, Secunderabad, Telangana, India

P. Divya Sruthi
ITC Spices (ITC Agri Business Division), Guntur, Andhra Pradesh, India

S. Sarkar
Department of Biotechnology, Vignan University, Guntur, Andhra Pradesh, India

C. Kuppam
Green Processing, Bioremediation and Alternative Energies (GPBAE) Research Group,
Faculty of Environment and Labour Safety, Ton Duc Thang University,
Ho Chi Minh City, Vietnam

M. Chavali (✉)
Shree Velagapudi Ramakrishna Memorial College (PG Studies-Autonomous),
Acharya Nagarjuna University, Guntur, Andhra Pradesh, India

MCETRC, Guntur, Andhra Pradesh, India

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Abbreviations

0D	Zero-dimensional
1D	One-dimensional
2D	Two-dimensional
3D	Three-dimensional
Ag	Silver
ATP	Adenosine triphosphate
Au	Gold
BES	Bioelectrochemical system
C_{60}	Fullerene
CNT	Carbon nanotube
CRISPR	Clustered regulatory interspaced short palindromic repeat
ENM	Engineering nanomaterial
ENP	Engineered nanoparticle
$h\nu$	light energy
LDH	Layered double hydroxide
LEEP	Lipid exchange envelope penetration
MFC	Microbial fuel cell
PAMAM	Polyamide amine dendrimer
PD	Protein drug
PEI	Polyethyleneimine
PEM	Proton exchange membrane
QD	Quantum dot
VLP	Virus-like particle

6.1 Introduction

Nanoscience is simply understanding of the properties of matter with a length scale of between 1 and 100 nm. Nanotechnology is a tool for manipulation at this scale in order to build nanosized entities. A nanomaterial has a critical dimension on the scale of 1–100 nm; a more specific definition of a nanomaterial is a substance that exhibits properties that are absent in its molecular state or in its bulk solid state, owing to its existence at a critical nanoscale in this range. The increasing roles of nanomaterials in various advanced technological applications have created a special need to devise new means of obtaining nanoparticles with specific nanostructures and properties.

Nanomaterials are the most advanced technology in today's world. These materials are defined as materials whose dimensions measure less than approximately 100 nm. Researchers are interested in these materials because they possess unique magnetic, optical, electrical, and numerous other properties, which will have huge impacts in various field of science. Some nanomaterials occur naturally and some are engineered; the latter are particularly designed for use in various commercial products such as cosmetics, electronic items, stain-resistant clothing, and drug delivery systems. The larger surface area–to–volume ratios of these nanomaterials affect their strength and chemical reactivity. Quantum effects also affect their material properties and characteristics, leading to novel products in various fields (Alagarasi 2011). Engineered nanomaterials (ENMs) have remarkable physiochemical characteristics, which are suitable for various applications in various sectors of research such as biotechnology, energy, cosmetics, pharmaceuticals, and many other fields of research. ENMs can enter the environment through recycling processes or waste conversion during their manufacturing processes. ENMs have caused great concern regarding their potential effects on living organisms (biotic ecosystem components) and on nonliving (abiotic) ecosystem components because of their rapidly increasing applications. Plants play a significant role in maintaining ecological systems and also play important roles in bioaccumulation and transport of ENMs in food chains at different trophic levels. ENMs can easily enter plant cells, interacting/interfering with intracellular metabolic pathways and structures.

Researchers responded in both positive and negative ways towards mode of application of nanoparticles on plant species growth and development underlying their synthetic procedures and properties of nanomaterials. Depending on their types and concentrations, these materials have positive or negative impacts on processes such as photosynthesis. Therefore, plants are considered one of the core elements present on the globe that will be directly affected by these ENMs, since they directly act together with the biosphere mechanism (Hatami et al. 2016).

6.2 Roles of Nanomaterials in Plant Growth

The word "nanomaterials" covers various shapes of nanostructured materials with at least one dimension in the nanometric range. Nanomaterials have a specific set of features in between those of bulk materials and atoms. These properties of nanomaterials are significantly different from those of bulk materials and atoms. Typical nanomaterials are (i) nanocrystals and clusters, with a diameter of 1–10 nm; (ii) nanowires, with a diameter of 1–100 nm; (iii) nanotubes, with a diameter of 1–100 nm; (iv) dimensional nanoparticle arrays, with areas between several square nanometers and square micrometers; (v) surfaces and thin films, with a thickness of 1–100 nm; and (vi) three-dimensional (3D) structures or superlattices, measuring several nanometers in all three dimensions.

Because of their smaller dimensions, these nanomaterials have enormously large surface area–to–volume ratios, which gives a large fraction of these materials more

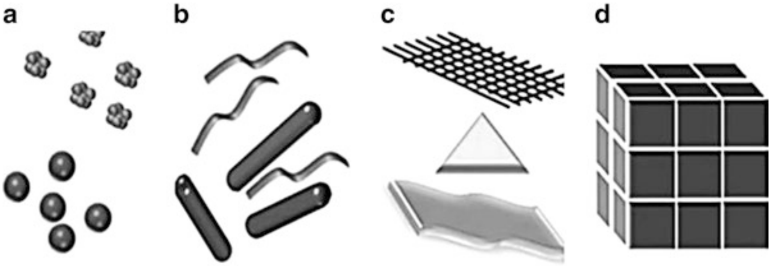

Fig. 6.1 Classification of nanomaterials. (**a**) Zero-dimensional (*0D*) spheres/clusters. (**b**) One-dimensional (*1D*) nanofibers, nanowires, and nanorods. (**c**) Two-dimensional (*2D*) nanofilms, nanoplates, and networks. (**d**) Three-dimensional (*3D*) nanomaterials

surface-dependent material properties. If the nanomaterial size is comparable to the Debye length, then the entire material will be affected by the surface properties of these nanomaterials. Nanoscience and nanotechnology is a highly interdisciplinary area of research, and development activity has seen explosive growth worldwide in the past few years.

Nanomaterials can have nanoscale proportions in one dimension (1D; e.g., surface films), two dimensions (2D; e.g., strands or fibers), or 3D (e.g., particles), and they also exist as single, aggregated, or agglomerated fused forms with spherical, cylindrical, tubular, and irregular shapes. Siegel's classification (Siegel et al. 1997) of nanostructured materials as zero-dimensional (0D-atomic clusters, filaments and cluster assemblies), one (multilayers), two (ultrafine-grained over-layers or buried layers), and three (nano-phase materials consisting of equiaxed nanometer sized grains), 1D, 2D, and 3D nanostructures is shown in Fig. 6.1. The most common types of nanomaterials are nanotubes, quantum dots (QDs), dendrimers, and fullerenes (C_{60}). Nanomaterials have promising applications in nanotechnology, displaying different physical–chemical characteristics from those of normal chemicals (e.g., Ag, Au nano, carbon nanotubes (CNTs), fullerene, photocatalysts, carbon nano, and silica).

Nanomaterials are the key components of nanoscience and nanotechnology, showing tremendous potential for revolutionizing the ways in which nanodevices/nanoproducts are created and the nature of functionalities that can be opened up. They have already had a noteworthy commercial impact, and this will assuredly increase in the future. Nanomaterials offer boundless opportunities in the field of agriculture because of their unique physicochemical properties. The interaction of nanoparticles with plants results in various morphological, physiological, and genotoxic changes, and understanding of these is of utmost importance for practical use of nanotechnology in agriculture. With the awe-inspiring advancements in the field of nanotechnology, ENMs have been widely used in countless areas of plant systems, yielding excellence in quality improvement, growth, enhancement of nutritional values, gene preservation, etc. There have been several published reports on the influence of ENMs on growth enhancements and growth inhibition, as well as on certain impacts of ENMs on plants, observed in studies on ENM uptake, growth responses, translocation and biotransformation of ENMs, and mechanisms of stress

Table 6.1 Effects of engineered metal oxide nanoparticles on the growth of plants

Nanoparticles	Plants	Effects on plants
Aluminum oxide	Carrot and cabbage	Reduced root growth
Cerium oxide	Tomato, maize, and cucumber	Reduced shoot growth
Iron oxide	Clove	Reduced aboveground and belowground biomass
Cerium oxide	Rice	Reduced hydrogen peroxide generation in roots and shoots
Combination of SiO_2 and TiO_2	Soybean	Increased germination and shoot growth, enhanced antioxidant system, increased nitrate reductase activity
Magnetite (iron oxide)	Soybean	Increased chlorophyll
Nanoanatase	Spinach	Enhanced messenger RNA expression, protein activity, and photosynthetic activity
Inorganic bentonite clay (TiO_2)	Maize	Inhibited hydraulic conductivity, leaf growth, and transpiration

modulation by ENMs in plant systems. The risks of application of nanomaterials to agriculturally important crops have been a recent focus of research to understand the biochemical, physiological, and molecular mechanisms of nanoparticle interactions with plants.

Plants experience a combination of biotic and abiotic stresses, starting at the time of seed germination, which is the first stage in the growth of the plant. Researchers have identified certain nanomaterials that are helpful for successful growth of plants in terms of nitrogen metabolism, photosynthetic activity, and other advantages, as listed in Table 6.1. Successful penetration of nanomaterials results in activation of genes responsible for water channel proteins; subsequently, better cell growth occurs through regulation of the cell cycle. Successful execution of seed germination depends upon deployment of stored food resources by enzymes such as amylase and protease for survival of young plants until they are capable of generating their own energy resources through photosynthesis (Khan et al. 2017).

6.3 Plant Nanobionics

The wider vision is to create an extensive array of wild-type plants that are skilled in imaging objects in their environment, infrared communication devices, functioning as self-powered light sources, and also functioning as self-powered groundwater sensors. Plants are uniquely suited to perform these roles because of their ability to generate energy from sunlight via photosynthesis. In the field of nanobiotechnology, researchers aim to develop bionic plants that exhibit the highest possible photosynthesis efficiency and biochemical sensing.

Plant nanobionics is a new field in the area of bioengineering, where nanoparticles are inserted into plants and the functions of plant tissues or organelles are altered or amplified (Ghorbanpour and Fahimirad 2017). Plants can continuously exchange various gases with their surroundings. Plants also conduct a process known as transpiration, where the plants channel water through their roots and give off water vapor through their leaves. This process is characterized by various characteristics such as (a) stabilization and flow of water (large pressures), (b) heat transfer with evaporation of water (continuous), and (c) extraction of water from subsaturated sources (continuous) (Wong et al. 2017). Biomaterials created by conventional approaches rely on reverse engineering of biological structures for enhancement of the process of photosynthetic activity by engineered materials with synthetic nanoparticles in combination with plant organelles.

6.3.1 Architecture of the Plant Cell Wall in Terms of Nanobionics

A bionic material made up of plant cells and CNTs exhibits greater temperature sensitivity, such that this particular material outperforms the best man-made materials. Ionic conductivity, which interconnects cellulose microfibrils in the plant cell wall with the pectin backbone, is the basic mechanism involved. The use of CNTs helps to prevent cell death and stabilize the response of dried cells at higher temperatures. The architecture of the plant cell wall is designed in such a way that it has a highly complex macromolecular architecture with very dynamic structural features. The cell wall is present outside the plasma membrane and is made up of microfibrils. The transportation of ions within the cell wall is influenced by various factors such as the charge, porosity, pH balance, and surface charge. Pectins contain negatively charged saccharides, which bind cations that form cross-links, giving strength to the cell wall (Di Giacomo et al. 2015). The thylakoid membrane in the chloroplasts is the main machinery causing photosynthetic activity to take place. Chloroplasts absorb light in the visible range of the light spectrum, which comprises 50% of the incident solar radiation energy (Ghorbanpour and Fahimirad 2017). Giraldo et al. (2014) were able to successfully design a system with highly charged single-walled CNTs (SWCNTs) coated with DNA and chitosan, which were able to enter chloroplasts.

6.3.2 Supercharged Photosynthesis: Processes Involved in the Photosynthetic Machinery

Chloroplasts are the major elements present in plants that conduct the process known as photosynthesis. At the first stage, chlorophyll absorbs light, which excites electrons, causing them to flow through the thylakoid membrane of the chloroplasts. This converted electrical energy is used by the plant to make sugars at the second

Table 6.2 Roles of nanoparticles in the photosynthetic process

Nanoparticles	Activities
Silicon oxide nanoparticles	Improves the rate of photosynthesis by improving the activity of carbonic anhydrase and synthesis of photosynthetic pigments
Nanoanatase TiO_2 nanoparticles	Improves light absorbance, and the transformation from light energy to electrical and chemical energy, Induces carbon dioxide assimilation Enhances photosynthetic carbon assimilation by activating RuBisCO, which helps in improvement of plant growth
Metal nanoparticles	Can induce chemical energy
Nanomesoporous silica	Induces stable activity of photosynthetic oxygen-evolving reaction

stage of photosynthesis. When chloroplasts are removed from plants they can still perform these reactions, but after a certain time they break down because of light and oxygen damage to the photosynthetic proteins. Hence, to protect chloroplasts against damage, researchers have delivered cerium oxide nanoparticles (which are known as nanoceria and are strong antioxidants) to the inside of these chloroplasts through a technique called lipid exchange envelope penetration (LEEP). Packing of such particles in polyacrylic acid (an extremely charged molecule) allows the nanoparticles to penetrate the fatty hydrophobic membranes that surround the chloroplasts. The level of damage is reduced instantly. Using a method known as vascular infusion, researchers have applied nanoparticles to the underside of leaves and observed that CNTs moved into the chloroplasts and boosted the electron flow in photosynthesis by 30% (Strano et al. 2014). Table 6.2 lists the roles of some nanoparticles in the photosynthetic process.

6.3.3 Engineered Nanomaterials and Photosynthesis

Some nanomaterials are found naturally, but of specific interest are ENMs, which are used in many commercially available products and processes such as sunscreens, cosmetics, stain-resistant clothing, electronics, sporting goods, tires, and many other day-to-day items. They are also used in medicine for the purposes of imaging, diagnosis, and drug delivery. ENMs are resources designed at the molecular (nanometric) level to take advantage of their small size and novel properties that are generally not seen in their conventional, bulk-form counterparts; these properties are mainly due to the increased relative surface area and quantum effects.

Plants make use of light energy ($h\nu$) from sunlight to make their own food products and transport it to the rest of the parts of its cells. Photosynthesis is the process of conversion of light energy into chemical energy by living organisms. Moreover, photosynthesis is responsible for the creation of fossil fuel energy deposits, which have accrued over a period of millions of years (Szabó et al. 2015). Plants convert only 2–4% of the total energy available for the growth of the next generation (Siddiqui et al. 2015). Hence, to increase the pace of these chemical reactions, researchers are working on RuBisCO, which is considered to be an important enzyme for catalyzing these reactions. Chloroplasts contain light-sensitive pigments, which capture solar energy, and the chloroplast is also a place where highly complex photosynthetic reactions occur, including absorption of light and charge separation based on light and electron transfer between photosystems. This energy is transformed into various sugars such as maltose, triose phosphate, and glucose. This photosynthetic process is also used to synthesize adenosine triphosphate (ATP) in plants. ENMs have been found to have both positive and negative effects on the photosynthetic process. The negative effects include reductions in chlorophyll and carotenoid, enzyme activities due to membrane lipid peroxidation, and oxidative stress caused by the ENMs. Chlorophyll *a* is the most essential pigment for photosynthetic organisms. It is the most sensitive form of chlorophyll and degrades easily upon exposure to light. ENMs could play a significant role in the design of efficient biomarkers (Hatami et al. 2016).

The effects of cerium oxide, titanium oxide, and copper hydroxide at different concentrations resulted in decreases in the rates of photosynthesis and CO_2 assimilation in plants grown under conditions of stronger light and high levels of nutrients. The ENMs disrupted photosynthesis in plants grown under severe stress conditions, such as very strong light intensity and nutrient limitation, by preventing photo-oxidation of the photosystem II reaction center. Many researchers are working to improve photosynthetic efficiency through gene manipulation techniques by incorporating cyanobacteria carbon-fixing genes into tobacco plants, replacing the RuBisCO genes in the plants. Researchers are also developing nanobionic plants, which possess better photosynthetic efficiency and biochemical sensing. Incorporation of SWCNTs into plants has been reported to triple photosynthetic activity, enable plants to sense nitric oxide, and enhance electron transport rates (Siddiqui et al. 2015).

6.4 Applications of Nanomaterials

6.4.1 Food and Agriculture

Nanotechnology and nanobiotechnology are emerging fields with tremendous potential to modernize agriculture and related fields. Nanotechnology research in agriculture is currently focused on farming and involves the use of nanoparticles to boost crop and livestock productivity. Nanotechnology applications can be found in agricultural production, animal feed, food additives, food processing, and food contact materials (Prasad et al. 2017a, b). A great diversity of nanomaterials have reportedly been used in numerous agricultural and food-related applications, while new nanomaterials and applications are reportedly in development. It is estimated that applications of nanomaterials in food and agriculture products will increase in the coming years and thereby increase nanomaterial exposure in humans and in the environment.

Nanotechnology applications—such as processing, packaging, and food supplements—are currently being researched and tested across the entire spectrum of food

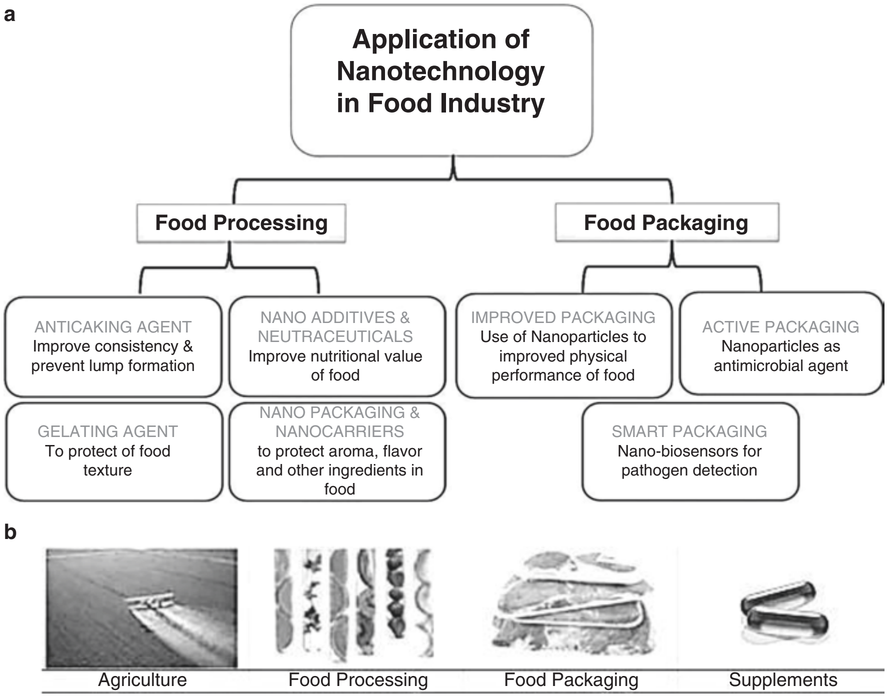

Fig. 6.2 Nanotechnology applications in (**a**) the food industry sector and (**b**) the agriculture sector and other food sectors

technology from agriculture to the food industry. Specifically, in agriculture, technical innovation is of importance with regard to addressing global challenges such as population growth, climate change, and the limited availability of important plant nutrients such as phosphorus and potassium. Nanotechnology could play a fundamental role when applied to agricultural production, and research on agricultural applications has now been ongoing for about a decade. This also touches on the issue of nanotechnology in developing countries. Possible applications in the agriculture and food sector are shown in Fig. 6.2.

Despite the prospective advantages of nanotechnology in the agricultural industry, its application is still comparatively marginal and it has not yet made its mark on markets, in comparison with other sectors of nanotechnology. The potential application of nanotechnology in the agriculture industry is large, but there are still some issues to be addressed, such as the need for increases in production, processes, and cost reduction, as well as risk assessment. In view of these issues, nanoparticles derived from biopolymers—proteins and carbohydrates with only minor impacts on human health and the environment—are particularly attractive to researchers. For instance, starch-based nanoparticles are nontoxic and have the potential to act as sustainable delivery systems/carriers for agrochemicals, and biostimulants are being extensively evaluated by research groups. In recent years, agricultural waste has also attracted attention as a source of renewable raw materials to be processed for various different applications, as well as raw materials for production of nanomaterials (as substitutes for fossil fuel resources). Biomaterial-based nanocomposites have highly beneficial properties in comparison with traditional micro- and macro-composite materials; additionally, their production is sustainable. Nowadays, many production processes are being developed to obtain useful nanocomposites from traditionally harvested materials, using novel methods. From a commercial viewpoint, existing agrochemical companies are studying the potential of nanotechnologies and, in particular, nanosized active ingredients, which can yield increased efficacy or greater penetration of useful components in plants. However, they have not demonstrated key improvements in products, such as cost reductions and large-scale production. Some specific nanoproducts for the agricultural sector have been marketed by technology-oriented smaller companies, such as soil enhancer products that promote even water distribution and storage, and consequently water savings, etc. However, only small-scale commercial market application of these products has been achieved so far, because of the high costs of these products. These costs are normally compensated for by higher returns in the medical or pharmaceutical sectors, but so far there are no such returns in the agricultural sector. Research continues in the commercial agrochemical sector, evaluating the potential advantages of these products. Companies are also facing challenges due to stringent regulations. Nanoscale formulants (e.g., clay, silica, polymers, pigments, and macromolecules) have been used for many decades and are also ubiquitous in many everyday household products.

6.4.2 Gene Delivery Systems

Gene therapy is the latest tool being used by many researchers for treatment of many diseases by replacement/correction of absent genes. The theoretical knowledge is very good, but there are certain limitations in practical applications, which need to be corrected. The success rate of practical applications of gene delivery systems is not that high. Certain challenges that gene therapy faces include development of safe and efficient vectors for delivering genes to intracellular sites with degradation. Gene delivery systems can be subclassified into viral and nonviral vectors. The initial delivery of therapeutic genes was first achieved using viral vectors because they have the capacity to carry genes efficiently and ensure long-term expression at the relevant site (Sun et al. 2017).

Nanomaterials are being used for drug delivery systems in various pharmaceutical fields. With use of these drug delivery systems, the pharmacokinetics of drugs can be improved through controlled delivery of vital constituents to the desired sites and enhancement of the process for release of drugs (Jacob et al. 2018). Polymeric vectors are promising sources of nonviral vectors because of their physiochemical characteristics such as DNA-binding ability, chemical modifications, and low immunogenicity. The different generations of cationic polymers include first- and second-generation cationic polymers. First-generation polymers include poly-L-lysine, which binds to DNA and spontaneously condenses it into compact structures. Second-generation polymers include polyethyleneimine (PEI) and polyamide amine dendrimers (PAMAMs) (Jacob et al. 2018). There are many established drug delivery systems available; among them, inorganic nanomaterials have attracted substantial interest as potential delivery systems. Some other drug delivery systems are shown in Fig. 6.3.

Plant nanoparticles possess a good number of advantages over nanoparticles such as liposomes, dendrimers, and QDs. The advantages include flexible methods for preparation, safety to humans, degradability, and the ease of performing genetic and chemical modifications.

There are a variety of types of nanoparticles available, such as polymers, lipids, CNTs, and viruses. Among these various types, viral nanoparticles are the most widely used type (Table 6.3) because of their various advantages, as mentioned above. Viruses are small particles whose structure is made up of nucleic acids (both DNA and RNA), and they encode genetic information and various protein molecules that can assemble to form a shape of hollow packing to protect vital information. The major advantage of these viruses is that they can withstand high temperatures and remain intact at various pH values in the presence of organic solvent–water mixtures. Viral nanoparticles are being widely used and are having a strong impact, since they possess various properties such as uniformity of size and distinct forms, and they can withstand a range of temperatures and pH values. The multiple sites present on viral capsids are another advantage because these capsids can be used for introduction of foreign components (peptides or ligands). The properties of targeting viral particles can be enhanced by creation of polyvalent scaffolds (Alemzadeh et al. 2018). Various production platforms for the production of different virus-like particles (VLPs) are shown in Fig. 6.4.

Protein drugs (PDs) can be inserted into lyophilized plant cells, since they are stable at ambient temperatures for many years through preservation of their folding and their efficiency. When these drugs are taken, they are confined by a cover encapsulated in the sheet. The sheet is protected from intestinal fluids (which are acidic in nature) and subsequently the drug gets released upon contact with microbes present in the gut lumen, which digest the plant cell wall. If an intact plant cell containing a PD reaches the gut, commensal microbes digest the cell wall of the plant and release the PD. Human digestive enzymes are incapable of breaking down all glycosidic bonds in plant cell walls. Receptor-binding proteins fused to PDs cross the intestinal epithelium and are delivered to the immune system. Sole protein receptor–binding sites have been developed recently. Mucopolysaccharides are the substrates from gut bacteria that degrade the mucin glycoprotein, allowing penetration of the mucous layer (Kwon and Daniell 2016).

VLPs, in general, are extremely stable; those types that can withstand large variations in temperature and other conditions will very likely be beneficial both for and during manufacturing and distribution. VLPs are engineered to withstand storage and transport at diverse temperatures and can facilitate logistics in vaccine deployment, particularly in areas of the developing world, where it is difficult to maintain

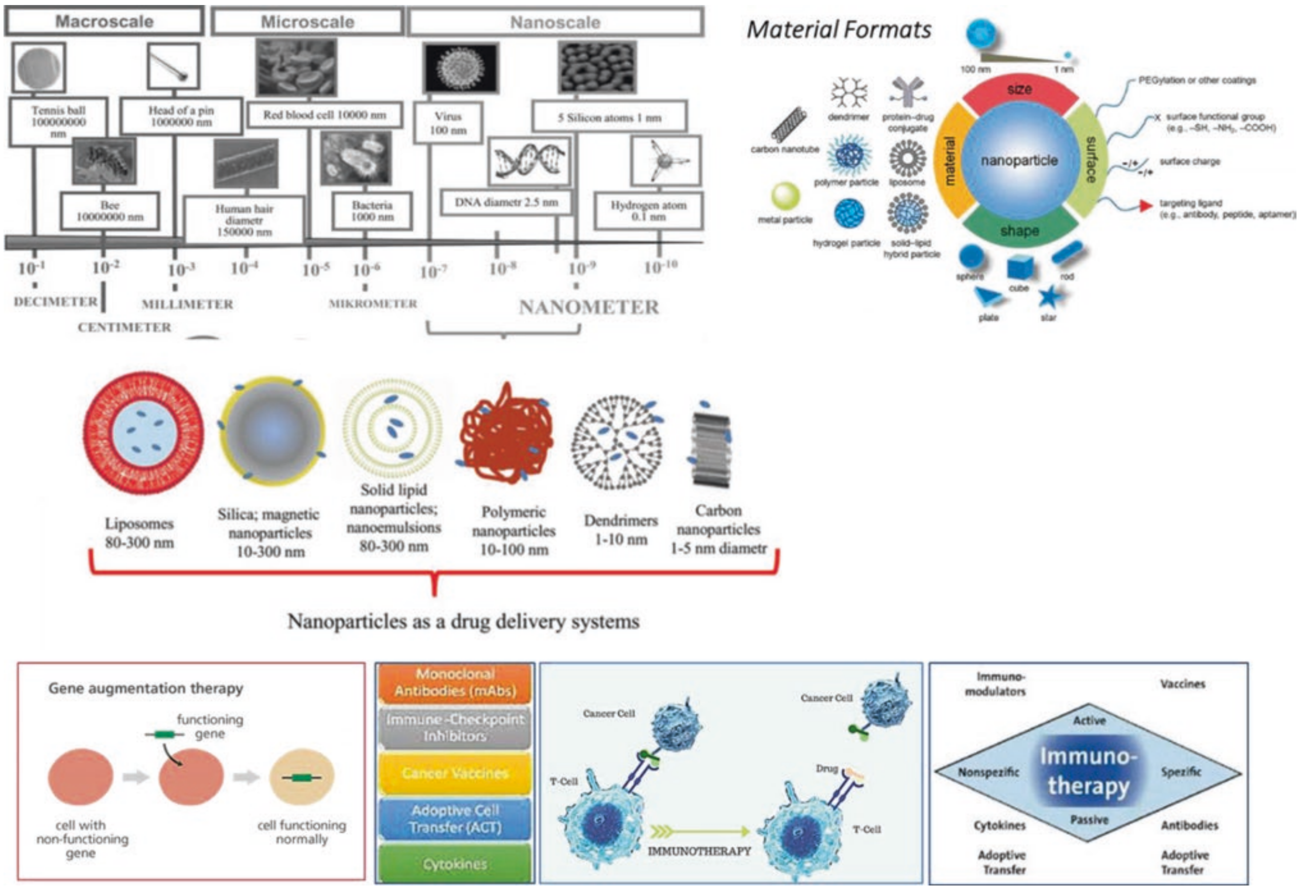

Fig. 6.3 Drug delivery systems on the macro-, micro-, and nanoscales, and material formats

Table 6.3 Viruses and their properties

Viruses and their families	Properties
Brome mosaic virus and Bromoviridae	Genome with nuclease- and protease-resistant virions; these are stable at low detergent and high salt concentrations
Red clover necrotic mosaic virus and Tombusviridae	They can undergo significant structural changes upon removal of the Ca^{2+} and Mg^{2+} ions in the shell and interior of the capsid, resulting in the formation of surface pores; this is helpful in the packaging of molecules inside the capsid
Cowpea mosaic virus and Secoviridae	Extremely robust at a wide range of temperatures (up to 60 °C), at pH values from 3.5 to 9.0, and in the presence of certain organic solvents
Cucumber mosaic virus and Bromoviridae	Single-stranded genome; its virions are susceptible to anionic detergents and high-ionic-strength buffers
Hibiscus chlorotic ringspot virus and Tombusviridae	Virions are stable at acidic pH, but above pH 7 and in the presence of EDTA they become unstable; virions are insensitive to organic solvents and nonionic detergents, and are resistant to high temperatures (80 °C)
Tobacco mosaic virus and Virgaviridae	These are single-stranded, positive-sense RNA molecules; particles are stable at pH values ranging from 2 to 10 and in organic solvents, with a thermal inactivation point of 90 °C
Potato virus X and Alphaflexiviridae	The thermal inactivation point is between 68 °C and 74 °C for 10 min

EDTA ethylenediaminetetraacetic acid

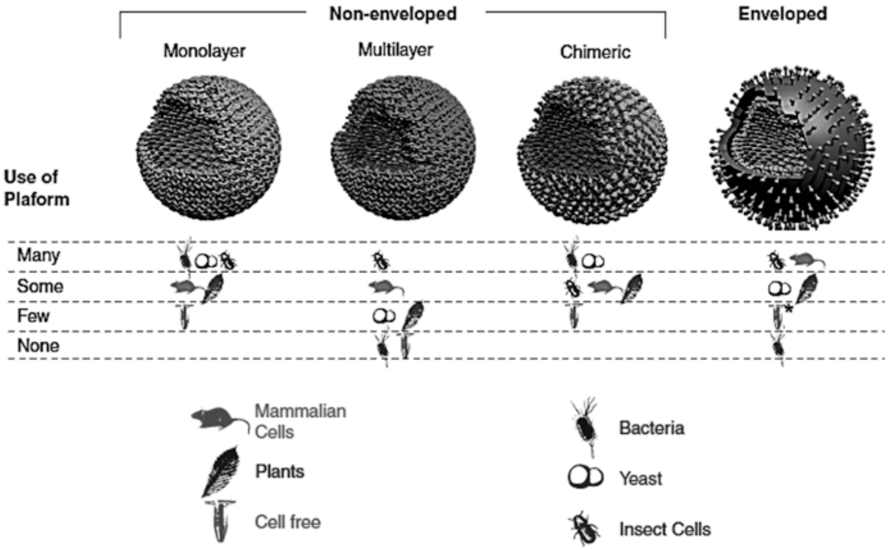

Fig. 6.4 Production platforms used for various virus-like particle (*VLP*) configurations

a cold chain. At the same time, improvement in the stability of VLPs reduces the cost of vaccines by allowing a longer shelf life and also reduces energy costs associated with cold storage. VLPs have also been modified to enhance structural stability. These modifications facilitate the engineering of recombinant VLPs (as described above) but also have been undertaken with other downstream applications in mind. Hepatitis B core antigen VLPs have enhanced stability. Postproduction methods, such as lyophilization or spray drying of VLPs, can also enhance thermostability and allow long-term storage.

6.5 Microbial Nanobionics

In recent years, economically feasible and eco-friendly renewable energy fuel production has been the world's greatest demand to simultaneously replace conventional fuels and reduce environmental concerns. The production of various biofuels by use of microorganisms has been steadily increasing in recent years. To generate renewable energy, fuels are being produced by treatment of biomass and biological waste with versatile microorganisms, which could diminish energy security concerns and environmental concerns to a large extent.

6.5.1 Microbial Cell Factories

Microbial cell factories perform well in various processes, permitting cost-effective biorefinery. Biomass derived from pentose and hexose is converted into target compounds through optimization of metabolic pathways. Direct saccharification of biomass and stress tolerance under harsh conditions during fermentation need to be considered in development of microbial cell factories (Kondo et al. 2013). Microbial secondary metabolites are widely exploited for various biological activities for the well-being of humans. These are used as antibiotics, other medicinal compounds, toxins, pesticides, and plant and animal growth factors (Nielsen and Nielsen 2017). Although a variety of species exist, research on secondary metabolites has been majorly focused on actinomycetes species because the majority of the metabolites are based upon the genus *Streptomyces*. Microbial cell factories are reliable in terms of metabolic functions; engineering strategies are required to develop these cell factories with optimized performance by integrating and modifying metabolic pathways. In industrial production of bioethanol, *Streptomyces cerevisiae* is an ideal host for biorefinery processes because of its volume for recycling of cells in fermentation and its tolerance of various stresses such as low pH and high temperature. This yeast organism is a well-characterized model in the field of metabolic engineering to sequence the complete genome. The metabolic system of this species is very complex, allowing researchers to predict the consequences of metabolic modification (Kondo et al. 2013). Of the well-known microbial antibiotics, 45% come from actinomycetes, 38% come from fungi, and 17% come from unicellular bacteria. Among this range of antibiotics, only a few are in use for human therapy (Nielsen and Nielsen 2017). A number of *Aspergillus* strains, which are closely related to each other in terms of their phylogenetic tree construction, have been utilized for production of organic acids because of their strong capability to secrete large amounts of desired organic acids. Various organic acid products, especially low-molecular-weight carboxylic acids, have an important status in biotechnological production. Quite a few organic acids are currently produced by means of biotechnological processes, such as citric acid and itaconic acid production by *Aspergillus niger* and *Aspergillus terreus* (Yang et al. 2017).

Apart from production of various secondary metabolites, microbial electrosynthesis is a new technique that can replace various synthesizing techniques with modern techniques in which various biocommodities are produced by reduction of substrates with microbial catalysts and an external electron supply. These bioelectrochemical systems (BESs) utilize a consortium of microorganisms as bioelectrocatalysts in electrochemical reactions. They have both biological advantages (such as self-replication) and electrochemical advantages (such as a mass-free supply of redox equivalents). Currently, there are various techniques in which microbial fuel cells (MFCs) are being utilized, such as microbial desalination and microbial electrosynthesis. Among these techniques, microbial electrosynthesis is a promising technology as a microbial cell factory because organic matter can be produced using microbial electrocatalysts (Shin et al. 2017). Apart from the various microbial consortiums being utilized for microbial cell factories, the eukaryotic species known as cyanobacteria are also being utilized for extensive applications in various fields such as biofuels, enzyme production, and protein synthesis. Photosynthetic cell factories have been found to be a promising source for sustainable and economical fuel production and chemical synthesis. When these photosynthetic cell factories are optimized and evaluated in optimal conditions, this can help in obtaining a stable pattern of cell growth and product accumulation (Luan and Lu 2018). Some of the various microbes that are used for biofuel production are listed in Table 6.4 (Enamala et al. 2018).

Table 6.4 Microorganisms that produce biofuels or precursors for biofuel production

Microorganisms	Biofuels	Biofuel yields (g L^{-1})
Zymomonas mobilis	Ethanol	NA
Escherichia coli	Butanol, ethanol	30, 25
Trichoderma reesei	Ethanol	10
Saccharomyces cerevisiae	Fatty acids	0.38
Clostridium thermocellum	Isobutanol	5.4
Clostridium acetobutylicum	Butanol	3
Yarrowia lipolytica	Fatty acids	55
Synechococcus sp.	Limonene	0.04
Synechococcus elongates	1,3-Propanediol	0.28
Cryptococcus vishniaccii	Lipids	7.8
Caldicellulosiruptor bescii	Ethanol	0.70

NA not available

Apart from these normal microbial cell factories, metabolic engineering in the last two decades has emerged as a game-changing key factor with the introduction of the clustered regulatory interspaced short palindromic repeat (CRISPR)–Cas system. It is clear that even with model organisms, metabolic engineering is a challenging task in building or rebuilding metabolic pathways for the production of various biobased products. Establishment of new pathways requires significant modifications in both integration and deletion of genes, balancing key enzymes for the expression of genes and optimization of non-native gene codons. Hence, it is no surprise that the invention of the CRISPR–Cas system has sparked a new era in the field of precision genetic engineering (Jakočiunas et al. 2016). Biopharmaceutical proteins are being widely used in the treatment of cancer, diabetes, chronic viral hepatitis, inflammatory conditions, and autoimmune diseases. Currently, many of these proteins are being produced from expression of proteins by *Escherichia coli*, since it possesses small proteins with non-posttranslational modifications. In recent research, heterologous studies have improved metabolic engineering by performing complicated posttranscriptional modifications including the disulfide formation process. In comparison with the bacterially sourced vaccines used in recent times, vaccines produced from viruses will play an important role in global health by reducing side effects and improving immunogenicity. These VLPs are multi-subunit protein complexes capable of self-assembly, forming structures that imitate the 3D conformation of native viruses. They lack viral genetic material, making them non-infectious and unable to replicate. They are considered safer than traditional vaccines based on attenuated or inactivated viruses (Rodríguez-Limas et al. 2013).

6.5.2 Microbial Fuel Cells

Microbial fuel cells are devices that facilitate the conversion of organic waste material into electrical energy with the help of microorganisms, which act as biocatalysts (Shah et al. 2019). This is an environmentally friendly process, which has been gaining global attention in recent years as an advanced technology for both electricity generation and waste treatment. In a common MFC, the apparatus consists of a dual-chamber system, consisting of an anode chamber and a cathode chamber, separated by a proton exchange membrane (PEM). The mixed consortium of bacteria present in the anodic chamber oxidizes the energy and generates electrons and protons. Electrons are then passed through the cathode chamber through an external circuit and, finally, a current is generated (Zhao et al. 2013). In such an arrangement, oxygen must be continuously supplied in the reaction at the cathode, supplying extra energy (Liu et al. 2015). These MFCs can recover renewable energy from organic sources and convert this energy from chemical energy into electrical energy during wastewater treatment (Shah et al. 2019). Other applications of these MFCs include degradation of bioremediation contaminants (Fang et al. 2013). The ideal performance of an MFC depends upon the electrochemical reactions that occur between the organic substrate (such as glucose), with a low potential, and a final electron acceptor (such as oxygen), with a high potential. The performance of an MFC depends upon various factors (Mishra et al. 2017), such as the type of microorganisms, the fuel biomass type, the pH, the temperature, and the configuration of the rector (Siegert et al. 2019).

Velasquez-Orta et al. (2009) conducted an experiment and concluded that microalgae and macroalgae used for energy generation can be grown on a large variety of substrates (such as carbon dioxide), require little space for cultivation, have high growth rates, and, when used for generation of electricity, produce relatively high power densities. With many improvements likely to be made in this technology—such as the use of various substrates in the MFC for current production and wastewater treatment—there is scope for many newer substrates to be discovered in the coming years, with improved power output in terms of power generation, as well as wastewater treatment, and also monitoring of pollution, which has become one of the major causes of global warming (Behera 2015). There is also a lot of interest in the study of photosynthetic microorganisms such as microalgae, as well as macroalgae, in the field of generation of a microbial current, using the same principle that has been used in the generation of current using bacterial species. This integration could be achieved in three possible ways (Xiao and He 2014):

(i) Phototrophic microorganisms could function as (or provide) a substrate for supplying electrons.
(ii) Photoheterotrophic microorganisms could catalyze the anode reaction.
(iii) Photoautotrophic microorganisms could provide oxygen as an electron acceptor for the cathode reaction.

6.6 Nanobionic Engineering of Plant Organelles

Nanotechnology has been improved to a great extent, where nanoscale materials are tailored for delivery of drugs onto specific cells or tissues. Nanoparticles have the ability to improve the stability of the drug, the pharmacokinetics, and the formulation of therapeutics into nanoparticles, which could reduce toxicity. The development of these nanoparticle drug delivery systems takes a long time, and production of these drugs on a larger scale also takes time, representing major hurdles to success. Plant viruses are an emerging class of biologics used in drug delivery systems (Czapar and Steinmetz 2017). The major advantage of using these plant sources to produce biologics is that the plant cell wall protects expressed PDs from acids and enzymes in the stomach via bioencapsulation. However, gut microbes have evolved to break down every component of plant cell walls; thus, when intact plant cells containing PDs reach the gut, commensal microbes digest the cell walls and release the proteins. When fused to PDs, tags (receptor-binding proteins) efficiently cross the intestinal epithelium (the largest mucosal area in the body, measuring 1.8–2.7 m^2) and are delivered to the circulatory system or the immune system (Kwon and Daniell 2015).

Plant cell walls are composed of various polysaccharides. The cell wall serves as a barrier for preventing entry of foreign particles and nanoparticles into the cell, where they could cause damage to the internal parts of the cell. Layered double hydroxides (LDHs) are a new class of nanoparticles and been reported to effectively deliver biomolecules into plant cells. The major advantages of using LDH nanoparticles are that RNA activity is protected and their penetration through cell walls into intact cells incurs only minimal damage.

In general, LDHs are usually represented as $[M^{2+}{}_{1-x}M^{3+}{}_{x}(OH)_2][A^{n}-]x/n\bullet zH_2O$, where M^{2+} and M^{3+} are divalent and trivalent metal ions, respectively, and A^{n} is an interlayer anion. The positively charged ion sheets are intercalated with charge-balancing anions to constitute the LDH complex, which is tunable, and the ion sheets can be delaminated into ultrathin nanostructures. LDHs possess very favorable properties such as good compatibility, easily biodegradable, low cytotoxicity, and controlled release of drugs (Bao et al. 2017).

ENMs have amazing physicochemical features (Table 6.5) suitable for various applications in medicine, biotechnology, energy, pharmaceuticals, cosmetics, and electronics because of their ultrafine size and high surface reactivity. Engineered nanoparticles (ENPs) have made a strong impact over the past few decades, and they tend to possess properties such as a large capacity to absorb target molecules, ability to release molecules more effectively within target cells or to specific organelles, and ability to penetrate cell walls without causing damage.

ENMs play a role by entering plant cells and interacting with metabolic pathways and intracellular structures, which may cause toxicity or promote plant growth and development by varied mechanisms.

Table 6.5 Effects of engineered nanomaterials on the biosynthesis of secondary metabolites

Plant species	Nanomaterials	Sizes (nm)	Effects on secondary metabolites
Hyoscyamus niger	TiO_2	10–15	Enhanced content of tropane alkaloids and total alkaloid yield
Salvia officinalis	TiO_2	10–15	Increased content of monoterpenes, total phenolics, flavonoids, and essential oils
Pelargonium graveolens	Ag	5–35	Increased content of major essential oil constituents (citronellol, geraniol, and citronellyl formate)
Artemisia annua	Ag	101.8 ± 8.9	Increased content of artemisinin (a sesquiterpene lactone)
Momordica charantia	$C_{60}(OH)_{20}$	1.5–5.0	Enhanced content of anticancer phytomedicines (cucurbitacin B and lycopene) and antidiabetic phytomedicines (charantin and insulin)
Calendula officinalis	Ag	25	Decreased content of total anthocyanin and saponin
Thymus kotschyanus	Ag	32	Increased essential oil composition and α-terpinyl acetate content, and reduced thymol content
Glycyrrhiza glabra	ZnO, CuO	50	Increased content of glycyrrhizin, total phenolic compounds, flavonoids, and anthocyanins
Raphanus sativus	CeO_2	8 ± 1	No effects on phenolic, flavonoid, and nutrient accumulation in tubers and leaves of adult plants
Cucumis sativus	Cu	40	Cu nanoparticles at different concentrations interfere with uptake of a number of micro- and macronutrients (such as Na, P, S, Mo, Zn, and Fe) and trigger significant metabolic changes in plant leaves and root exudates

6.7 Conclusions and Future Work

The use of nanoparticles to create nanobionic plants is becoming a reality. Plant enabled sensors will be helpful in providing real-time information. In the future, humans will be able to communicate with plants in terms of their growth factors, temperature, humidity factors, and pollutants by integration with smart technology, and the reasons for effects on plants will also be known. Research is still being done to increase the number of sensors related to plants to monitor plant growth, plant signaling pathways, drought, pest infections, etc. This technology will be revolutionary in the agricultural field. Apart from this, the genetic response of plants to the presence of nanoparticles is also a major topic of discussion. Nanoparticles travel in different directions and reach vascular tissues. Detailed research on the delivery of nanoparticles to particular parts of plants must be performed. Nanotechnology applications in the field of agriculture will bring major benefits to farmers and to the food industry, with novel products being developed. Nanosensors and nanobiosensors are currently used for detecting pathogens and soil quality, and nanoenabled biofertilizers have also been studied in recent times. The use of nanomaterials in crop disease suppression is yet to be explored. Looking at the above discussion, it is clear that plant nanobionics will definitely rule the future of the agricultural industry, and farmers will undoubtedly benefit from this in numerous ways.

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Chapter 7

Nanomaterials, Polymers, and Smart Packaging for Food Materials

M. Q. Marin-Bustamante, J. J. Chanona-Pérez, N. Güemes-Vera, J. A. Mendoza-Pérez, C. A. Reséndiz-Mora, R. G. Cásarez-Santiago, and L. E. Rojas-Candelas

Contents

7.1 Introduction to Nanotechnology

The US National Nanotechnology Initiative (2018) provides a clear definition of nanotechnology as a scientific field focusing on the ability to control, produce, process, and restructure matter at sizes of less than 100 nm. Nanotechnology stands out as an emerging science area that allows us to bring together disciplines such as chemistry, physics, biology, and engineering to develop the characterization, fabrication, and manipulation of new nanostructures or nanomaterials that can be applied

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M. Q. Marin-Bustamante · J. J. Chanona-Pérez (✉) · J. A. Mendoza-Pérez
C. A. Reséndiz-Mora · R. G. Cásarez-Santiago · L. E. Rojas-Candelas
Instituto Politécnico Nacional, Escuela Nacional de Ciencias Biológicas, Unidad Profesional Adolfo López Mateos, Av. Wilfrido Massieu s/n Instituto Politécnico Nacional, Mexico City, Mexico

N. Güemes-Vera
Instituto de Ciencias Agropecuarias, Universidad Autónoma de Hidalgo (CICyTA), Av. Universidad s/n Rancho Universitario, Tulancingo, Mexico

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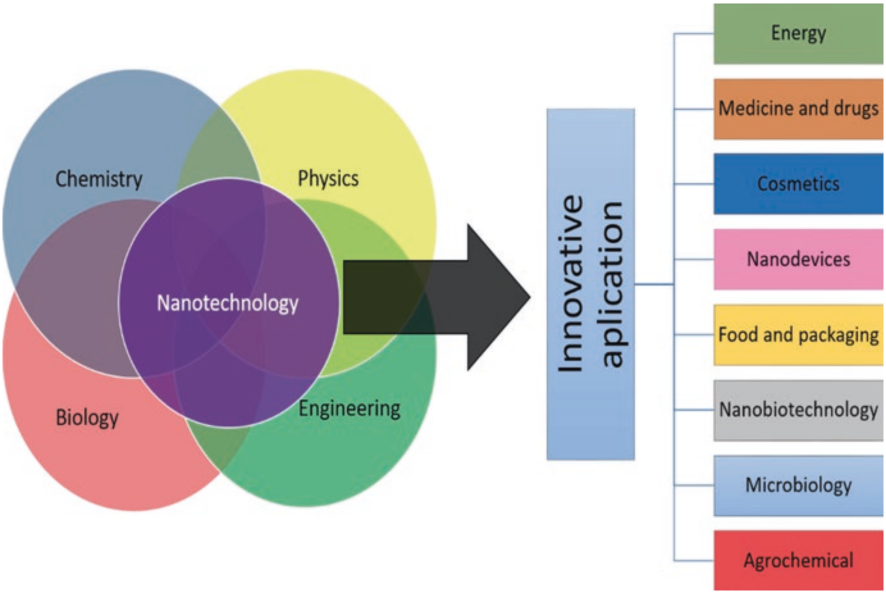

Fig. 7.1 Conceptual framework of nanotechnology, its applications, and its impacts on different industries

in the food industry (Fig. 7.1). The success of an innovative product is associated with the technology that is applied to make it (O'Callaghan and Kerry 2016).

Nanotechnology has great potential to fabricate innovative products and improve processes by virtue of the unique properties of nanomaterials, such as small size with a large surface area. This is desirable for purposes in the food industry and issues related to improved water absorption, release and bioavailability of flavors. The particle size usually relates to the functionality of food materials. The main approaches that are used to perform nanotechnology research are top-down and bottom-up approaches.

The top-down approach involves physical machining to generate nanoparticles or nanofibers from bulk materials, using milling, attrition, etching, ultrasound, emulsification, and photolithography to reduce the size to the nanometric scale. The main processes used to obtain nanoparticles by the top-down approach are dry grinding and milling. This last one is a traditional method in which mechanical energy is applied to physically break down materials. However, this process is limited by the resolution of the tools used; therefore, the rate of production is slow.

The bottom-up approach is based on the building of nanomaterials from molecules or individual atoms; in other words, it controls the ability of self-assembly, offering huge economic potential with a higher level of control to avoid defects. Consequently, more homogeneous materials are obtained (Dahman 2017). The usual methods to produce nanomaterials by the bottom-up approach are linking of inorganic materials via chemical reactions, nucleation, and growth processes to promote the formation of clusters. The different top-down and bottom-up approaches

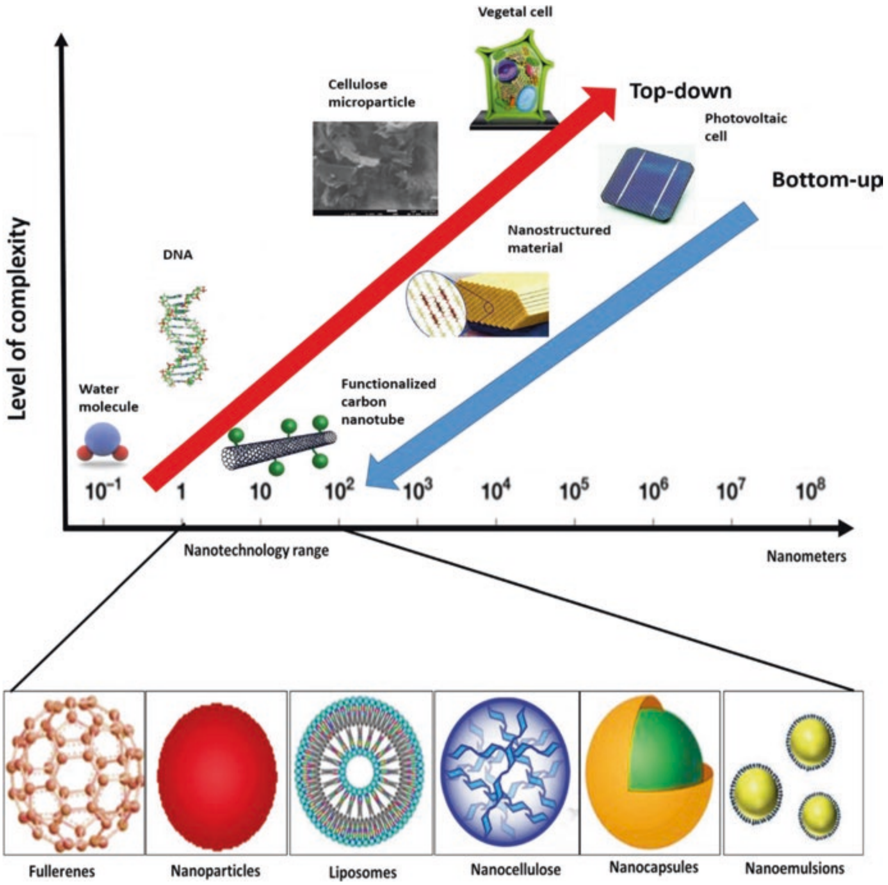

Fig. 7.2 Scale of systems and methods used to produce nanomaterials

used to create nanomaterials (Fig. 7.2) have changed the ways in which products are fabricated, and they offers greater levels of control to obtain nanostructures.

7.2 Nanostructured Materials Used in the Food Industry

Recent applications of nanotechnology in food science have had a major impact on the food industry, with molecular synthesis of new food products or ingredients that increase the safety and shelf life of food. The development of nanostructured materials includes physical, chemical, and biological properties that are considerably different from those of their bulk equivalents in food systems. The potential applications of nanotechnology in the food sector include food safety and packaging that leads to improved quality and preservation of foodstuffs. Also, some foods, such as

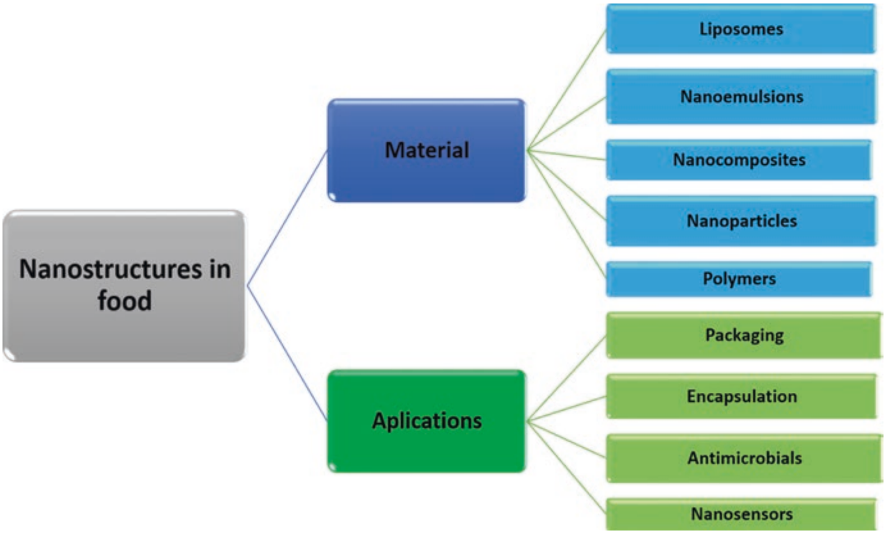

Fig. 7.3 Overview of nanostructures used in the food industry and their applications

milk and milk derivatives, contain nanoscale ingredients such as casein and other milk proteins (Pathakoti et al. 2017).

The main applications of nanostructured materials in food are liposomes, nanoemulsions, nanocomposites, nanoparticles, biopolymeric nanostructured films, proteins, and cellulose-based nanoparticles (Fig. 7.3). These materials facilitate controlled release, enhance solubility, improve bioavailability, and protect bioactive components during manufacture and storage.

Currently, nanotechnology in food production is focused on the development of nanostructured food ingredients and additives, delivery systems for bioactive compounds, and innovative food packaging. The food industry is always searching for new and less expensive methods to produce and preserve its products. Nanotechnology offers many options in food manufacture such as nanoencapsulation, nanofiltration, and engineering of nanoparticles. Nanotechnology is useful to maintain the microbial safety, nutritional profile, and quality of food in accordance with consumer demands. Some examples of functional ingredients incorporated into nanostructured systems in food fortification are vitamins, antimicrobials, antioxidants, probiotics, prebiotics, peptides and proteins, carotenoids, omega fatty acids, flavorings, colorants, and preservatives.

New food products that contain nanostructures have been introduced or are currently being developed for different purposes to optimize and modify the sensory characteristics of food products and create new consumer sensations, such as texture, consistency, development of new tastes or taste masking, flavor enhancement, and color alteration. Also, nanotechnology is widely used in the food sector to enhance the bioavailability of poorly soluble functional food ingredients and thus improve their nutritional value; increase the shelf life of food by protecting it from oxygen and water; protect nutraceuticals against degradation during manufacturing, distribution, and storage; improve food stability; produce low-fat, low-carbohydrate, or low-calorie products; and control functional food ingredient delivery. In the case of encapsulation, this technology allows designed controlled release of active ingredients in drugs wherein the gastrointestinal retention time can be prolonged and the site of release of the active ingredients can be adjusted according to the needs of the dosage (Dasgupta et al. 2015).

7.2.1 Liposomes

Liposomes are spherical, bilayered vesicles of phospholipids and play a key role in the design of biosensing assays. Numerous approaches have been developed to obtain liposomes; the conventional methods include sonication, membrane extrusion, reverse-phase evaporation, and microfluidic technology. Liposomes are usually 20 nm to 10 µm in diameter, with the phospholipid bilayer being 4–5 nm thick (Mazur et al. 2017). Because of the similarity of their components and structures to those of cell membranes, they have been frequently used in the food industry to encapsulate functional ingredients and have also been studied for their ability to be carriers (Fig. 7.4). Moreover, liposomes have been applied as antimicrobials to protect food against spoilage and growth of pathogenic microorganisms, and to enhance the safety and shelf life of foods. In particular, their amphiphilic nature allows incorporation of water-insoluble molecules, which also help in control and specific delivery of vitamins, nutrients, enzymes, nutraceuticals, antimicrobials, and additives. Liposomes have a larger surface area for contact with biological tissues and thereby provide greater bioavailability of encapsulated compounds.

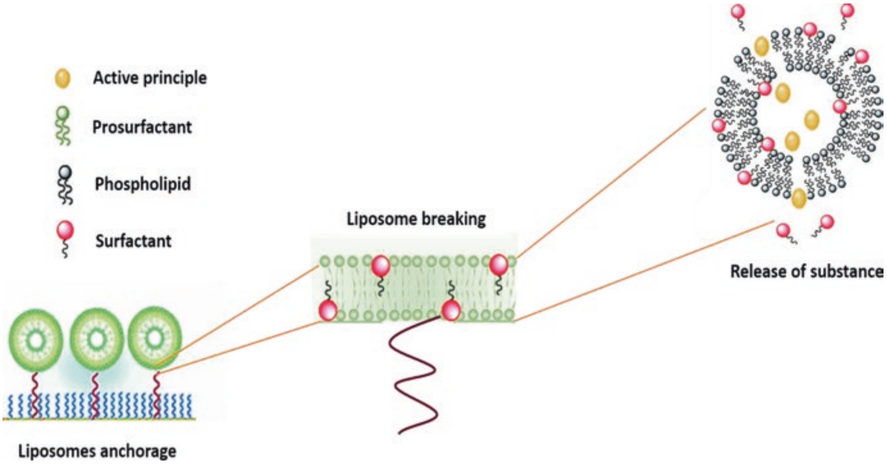

Fig. 7.4 Simplified representation of the mechanism of release of active substances from liposomes

7.2.2 Nanoemulsions

Nanoemulsions are systems of colloidal dispersions with two immiscible liquids consisting of a fine dispersion in nanodroplets. Their stability depends on the method of preparation. Usually, emulsifiers or coemulsifiers are used to create the interfacial layer.

Two main types of methods are to prepare nanoemulsions, according to the energy stored in the system to promote the formation of droplets: the high-energy method (high-shear stirring, high-pressure homogenizers, and ultrasonic generators) and the low-energy method (emulsification and low-energy emulsification). Nanoemulsions are classified into three types according to their components: (i) water in oil (W/O), where water phases are dispersed in continuous oil phases; (ii) oil in water (O/W), where oil phases are dispersed in continuous aqueous phases; and (iii) multiple emulsions, where microdomains of oil and water phases are inter-dispersed within the system. Common ingredients used in food nanoemulsions are listed in Table 7.1.

Nanoemulsions are used in the food industry because functional food components can be integrated into their droplets to enhance products such as beverages; sweeteners; salad dressing; flavored oils; and milk fortified with vitamins, minerals, and antioxidants. Another important property of nanoemulsions, which is controlled through their formulation, is digestibility; this property is valuable for several food applications. Nowadays, nanoemulsions are widely used in the design of functional food systems, by means of encapsulation technology, as ripening retardants, for protection of sensible substances, and for delivery of nutraceutical compounds.

Table 7.1 Common ingredients used in food nanoemulsions

Components	Examples	References
Functional ingredients	Carotenoids; omega-3, -6, and -9 fatty acids; vitamin E; curcumin; phytosterols; coenzyme Q	Qian et al. (2012), Laouini et al. (2012), Saberi et al. (2013)
Emulsifiers	Sodium dodecyl sulfate; phospholipids; Tween® 20–80; Span® 20–80; whey protein; soy protein; casein	Lam and Nickerson (2013), Adjonu et al. (2014), Guttoff et al. (2015)
Oils	Sunflower, fish, soybean, mineral, olive, basil, corn, cinnamon, castor, coconut, and essential oils	Donsì et al. (2011), Ghosh et al. (2013), Lane et al. (2014)
Ripening retardants	Long-chain triglyceride; mineral oil; ester gum	Joe et al. (2012), Ghosh et al. 2014

7.2.3 Polymeric Nanocomposites

A nanocomposite has a multiphase in which at least one of the phases is of a size less than 100 nm, while the other phases are bulk sized and reinforced with nanofillers. These nanofillers can be obtained by bottom-up or top-down approaches and include nanoparticles, nanosheets, nanorods, nanotubes, nanowires, and nanofibers.

Nanocomposite packaging is an alternative to conventional materials (glass, paper, and metals) used for packaging of food products because it has enhanced properties such as mechanical reinforcement, antimicrobial activity, low gas and liquid permeability, low cost, and improved functionality. The extraordinary versatility of the chemical functionality of nanocomposites makes them suitable for the development of barrier properties (Pandey et al. 2013).

The use of polymers to control packaging permeability improves food quality by extending the shelf life and preserving flavors and aromas. Various polymers (such as polyamide, polystyrene, nylon, and polyolefins), chitosan, cellulose, and carrageenan have been used in food packaging. However, because of environmental concerns, there is a growing demand for biodegradable packaging based on biopolymers. Nowadays, various methods are applied to obtain nanocomposites based on biopolymers (Fig. 7.5) for food-packaging applications. Manufacturing industries use nanocomposites for development of improved layers in cans and glass bottles, and other packaging is applied in the food industry to lower costs. Depending on their chemical nature, the building blocks can be categorized as organic (cellulose-based or protein-based nanoreinforcements) or inorganic nanoparticles (gold, silver, and so on).

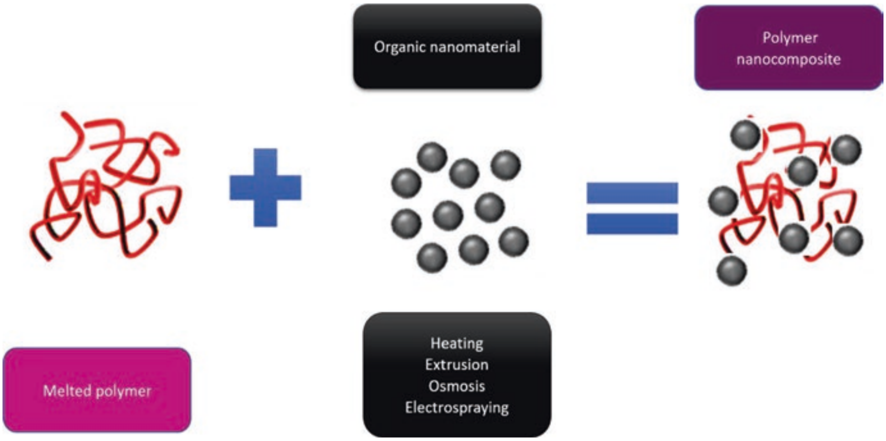

Fig. 7.5 Simplified representation of a method used for preparation of nanocomposites

7.2.4 Nanoparticles

The ASTM E2456-06[2] standard defines nanoparticles as "a sub-classification of ultrafine particles with lengths in two or three dimensions greater than 0.001 micrometer (1 nanometer) and smaller than about 0.1 micrometer (100 nanometers) and which may or may not exhibit a size-related intensive property" (ASTM 2008).

The most notable change in material properties at the nanometric scale is due to the increase in the surface area caused by a reduction in the particle size of the material. Figure 7.6 explains how this phenomenon works. Starting with a defined figure—a cube of 16 × 16 × 16 cm—the total volume is 4096 cm^3 and the contact area on the surface is 1536 cm^2, representing around 37% of the total volume. If the cube is divided into eight equal parts, their combined volume remains the same; however, the total surface area increases to 3072 cm^2, representing 75% of the total volume. If the eight equal parts of the original cube are then each subdivided into eight equal parts, their combined surface areas reach 6144 cm^2, increasing the contact area to 150%, four times that of the original cube.

This size reduction increases the surface area and changes other physical properties such as density, viscosity, hardness, and conductivity. The reason why the mechanical and barrier properties are improved is because the interfacial area of the reinforcing particles is very large; meanwhile the particle sizes are in the order of nanometers, and the nanoparticles can have a large interaction with the polymer and reinforce the material.

Since nanotechnology was introduced in food science, several studies have been focused on application of nanoparticles in food packaging as reinforcements and as carriers of antimicrobial compounds. So far, some methods have been applied, but

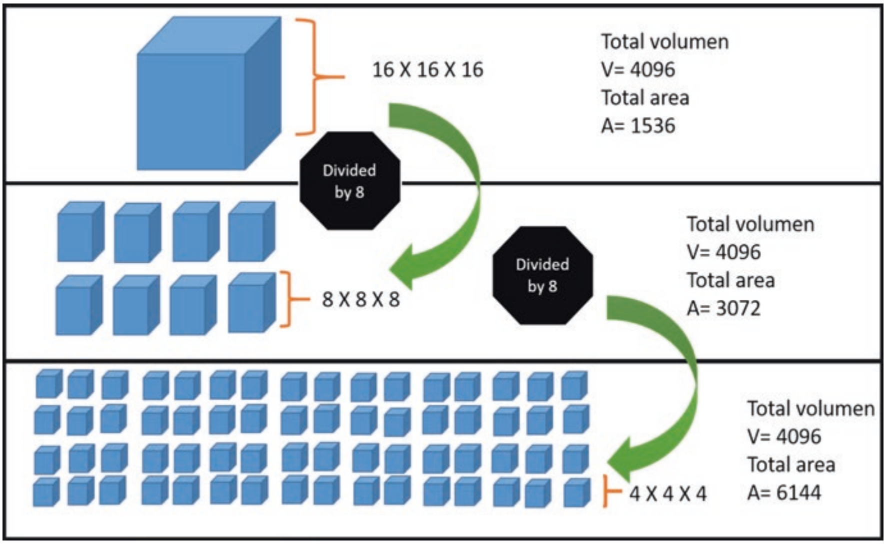

Fig. 7.6 Changes in the surface area of materials caused by size reduction

there is a scarcity of studies identifying, characterizing, and monitoring the potential long-term toxic effects of nanoparticles. Also, study of nanodelivery is important to understand its benefits and its potential toxicity in food materials.

Nanoparticles applied in packaging have the potential to provide some solutions in the food supply chain, such as increased food shelf life, improvements in food safety and security, and minimization of food spoilage caused by bacterial attack. One of the important advantages of nanoparticles in food processing is upgrading of food stability, color, and flow properties. Several approaches related to nanotechnology have been used to improve the antimicrobial efficacy of preservatives, physical stability, shelf life, biocompatibility, and biodegradability; and to ensure the availability of delivery systems at low cost (Hajji et al. 2017; Makwana et al. 2015; Tang et al. 2012; Laxmeshwar et al. 2012; Tripathi et al. 2011; Prasad et al. 2017).

Biobased reinforcement materials have been the subject of research in recent years, mainly based on ecological and climatic factors along with their superior strength, low density, nonabrasiveness, low cost, and biodegradable properties, which make them adequate for use and exploitation. The use and production of biological nanoparticles for use as reinforcements and as nanocomposites in materials have gained increasing attention because of their high strength and stiffness combined with low weight, allowing increased biodegradability and renewability.

An alternative to obtain biological nanoparticles is recovery of cellulose from agrowaste. Cellulose is the most abundant polymer in the world, and its annual production is estimated to be more than 75 billion tons (Ferrer et al. 2017). Cellulose can be obtained from various sources through mechanical and chemical processes. Common sources are wood, sugar beet, potato tubers, cotton, hemp, flax, wheat straw, mulberry bark, ramie, Avicel®, tunicin, and cellulose from algae and bacteria. Nanocellulose has many uses and many forms; the most common are nanoparticles, microfibrils, nanocrystals, and whiskers (Talegaonkar et al. 2017).

Nanocellulose is an appropriate material to be used as a reinforcement material in food packaging because of its large surface area, low density (around 1.6 g/cm^3), very low coefficient of thermal expansion, and reactive surface, due to –OH groups that facilitate functionalization with chemical species to achieve different surface properties. Cellulose is also a renewable and low-cost material; moreover, it is biodegradable, environmentally friendly, and easy to recycle (Azeredo et al. 2011).

Production of cellulose nanoparticles can be achieved by mechanical treatments (Marin-Bustamante et al. 2017; Neri-Torres et al. 2016; Hettrich et al. 2014), chemical processes (Ponce-Reyes et al. 2014; Fernandez et al. 2017), or enzymatic techniques (Eichhorn 2011; Jonoobi et al. 2009). Nanocellulose has amorphous regions and crystalline regions. Nanocellulose can be obtained in the forms of whiskers, nanorods, or crystals. Whiskers can be isolated from microfibrils by chemical methods, the most common of which is acid hydrolysis. Microfibrils are actually bundles of molecules, elongated and stabilized by hydrogen bonding. The diameters of the microfibrils are on the nanoscale (around 2–20 nm) and the lengths are in the range of micrometers (Robles et al. 2018).

7.2.5 Films

Research on films reinforced with nanocellulose is currently increasing and provides an opportunity to enhance food packaging. The main attraction of nanocellulose is its high barrier properties provided by its nanostructured network and its low permeability to gases (for instance, water vapor and oxygen). This feature allows extension of the shelf life of food when nanostructured films are used as food packaging. Another important issue is understanding the role of nanocellulose in the polymeric structure of packaging by describing molecular diffusion through films that are reinforced and non-nanostructured to highlight the differences between them.

Molecular diffusion into the films is a process with three different stages. At the first stage, the sample surface adsorbs the diffusing molecule (usually oxygen or water vapor), then the diffusing molecule goes through the film (stage two). At the third stage, the diffusing molecule is desorbed on the other side of the film surface (Chaoudalakis and Gotsis 2009). A diagrammatic representation of reduction of the diffusion pathway within films reinforced with nanocellulose in comparison with a nonreinforced film is shown in Fig. 7.7.

The permeation rate (*P*) is used to evaluate the ability of a gas or liquid molecule to pass through a film or membrane, and is given by the equation:

$$P = \frac{c \quad t}{A \quad T \quad \varnothing p}$$

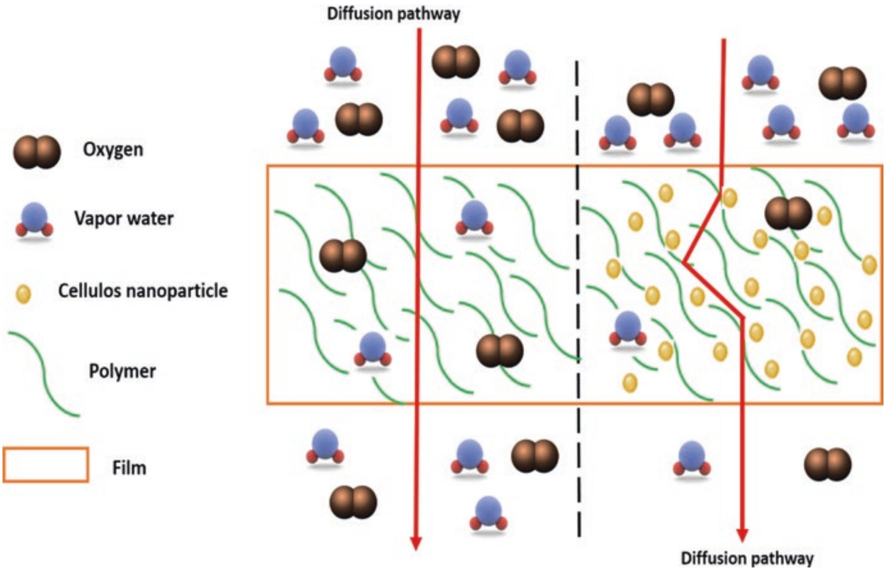

Fig. 7.7 Reduction of the diffusion pathway within films reinforced with nanocellulose in comparison with a nonreinforced film

Table 7.2 Classification of different film-forming biodegradable biopolymers

Types	Sources	Biopolymers
Natural (agricultural waste)	Starches; mucilage; pectin; chitosan; agar; carrageenan; gums; lignocellulosic materials from fruits, woods, grains, agave, cotton, and crustacean exoskeletons	Polysaccharides
	Casein; whey; collagen; gluten; zein; soy	Proteins
	Beeswax; free fatty acids	Lipids
Microbial	Fermentation of algae, microorganisms, fungi, and yeasts	Pullulan, polyhydroxyalkanoates
Synthetic (chemical)	Monomers obtained from natural raw materials	Polylactic acid

where c represents the initial concentration of the gas under a stated condition, t is the film thickness, A is the film area, T is the time of diffusion, and $\varnothing p$ is the pressure difference. A reinforced film can delay the diffusion process; this can be because the formed network structure is denser than that of a single-polymer film (Fig. 7.7).

Polysaccharides, proteins, lipids, and polyesters—and blends of them (Peña-Reyes et al. 2017; Farhad et al. 2017; Wang and Rhim 2015; Cha and Chinnan 2004)—are the biopolymers most commonly used for construction of films (Table 7.2). Packaging materials must be designed with suitable barrier properties against oxygen at low and intermediate relative humidity, good optical properties, acceptable mechanical strength, poor moisture, and a good barrier against water vapor. These properties and other advantages of films based on biopolymers—such as renewability, nonfood agricultural-based sources, biodegradability, biocompatibility, low cost, and low energy consumption—have motivated their use and application in several areas to improve economic sustainability and reduce the use of fossil energy sources. In addition, the US Food and Drug Administration (FDA 2015) has classified these materials as "generally regarded as safe"; thus, there is great motivation to use them for food contact packaging applications.

7.3 Smart Packaging

The fundamental purposes of food packaging are to prevent physical, chemical, or microbial degradation of food and to avoid the loss of its organoleptic properties—such as its aroma, flavor, color, texture, and appearance—while at the same time maintaining the quality of the product during its extended shelf life. Petroleum-based polymers have the ability to accomplish all requirements of the food industry. However, they are not biodegradable, are nonrenewable, and are noncompostable; therefore, they present huge environmental problems such as accumulation of waste and generation of contamination—issues that are of worldwide concern. According to reports, 275 million tonnes of plastic waste was generated in 2010 (Jambeck et al. 2015).

Table 7.3 Classification of packaging types according to their interaction with food products

Types	Characteristics and objectives	Examples
Passive	Covering material: protection, preservation, and brand labeling	Traditional packaging such as polypropylene, polyethylene, polystyrene, and derivatives such as expanded polystyrene
Active	Maintenance of the environment; increased shelf life; oxygen scavenging; antimicrobial effects; ethylene scavenging; heating or cooling; odor and flavor absorption or release; moisture absorption	PETE polysaccharide particles that encapsulate antimicrobial compounds
Intelligent design	Innovations in the design of packaging useful to the consumer structure, making it convenient for the user to consume the product without the need for any other accessory	Ergonomic, multifunctional, traditional packaging such as polypropylene or polyethylene
Smart	Time–temperature history; microbial growth indicators; (photochromic) light protection; physical shock indicators; leakage and microbial spoilage indicators; response to stimuli generated by the environment, transportation, and shelf life	Use of chemicals; electrical, electronic, or mechanical technologies; any combinations of these Nanosensors; nanocomposites; films based on biopolymers

PETE polyethylene terephthalate

Concern regarding environmental issues increases each day because of the pollution that is generated and the limited number of disposal methods that are used. Thus, biodegradable polymers are sought as an alternative to replace petroleum-based polymers. As previously mentioned, biopolymers can be classified into three groups, according to their sources of production (natural, microbial, or synthetic). However, the main problem is that polymers cannot be produced at the rate demanded by consumers. Therefore, it is important to offer types of packaging with better qualities than the existing options and to promote the use of them. Current packaging technologies are expected to generate multifunctional products, such as smart, active, and intelligent packaging.

To explain the terminologies used for packaging, these can be classified into four types (Table 7.3): passive, active, intelligent (design), and smart packaging (Nandanwade and Nathe 2013). Nanotechnology offers food safety in terms of packaging to ensure a longer shelf life by avoiding spoilage or loss of food nutrients or organoleptic properties. Moreover, nanotechnology has become a more reliable technique to aid food storage—for example, by use of nanosensors incorporated into packaging to sense changes in certain properties of food products and report them to the customer.

7.3.1 Applications and Uses of Smart Packaging

The existing technologies of packaging cover only the basic needs of food conservation. Improvements in this area are focused on avoiding chemical changes, enzymatic changes, microbial changes, and external pollution as much as possible.

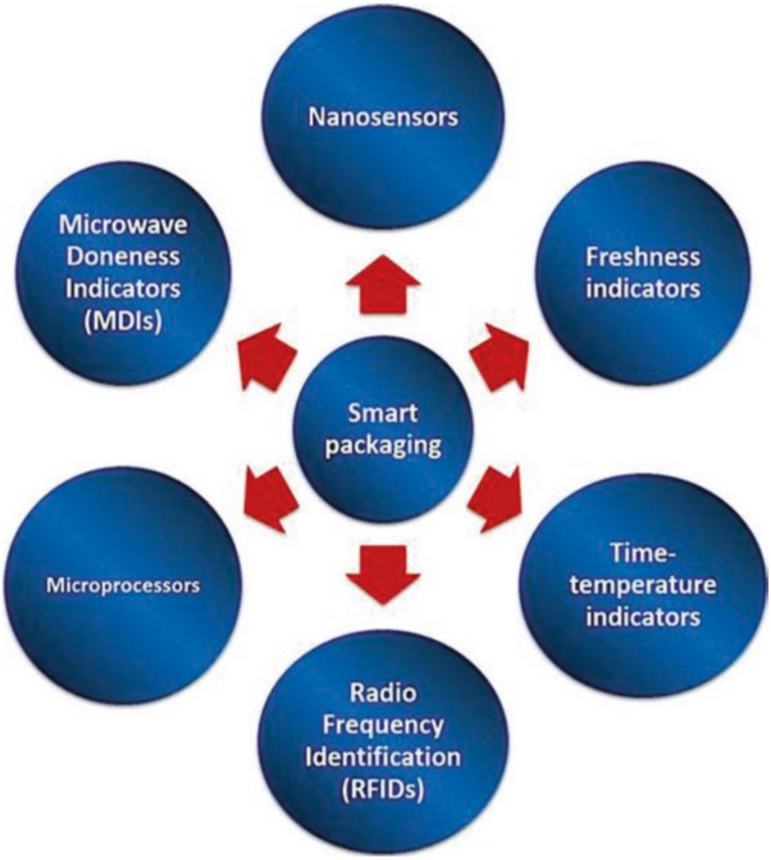

Fig. 7.8 Different types of intelligent packaging enhanced with nanotechnology for use in the food industry

Packaging systems provide information about product quality, safety, and preservation. However, for packaging to be classified in the smart category, the systems must be activated easily; in other words, they must be extremely sensitive to changes in temperature, color, acidity, microorganism metabolites, pollutants, and photoprotection. Nanotechnology offers all of these advantages through the implementation of devices such as nanosensors (Fig. 7.8), including freshness indicators, time–temperature indicators, radiofrequency identification (RFID), microprocessors, and microwave doneness indicators (MDIs).

On packaging and labels, indicators have been applied to provide visual and qualitative information on food products. The information is commonly generated through a color change such as diffusion of a dye along a path in the packaging or an increase in color on the label. The information provided by smart packaging is an extension of food safety; for example, nanosensors are devices that detect, record, and transmit information into some sort of signal that is quantifiable. In general, there are two basic functional units in a sensor: a receptor part and a transducer part.

Table 7.4 Packaging systems for foods, applications, and action–response

Systems	Applications	Prevention	Response	References
Freshness indicators	Fruit ripening; vegetable stability; minimally processed foods	Oxidation; accumulation of metabolites (such as glucose, organic acids, carbon dioxide, biogenic amines, and sulfuric compounds); reduction of the respiration rate	Detection of spoilage metabolites through visible color change; detection of gases such as sulfur, nitrogen, and carbon dioxide	Kuswandi et al. (2013), Rukchon et al. (2014), Biji et al. (2015)
Temperature indicators	Perishable products such as meat, vegetables, ice cream, milk, and cheese (chilled/frozen products)	Microbial growth; physical and chemical deterioration; bad storage conditions; cold chain breaks	History of a perishable food from the point of production to the end consumer; dye diffusion; enzymatic hydrolysis of a lipid substrate; pH change	Singh (2000), Kerry et al. (2006), Biji et al. (2015)
Quality indicators	Products with modified atmospheres; photosensitive; vacuum sealed	Oxidative processes; deteriorations in safety, flavor, odor, texture, and color; rancidity; growth of aerobic microorganisms	Gas, water vapor, oxygen (presence or absence) ethanol, hydrogen sulfide, and carbon dioxide indicators; these systems are based on an organometallic response	Yam et al. (2005), Vu and Won (2013)
RFID tags	Traceability control	Identification; automation; asset tracking; security; supply chain management; less waste production	Electromagnetic wave transmission; packaging integrity; food quality; conditions of storage and transport; the information is stored on a chip	McFarlane and Sheffi (2003), Hong et al. (2011)
Nanosensors	Physical; chemical; biosensing; gas; electrochemical	Monitoring of food quality and packaging integrity; provision of information about chemical composition and the environment, which can be a liquid or gaseous phase	Detection of a specific analyte; transformation of chemical information into a detectable analytical signal; excellent detection sensitivity; enzymatic activity	Yebo et al. (2012), Eulises (2013), Vanderroost et al. (2014), Guadarrama-Fernández et al. (2014), Kuswandi et al. (2014)

RFID radiofrequency identification

Other devices in use are indicators of freshness, temperature, quality/integrity, and RFID; these provide direct information about the food from the time of its processing until the consumer obtains it. These nanodevices can provide qualitative and quantitative information about the product that will be consumed (Table 7.4).

7.3.2 *Biodegradability*

Cellulose applied in packaging is an alternative to petroleum-based polymers because it is biodegradable. It has been used as a reinforcement agent (in the forms of nanoparticles, whiskers, nanocrystals, and so on) for packaging materials, especially in the food industry, to increase the shelf life of products. Nanoparticles have also been used as biodegradable reinforcements for other biopolymers. According to Kummerer et al. (2011), the nanometric dimensions do not reduce the biodegradability; they found that nanoparticles such as cellulose and starch had a faster rate of degradation than their counterparts of macrometric sizes. Although a large amount of packaging ends up in landfills, the fact that they are based on nanocellulose will allow their easy reintegration into the environment without the polluting effects of petroleum-based plastics. Therefore, generation of social awareness among consumers to choose smart packaging based on cellulose should be a priority for the food industry. This will result in lesser amounts of polluting packaging in the environment and lower costs due to the renewability of such packaging.

7.4 Future Perspectives

Nanodevices are now a reality and are applied in the food industry, independent of regulations, which have not been fully established, as any system at the early ages still presents some setbacks. However, research is expected to advance improvements in sensitivity, release of substances, and manipulation of carriers, as well as biocompatibility, allowing improvements in quality in terms of the taste, smell, texture, and freshness of food products.

Smart packaging applications should be fully investigated—with help from the fields of immunology, microbiology, electrochemistry, and engineering—to make specific films of biopolymers reinforced with nanoparticles to aid easy detection of damage to food or to its packaging system. The new nanodevices that are used should all focus on achieving an environmentally friendly status as well as minimizing toxic effects on consumers and the food itself. The effects of nanotechnology introduction in the food industry have resulted in a multitude of changes in aspects such as packaging, preservation, and processing. These changes have significantly increased the shelf life of foods, improved early detection of food product spoilage, and enabled efficient management that allows extension of shelf life and food freshness, and even can be used to help enhance the distribution of chain supplies of foods.

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Chapter 8
Polymeric Nanoparticles in Foods

Ricardo M. González-Reza, María L. Zambrano-Zaragoza, and Humberto Hernández-Sánchez

Contents

R. M. González-Reza · H. Hernández-Sánchez (✉)
Escuela Nacional de Ciencias Biológicas, Instituto Politécnico Nacional, Departamento de Ingeniería Bioquímica, Mexico City, Mexico

M. L. Zambrano-Zaragoza
Universidad Nacional Autónoma de México, Facultad de Estudios Superiores Cuautitlán, Laboratorio de Procesos de Transformación y Tecnologías Emergentes de Alimentos, Cuautitlán Izcalli, Mexico

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8.1 Introduction

Currently, there is a great knowledge of the application of polymeric nanoparticles in the pharmaceutical industry (Mora-Huertas et al. 2010), however, this technology has also a good development in food science. The polymeric nanoparticles present great advantages when used for carrying bioactive substances of interest, since they serve as active vectors due to their controlled and/or modified release capacity (Peppas and Narasimhan 2014). The systems of submicron size have a surface area with properties that differ in behavior with respect to the systems of micrometric size and show a high rate of diffusion with low viscosity, which makes them easy to apply in different areas of food processing and conservation (González-Reza et al. 2018). They can also improve the stability and solubility of lipophilic compounds in aqueous media compared to micro and nanoemulsions.

There are several natural and synthetic polymers that have been used as encapsulating agents, which provide the characteristics of stability and protection of bioactive substances from degradation factors, such as light, pH, oxygen, etc. However, what defines the selection of the encapsulating material is the functionality that is desired in the system as well as the compatibility with the substance to be transported (Nedovic et al. 2011).

The bioactive substances of interest in food are numerous, given that each one fulfills different characteristics and functions within the nanometric system. Among the most studied functionalities in the food industry are the antioxidant and antimicrobial activities of the polymeric nanoparticles (Đorđević et al. 2014). In this chapter, a general semblance of polymeric nanoparticles is presented, as well as some of the novel developments that directly involve in vitro and in vivo investigations of these nanometric systems. This research ranges from antioxidants and antimicrobials to inhibitors of browning and the controlled release of bioactive substances.

8.2 Nanotechnology

The concept of nanotechnology was introduced by Richard Feynman in 1959 and later Nario Taniguchi in 1974 coined the term nanotechnology and used it to describe the handling of particles smaller than 1 μm (Prakash et al. 2018; Quintanilla-Carvajal et al. 2010). In this sense, when the average particle size of a system is below this threshold, the system presents significantly different physical and chemical properties in contrast to the same systems in their macrometric state (Duncan 2011).

The studies on nanotechnology have had a significant growth in recent years, awakening the interest of companies specialized in the manufacture of systems of submicron size, with medical applications, energy, computational, structural materials, etc. (Sekhon 2010). Given this great interest at industrial level, the projection for studies on nanotechnology will have an impact of at least $3 trillion on the world economy by 2020, and industries that require and offer nanotechnology as a tool around the world can require at least 6 million workers to support them by the end of the decade (Duncan 2011).

In this sense, nanotechnology has presented an important role in research in the field of the pharmaceutical industry, while in the food sector; this concept is a growing and recent interest of the industries as a delivery agent of natural ingredients.

8.3 Food Nanotechnology

Nanotechnology has become an increasingly important technology for the food sector, especially with the aim of increasing the conservation potential of bioactive substances (Prakash et al. 2018). Nanotechnology in food science refers to certain emerging disciplines that have presented great progress in recent years due to the attractive properties that have several materials related to nanoscale feeding. Understanding the basic principles of such properties is the basis for building a solid knowledge foundation to develop products with improved and novel characteristics (Hernández-Sánchez and Gutiérrez-López 2015).

However, the scientific community and the food industry have identified the potential uses of nanotechnology from agriculture (i.e. supply of pesticides and fertilizers) for food processing (i.e. encapsulation) of flavor or odor enhancers; texture modifiers, etc.), in the packaging of foods (i.e. pathogen sensors, UV protection and polymer films with greater rigidity and impermeability) to nutritional supplements (i.e. nutraceuticals with greater stability and bioavailability) (Duncan 2011; Prasad et al. 2017a, b).

Foods in which a nanotechnological technique or tool has been used or in which manufactured nanomaterials have been added, that is, any material that has been intentionally produced on a nanometric scale to have specific properties or specific compositions, are called nanofoods (Rai et al. 2015). The potential applications of nanotechnology in functional foods and the design of nutritional and nutraceutical supplements containing nano-sized systems and additives such as vitamins, antimicrobials, antioxidants and preservatives are currently available to improve taste, absorption and bioavailability (Pathakoti et al. 2017). Different systems of nanometric size have been developed in order to improve the properties of certain substances, among which we can mention nanoemulsions, nanolipid carriers, polymeric nanoparticles, etc. The latter have aroused great interest in the nanoencapsulation of bioactive agents.

8.4 Polymeric Nanoparticles

The polymeric nanoparticles (PNP) have had an important impact in the last decade, due to their properties and unique behaviors provided by their characteristic size. They can be prepared by polymerization and synthesis methods with preformed polymers. Their size is one of their fundamental characteristics, which is generally considered to be around 5–10 nm with a larger size limit of ~ 1000 nm, although the range generally obtained is 100–500 nm (Crucho and Barros 2017). Various researches reveal that nanostructured materials present a great potential in a wide range of applications, highlighting the delivery of bioactive substances of interest in food science. The advantages of PNP as carriers of bioactive substances include controlled release, protection of encapsulated agent molecules and their specific orientation (Crucho and Barros 2017).

The polymeric nanoparticles have been widely studied as carriers of active substances in different fields of knowledge, highlighting the pharmaceutical industry and recently the food industry. Recent research has presented clear information about the mechanisms of nanoparticle formation, its classification and methods of preparation (including optimal processing conditions) with various applications in the field of food.

PNP are widely used as biomaterials because of their characteristics in terms of simple processing and design, good biocompatibility, a wide variety of structures and remarkable bio-imitative characteristics (El-Say and El-Sawy 2017). Nanoparticles are defined as solid colloidal particles that include two forms: nanospheres and nanocapsules (González-Reza et al. 2015).

8.4.1 Nanocapsules

Nanocapsules (NCs) could be compared to nano-vesicular systems in which an active substance is confined in a cavity consisting of an internal liquid core surrounded by a polymeric membrane (core-layer). The cavity may contain the active substance in liquid or solid form or as a molecular dispersion. Also, this deposit can be lipophilic or hydrophilic according to the method of preparation and the materials used for its preparation. Taking into account the operating limitations of the preparation methods, the nanocapsules can also transport the active ingredient adsorbed on their surfaces or imbedded in their polymer membrane (Mora-Huertas et al. 2010).

Generally, there are six classical methods for the preparation of nanocapsules: nanoprecipitation, emulsion-diffusion, double emulsification, emulsion-coacervation, polymer-coating and layer by- layer (Mora-Huertas et al. 2010).

8.4.2 Nanospheres

Nanospheres (NSs) are defined as solid colloidal particles, in which the active molecules are dissolved, trapped or encapsulated, chemically bound to the polymers or adsorbed to the surface of the particle. These nanospheres have compact polymeric cores (to guarantee a good stability) but the cores are degradable. In other words, any nanosphere can be portrayed as a complete polymeric spherical mass in which, as a result, the active molecules can be trapped within the center of the sphere or adsorbed on the surface of the matrix (El-Say and El-Sawy 2017; Gref et al. 2012). Figure 8.1 shows the polymer nanoparticles, in which it is possible to find nanocapsules and nanospheres.

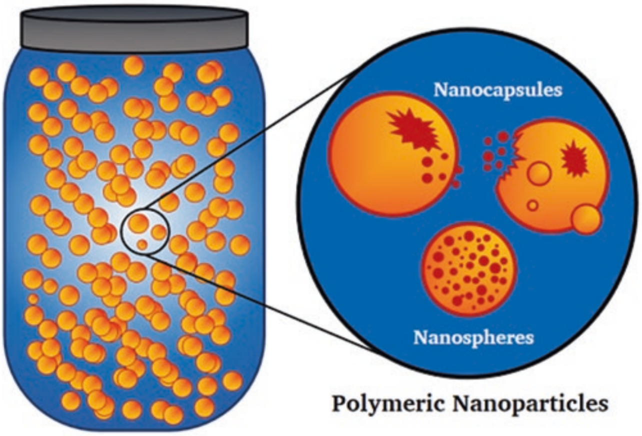

Fig. 8.1 Polymeric nanoparticles in foods (nanocapsules and nanospheres)

8.4.3 Polymers Used in the Formation of Nanoparticles

Biodegradable polymers have been the main object of the polymer nanoparticle developments. Among the biodegradable polymers reported in the literature as controlled release systems of bioactive substances are aliphatic polyesters and their copolymers (Sinha et al. 2004). In the case of poly (hydroxy acids) such as poly (lactic acid) (PLA)) or poly (lactic-co-glycolic) (PLGA)), the nuclei can be degraded by hydrolysis into innocuous elements that could be excreted (such as lactic acid and glycolic acid). Poly-ε-caprolactone (PCL)) has shown a good ability to encapsulate various active substances. By adjusting the physicochemical characteristics of these polymers, different properties of encapsulation and release kinetics could be obtained (Gref et al. 2012).

The polymers used in the formation of nano-sized colloidal systems depend on their compatibility with bioactive compounds. The polymeric nanoparticles in the delivery systems of bioactive substances are suitable for both hydrophilic and hydrophobic compounds. There are reports of the use of certain polymers in the pharmaceutical industry such as poly (D,L-lactide-coglycolide) (PLGA), poly (lactic acid) (PLA),, poly (glutamic acid) (PGA), poly (caprolactone) (PCL), N-(2-hydroxypropyl)-methacrylate (HPMA) copolymers, and poly(amino acids) (Shin et al. 2015).

In contrast, the food industry presents innovations in the use of natural polymers, such as cellulose, alginate, pectins, maltodextrins, chitosan, cyclodextrin, albumin, globulin and starch, etc., which have been used successfully in different nanometric systems to protect bioactive substances from intrinsic and extrinsic factors such as pH, water activity, enzymatic degradation, temperature and relative humidity (Prakash et al. 2018). The most important criteria for the selection of an encapsulation material are the possible restrictions for the coating material, the concentration of encapsulation, the type of release, the stability requirements and the economic limitations (Nedovic et al. 2011).

The polymeric nanoparticles must take into account different aspects, (i) they have to serve as a vehicle to carry a functional ingredient or active substance to the desired site of action, (ii) the protection of the functional ingredient from chemical or biological degradation has to be ensured (i.e. oxidation) during processing, storage and use; this keeps the functional ingredient in its active state, (iii) it must be able to control the release of the functional ingredient, such as the rate of release or the specific environmental conditions that trigger the release (i.e. pH, ionic strength or temperature), and (iv) the delivery system must be compatible with the other components in the system, in addition to being compatible with the physicochemical and qualitative attributes (i.e. appearance, texture, taste and shelf life) of the final product (Weiss et al. 2006).

8.4.4 Advantages of the Use of Polymeric Nanoparticles

The polymeric nanoparticles (PNP) have presented an outstanding progress for the effective delivery of bioactive compounds in specific sites and applications. The main advantage of PNP is the overcoming of the limitations of the traditional colloidal systems based on lipids, such as liposomes, emulsions and micelles. In this sense, the polymeric nanoparticles present a higher efficiency of encapsulation, greater stability and controlled release of active substances in contrast to the other colloidal systems with lipid base.

In the food industry, the nanoencapsulation of essential oils (which presents the highest reports and research) denotes numerous advantages, such as the increase in the ease of: handling of materials to be used in products with added value, stability, protection against oxidation, solubility, masking of unwanted flavors and controlled release (Prakash et al. 2018). Figure 8.2 shows some advantages of using polymeric nanoparticles on bioactive substances of interest in the food industry.

8.4.5 Controlled Release of Polymer Nanoparticles

Nanoparticulate systems are promising as active vectors due to their ability to release active substances, they can improve the stability of active substances and can be biocompatible with tissues and cells when they are synthesized from materials that are biocompatible or biodegradable (Mora-Huertas et al. 2010). In the ideal case, the required composition (type and amount of active substance, polymer and

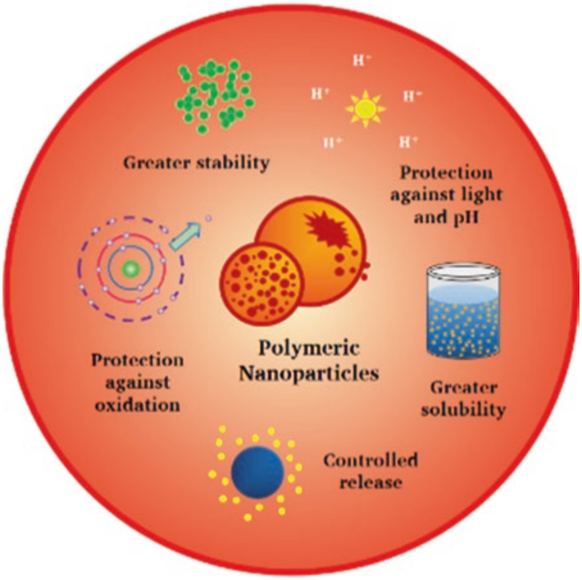

Fig. 8.2 Advantages of the use of polymeric nanoparticles in foods

additives) and the geometry (size and shape) of the new controlled active substance administration system designed to achieve a certain release profile can, theoretically, be predicted (Siepmann and Peppas 2012).

The classification of controlled release systems is based on the mechanisms of release of active substances having those controlled by diffusion, chemically controlled, osmotically controlled and swelling and/or controlled by dissolution (Peppas and Narasimhan 2014). Many existing models are based on diffusion equations, due to the fact that diffusion of the active substances is an important function of the structure through which diffusion is carried out, so the models must consider the morphology of the polymers. Diffusion, swelling and erosion are the most important speed control mechanisms of commercially available controlled release products. The diffusion can be described using Fick's second law (Siepmann and Peppas 2011, 2012).

8.5 Nanoencapsulation of Bioactive Substances

Encapsulation can be defined as a process to trap a substance within another substance. Currently, numerous encapsulation techniques are available and have been studied through innumerable scientific publications and patents, and some of them are already implemented on an industrial scale (Đorđević et al. 2014). The current technological advances where lipids, proteins and polysaccharides are used as additives are contributing to face this challenge, and have opened the door to new functionalities and applications for nanoparticle delivery systems (Acosta 2009).

Nanoencapsulation has been used by the food industry for natural ingredients and additives. These nanomaterials offer several advantages, such as the preservation of ingredients and additives during processing and storage, masking unpleasant flavors, controlling the release of additives, better dispersion of ingredients and food additives insoluble in water and better absorption of nutrients and supplements encapsulated (Rai et al. 2015).

The protection of bioactive compounds such as vitamins, antioxidants and antimicrobials can be successfully achieved using this technique for the production of functional foods with improved functionality and stability. The absorption and improved bioavailability has allowed the application of nanocapsules in food products that incorporate nanoscale vitamins, nutraceuticals, antimicrobial agents, antioxidants, functional ingredients, etc. (McClements 2015; Rai et al. 2015).

As mentioned above, the use of lipophilic substances in nanoencapsulation has had a great impact on research within the food area, which is why knowing optimal training conditions is necessary. Numerous investigations have been developed to solve this problem using conventional methods such as emulsification-diffusion (Esmaeili and Gholami 2015; Zambrano-Zaragoza et al. 2011) and nanoprecipitation (Noronha et al. 2013), in addition to the use of new technologies in their training such as ultrasound (Galindo-Pérez et al. 2018).

8.5.1 Important Bioactive Substances in Food

Functional ingredients are essential components of a wide range of industrial products in the food area. These functional ingredients are present in a variety of different molecular and physical forms, such as polarities (polar, non-polar, amphiphilic), molecular weights (low to high) and physical states (solids, liquids, gaseous). Functional ingredients are rarely used directly in their pure form, instead, they are often incorporated into some form of delivery system (Weiss et al. 2006). Next, novel findings in the nanoencapsulation of important bioactive substances in foods will be described, having as vectors polymeric nanoparticles.

8.5.1.1 Antioxidants

The Food and Drug Administration (FDA), defines antioxidants as substances used to preserve food by delaying spoilage, discoloration and rancidity due to oxidation. Food manufacturers have used food grade antioxidants to prevent the deterioration of the quality of the products and maintain their nutritional value. Antioxidant compounds are classified into natural and synthetic (Carocho et al. 2018; Shahidi 2000). As mentioned above, the encapsulation of antioxidants in polymeric nanoparticles is of great interest in foods, which is why some novel developments in this topic are included.

Liang et al. (2017) prepared chitosan nanoparticles coated with zein as a novel system of effective delivery of epigallocatechin gallate. Sizes lower than 250 nm and zeta potentials in a range of 20–30 mV were obtained in all cases. The release profile showed a burst effect, followed by a slow release. The antioxidant activity (determined by the DPPH technique) suggests that chitosan nanoparticles loaded with epigallocatechin gallate and coated with zein improved the antioxidant activity in a 95% ethanol solution, providing long-term protection against oxidation in food with high fat content.

Studies conducted by Pereira et al. (2018) presented a novel proposal of nanoencapsulation by the emulsion-evaporation method of a phenolic extract obtained from guabiroba fruit with poly (D, L-lactic-co-glycolic acid) (PLGA) as an encapsulating polymer (average particle sizes of approximately 140–250 nm were obtained). The antioxidant capacity determined by the inhibition of the DPPH and ORAC radical was greater in the nanoparticles loaded with the hydrophilic phenolic extract in both cases in a 65:35 ratio of PLGA.

Research on the formation of polymeric chitosan nanoparticles loaded with jujube fruit extracts by the ionic gelation method were developed by Han et al. (2015). They found that the particle size increases significantly when the extract concentration increases, presenting high encapsulation efficiencies (>80%). The antioxidant activity (determined by the inhibition of the ABTS and DPPH radical independently) was effectively improved by nanoencapsulation, directly related to the total polyphenol content.

Works carried out in the formation of polymeric nanoparticles based on PCL and poly(D,L-lactic-co-glycolic acid)-block-poly(ethylene glycol) carboxylic acid, containing fisetin prepared by nanoprecipitation (Sechi et al. 2016), showed particle sizes of 140–200 nm, with an encapsulation efficiency between 70% and 82%. The good elimination capacity of DPPH radicals showed a radical elimination of 65% at a nanoparticle concentration of 40 μg/mL, similar to the elimination of 70% of the ABTS radical at a concentration of 30 μg/mL. These findings imply the preservation of antioxidant capacity during the process of nanoparticle formation.

Biodegradable films and antioxidants based on methylcellulose have been developed, added with α-tocopherol nanocapsules (Noronha et al. 2014). The results revealed that the elimination activity of the DPPH and ABTS radicals of the films increased significantly with increasing concentration of nanocapsules. The films that had 70% of nanocapsules showed inhibition of the radical DPPH = 56.21% and ABTS = 223.5 TEAC μmol/g.

8.5.1.2 Antimicrobials

Antimicrobial agents have been the subject of numerous investigations worldwide given the needs to increase the safety of food and increase the shelf life of various food products. Their functionality lies in their effectiveness to inactivate or inhibit the growth of pathogenic and deteriorative microorganisms in foods. Antimicrobials widely used in food preservation include synthetic and natural compounds (Appendini and Hotchkiss 2002).

The development of polymeric nanoparticles for the delivery of antimicrobial substances with controlled release has been an important focus of attention in food science, given the needs of presenting alternatives that ensure the safety of food products. Various conventional and natural antimicrobials have been nanostructured and these developments are described below.

Sotelo-Boyás et al. (2017) synthesized chitosan nanoparticles and nanocapsules containing lime oil by the nanoprecipitation method. The antimicrobial activity was tested against four foodborne pathogens, *Staphylococcus aureus*, *Listeria monocytogenes*, *Shigella dysenteriae* and *Escherichia coli*, being higher for nanoparticles than for nanocapsules. The highest antibacterial activity was determined for chitosan nanocapsules incorporated with lime essential oil applied against *S. dysenteriae*, reaching a halo inhibition value of 3.5 cm for 40 mL of minimum inhibitory volume. Research conducted on the antimicrobial activity of silymarin nanocapsules using water soluble chitosan and poly-γ-glutamic acid was presented by Lee et al. (2017). The antimicrobial activity of silymarin was effectively improved when silymarin was trapped inside the nanocapsule compared to when it was not trapped. The values of minimum inhibitory concentration (MIC) of silymarin against *Bacillus subtilis, S. aureus,* and *E. coli* were investigated. Silymarin inhibited the synthesis of RNA and proteins in Gram-positive bacteria but not in Gram-negative bacteria. The MIC values of silymarin against *B. subtilis* and *S. aureus* decreased to 50% by nanoencapsulation, resulting in an increase in antimicrobial activity.

As it is known, certain essential oils possess antimicrobial and antioxidant activities, for which numerous investigations on polymeric nanoencapsulation have been developed. A clear example is the research carried out by Chen et al. (2009), where chitosan nanoparticles were prepared using eugenol and carvacrol as active substances (average particle sizes of 200–300 nm were obtained). Aldehyde groups were added in eugenol and carvacrol and the addition of these in chitosan was carried out by the Schiff base reaction. The antibacterial tests were carried out with *E. coli* and *S. aureus*. The chitosan nanoparticles loaded with the components of the essential oil achieved an antibacterial activity equivalent to or better than that of the unmodified chitosan nanoparticles.

8.5.1.3 Colorants

The dyes are preferred in the preparation of food and in the development of new products. Dyes from natural products have health and safety advantages, such as antioxidant and antimicrobial effects (described above) which provide functional food characteristics when applied to food processing (Özkan and Bilek 2014). The incorporation of natural dyes in food has a great impact due to their characteristic physical properties and also many have important biological properties. However, many of them have limitations due to their lipophilic nature such as carotenoids.

An example is the research developed by González-Reza et al. (2018) where β-carotene was nanoencapsulated using poly-ε-caprolactone by the emulsification-diffusion method. In this study, the physical stability of the dispersions was evaluated in relation to three factors: pH, sucrose concentration and different concentrations of nanocapsules of β-carotene. The results showed that no significant aggregation was detected, but that significant changes in chromaticity occurred during the storage period (28 days, 25 °C) in all samples analyzed. The particle size obtained during the monitoring was always less than 300 nm. The results revealed that these systems can represent an effective option as a component of functional foods and beverages, as well as of nutraceutical products.

The physical stability on the color profile parameters of PCL nanocapsules containing lycopene were reported by dos Santos et al. (2015) during storage for 28 days at 25 °C. The nanometric system formed showed values of particle size of 193 nm and zeta potential of −11.5 mV. The change in the color of the nanocapsules was significant, presenting increased luminosity and reductions in the parameters a∗ and b∗ due to the degradation of lycopene, leading to a loss of color and an increase in the component of the white component of the hue, related to the loss of lycopene around 50% (after 14 days of storage). Changes in the color profile parameters of lutein nanocapsules were evaluated for 60 days at 4 and 25 °C. For the preparation of the nanometric systems, the technique of interfacial deposition of the preformed polymeric poly-caprolactone was used. The initial results showed an average particle size of 191.9 nm with a zeta potential of −5.14 mV. After 60 days of storage at 4 °C, the nanocapsules remained stable without significant changes in color, in contrast to the samples that were stored at 25 °C. However, nanoencapsulation allowed the suspension of lutein in an aqueous medium and increased its stability at different temperatures.

8.6 Food Applications

Although studies conducted in vitro for polymeric nanoparticles containing bioactive substances may be promising, direct application in foods still has a large field of research at present, due to its complex composition and the possible interactions of nanostructured systems with the components of food, as well as storage conditions that could arise. In this section, some examples of direct applications of polymeric nanoparticles in different foods will be described.

8.6.1 Browning Inhibitors by Application of Nanocapsules of α-Tocopherol in Apple

PCL nanocapsules containing α-tocopheryl acetate were prepared by the emulsification-diffusion method (particle size = 239 nm, PDI = 0.086 and zeta potential = −44.7 mV), which were applied as edible coating to Red Delicious apple fresh cut (Zambrano-Zaragoza et al. 2014). The nanocapsules demonstrated effectiveness on the browning index of apples stored for 18 days at 4 °C. The nanometric systems can remain on the surface of the tissue, which decreased the respiration rate and consequently the polyphenol oxidase activity. Important findings are reported, one of them is respect to the firmness of the product, which in the control samples revealed a 60% loss in this parameter, in contrast to 15% when using nanocapsules.

8.6.2 Nanostructured Nisin in Orange Juice

Chitosan nanoparticles modified with monomethyl fumaric acid, functionalized with nisin, have been evaluated as a new direct food additive in orange juice. The nanoparticles were synthesized by the ionic gelation method (Khan et al. 2018). Average particle sizes were less than 210 nm in all cases, presenting good stability to aggregation and encapsulation efficiencies between 75% and 85%. The bacterial strains *S. aureus* ATCC 13565, *L. monocytogenes* ATCC 19119, *E. coli* O157: H7 ATCC, and *Salmonella enterica* ATCC 13076, which include both Gram-positive and Gram-negative bacteria, were used in the study. The application of the nanometric systems in orange juice, revealed a greater antimicrobial reduction for the nanoparticles against the Gram-positive and Gram-negative strains tested. The antimicrobial activity of the nanoparticles loaded with nisin was improved against Gram-negative bacteria. These results suggest that chitosan modified with monomethyl fumaric acid could be used as a nanovehicle for food-grade antimicrobial agents in foods. Chitosan nanoparticles modified with monomethyl fumaric acid, functionalized with nisin could be used as a potential alternative food preservative in beverages.

8.6.3 Conservation of Tuna Fish with Liquid Smoke Nanoparticles

Studies conducted by Saloko et al. (2014) are promising as an alternative to tuna fish conservation. Initially, nanocapsules of liquid smoke of coconut shell were prepared using chitosan and maltodextrin as wall agents for their application in the conservation of tuna fish. A mixture suspension of polymeric nanocapsules (1.5% chitosan and 8.5% maltodextrin) and a concentration of liquid smoke higher than 5% could maintain the freshness of the tuna up to 48 h at room temperature, presenting quantitatively the highest values in terms of total activity and total concentration of phenolic compound and acetic acid. For the antioxidant capacity of radical scavenging by DPPH, an inhibition of 58.97% was obtained. For the antimicrobial treatments, four strains of microorganisms were used for the test of antibacterial activity (*E. coli, Pseudomonas fluorescens*, *B. subtilis* and *S. aureus*). The highest antimicrobial activity was obtained against *E. coli* and *P. fluorescens*. Therefore, the suspension of nanocapsules of liquid smoke from coconut shell can be applied as a natural preservative for tuna fish.

8.6.4 Nanostructured Nisin Antimicrobials in Lean Beef

As for meat products, Zimet et al. (2018) made the proposal for nanoencapsulating nisin to improve antimicrobial activity when applied in food systems such as lean beef. Alginate nanoparticles were prepared by ionic gelation and an additional complex with chitosan. The nanocapsules had an encapsulation efficiency of 36.1%, an average particle size of 66.4 nm and a zeta potential of −31.7 mV. Lean beef samples were inoculated with *L. monocytogenes* and then nanocapsules were added. The encapsulated nisin was able to inhibit the growth of *L. monocytogenes* in refrigerated meat samples vacuum sealed for 10 days when it was applied at 400 IU/g and for 24 days when 800 IU/g was applied. These results suggest that the application of nanoparticles loaded with nisin would allow the use of lower concentrations with antimicrobial effect, and it can be applied as an agent in the bioconservation of refrigerated lean beef, stored under vacuum.

8.6.5 Controlled Release of β-Carotene in Fresh Cut Melon

Research have been reported on the rate of release of antioxidant agents in polymer matrices with direct application in food. Such is the case of the research developed by Zambrano-Zaragoza et al. (2017), where edible coatings were applied to fresh cut cantaloupe melon, using PCL nanocapsules containing β -carotene and nanospheres of PCL independently, combined with a matrix of xanthan gum, which were stored for 21 days at 4 °C. The release profiles of beta-carotene for the nanocapsule treatments were adjusted to a Higuchi type behavior for matrix systems. A correlation was also determined between the release by treatments with nanocapsules/xanthan gum on the whiteness index and the firmness of the samples, improving the properties of the coatings, increasing their storage time.

8.7 Conclusions and Future Trends

The polymeric nanoparticles are promising in terms of their functionalities, which some of them have direct potential application in food. One of the main synthetic agents used as polymer wall in the formation of nanoparticles is the poly-ε-caprolactone, as well as the efforts by the use of natural encapsulating polymers is largely focused on the chitosan. Several investigations have been listed, in which the formation of nanocapsules and nanospheres is carried on by different methods, which define the characteristics of the nanometric system, and additionally, some stability parameters are defined. Different bioactive substances have been encapsulated in order to improve and/or potentiate their beneficial effects, such as antioxidants, antimicrobials, vitamins, texture enhancers, browning inhibitors, and colorants. Future trends will be aimed at the combination of bioactive substances in the same nucleus, the modification of various wall polymers that have improved physical, chemical and release stability qualities, as well as improving and proposing applications at the laboratory level that could apply every day in the food industry.

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Chapter 9
Application of Nanoparticles in Crop Production and Protection

Aadil Rasool, Wasifa Hafiz Shah, Inayatullah Tahir, and Reiaz Ul Rehman

Contents

9.1 Introduction

The term nanotechnology was first introduced by Norio Taniguchi, a Japanese researcher (Taniguchi 1974). Nanomaterials or nanoparticles (NPs) are substances/materials which have a size less than 100 nm in at least one dimension (Laurent et al. 2010). Nanoparticles are of great scientific interest as they bridge the gap between bulk materials and atomic or molecular structures (Thakkar et al.

Author contributed equally with all other contributors.Aadil Rasool and Wasifa Hafiz Shah

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A. Rasool · W. H. Shah · R. U. Rehman (✉)
Department of Bioresources, University of Kashmir, Hazratbal, Srinagar, India

I. Tahir
Department of Botany, University of Kashmir, Hazratbal, Srinagar, India

R. Prasad (ed.), *Plant Nanobionics*, Nanotechnology in the Life Sciences,
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2010). Any material when attenuated at nanometer scale (less than 100 nm) exhibits new properties that are entirely different from its bulk counterpart due to small size and high surface-to-volume ratio. The science of nanotechnology is nowadays common to various fields like material sciences, electronics, and biotechnology (Bhatt 2003; Bohr 2002; James 1999; Portney and Mihrimah 2006; Sanjeeb and Vinod 2003; Prasad et al. 2014).The importance of these materials came to light when researchers found that size can influence the physiochemical properties of a substance like optical properties, solubility, boiling point, melting point, density/specific gravity, pH, corrosivity, and dissociation (Shin et al. 2015). The development of nanotechnology in conjunction with biotechnology has significantly expanded the application domain of nanomaterials in various scientific fields. The applications of nanoparticles are many including water purification, waste water treatment, environmental remediation, food processing and packaging, industrial and household purposes, medicine, and in smart sensor development (Jain 2005; Wei et al. 2007; Chau et al. 2007; Byrappa et al. 2008; Zhang and Webster 2009; Gao and Xu 2009; Qureshi et al. 2009; Lee et al. 2010; Zambrano-Zaragoza et al. 2011; Bradley et al. 2011; Prasad et al. 2017a, b). They are also used in studying the plant processes as well as for improving the plant growth and development.

9.2 Classification of Nanomaterials

Most current nanomaterials could be categorized into the following four types, viz., carbon-based materials, metal-based materials, dendrimers, and composites (Fig. 9.1).

9.2.1 Carbon-based Materials

Carbon-based materials have created noteworthy commercial interests due to their wide range of outstanding and novel features. Their unique physical and chemical properties like electrical conductivity, high strength, structure, electron affinity, and versatility determine a wide range of options for their practical applications (Astefanei et al. 2015). Based on these properties, they were repeatedly termed as “wonder materials” in the scientific literature (Kah and Hofmann 2015). These nanomaterials are composed of carbon, most commonly taking the form of hollow spheres, ellipsoids, or tubes. Spherical and ellipsoidal carbon nanomaterials are referred to as fullerenes, while cylindrical ones are called nanotubes (Khan et al. 2017).

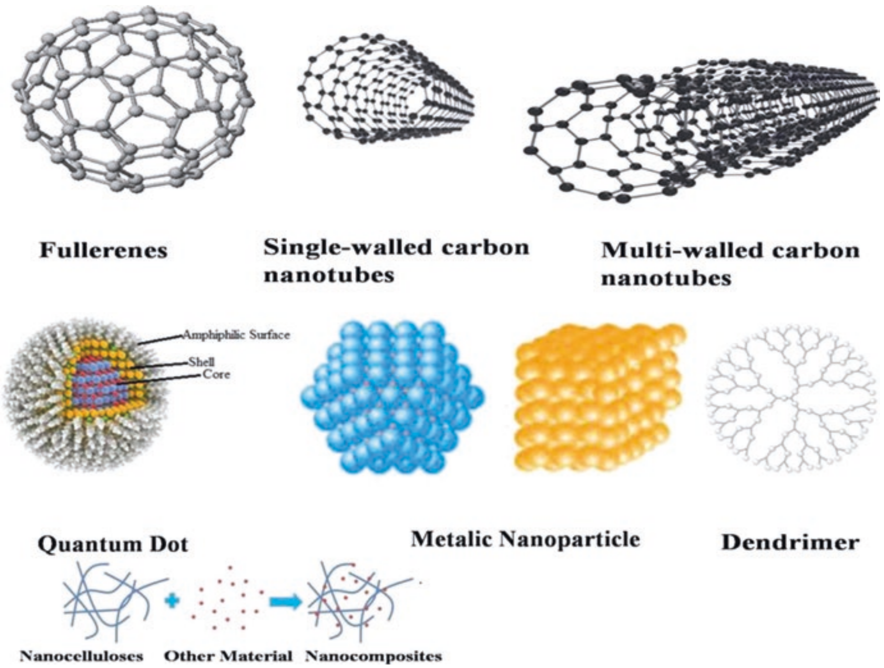

Fig. 9.1 Different types of carbon-based nanomateials

9.2.1.1 Fullerenes

In 1985, H. W. Kroto, R. F. Curl, and R. E. Smalley discovered fullerenes (Kroto et al. 1985). Usually, fullerene family includes less than 20 carbon clusters where carbon atoms are usually present in the sp^2-hybrid form and linked together by covalent bonds. Carbon atoms are usually located on the surface of the sphere at the vertices of pentagons and hexagon (Zaytseva and Neumann 2016).

9.2.1.2 Carbon Nanotubes (CNTs)

CNTs were discovered by S. Iijima, a Japanese researcher in 1991. Carbon nanotubes possess characteristic cylindrical structures which may vary in length, diameter, chirality, and the number of layers. CNTs are classified as single-walled carbon nanotubes (SWCNTs) and multi-walled carbon nanotubes (MWCNTs). SWCNTs have a diameter around 1–3 nm and a length of a few micrometers, while MWCNTs have a diameter of 5–40 nm and are around 10 μm in length (Zaytseva and Neumann 2016).

9.2.2 Metal-Based Materials

These nanoparticles made up of metals, semiconductors, or metal oxides are of great interest for their electrical, magnetic, optical, chemical, and mechanical properties (Hubler and Lyon 2013; Stephenson and Hubler 2015).These nanomaterials include quantum dots—a quantum dot is a closely packed semiconductor crystal comprised of hundreds or thousands of atoms and whose size is on the order of a few nanometers to a few hundred nanometers. Changing the size of quantum dots changes their optical properties. Metal-based materials mainly include metals and metal oxides like aluminum (Al), copper (Cu), gold (Au), silver (Ag), silica (Si), zinc (Zn) nanoparticles and zinc oxide (ZnO), and titanium dioxide (TiO_2) (Trivedi and Hemantaranjan 2017).

9.2.3 Dendrimers

Dendrimers were first discovered in 1978 by Fritz Vögtle and in the early 1980s by Donald Tomalia and his co-workers (Srinivasa-Gopalan and Yarema 2007). These highly defined artificial macromolecules are characterized by a combination of a high number of functional groups and a compact molecular structure (Tomalia and Frechet 2002). These nanomaterials are nano-sized polymers built from branched units (dendrons), which begin with a central atom or group of atoms considered as the core. The numerous chains present on the surface of dendrimer can be tailored to perform specific function like catalyzing reactions. The three-dimensional dendrimers contain interior cavities into which other molecules could be placed, and these may be useful for nutrient delivery (Esfand and Tomalia 2001; Kesharwani et al. 2014).

9.2.4 Composites

Composites combine nanoparticles with other nanoparticles or with larger, bulk-type materials like combination of mineral oxide nanoparticle and a shell of a transition metal oxide. The mineral oxide may be silica, alumina, or a mixture of such materials. For example, nano-sized clays are already being added to products ranging from auto parts to packaging materials, to enhance mechanical, thermal, barrier, and flame-retardant properties. A variety of biocomposite nanomaterials are being developed (Nair et al. 2010) which find a wide variety of applications like in packaging as polymeric film modifier, catalysts, metallic semiconductor junctions, optical sensors, etc. Due to their huge activity and specificity, nanoparticles have gained increasing attention and importance in their scientific and technological fields (Calandra et al. 2013). Due to the unique physiochemical properties of NPs such as chemical composition, reactivity, surface area, particle morphology, and tunable pore size, they have the potential to bring a positive shift in the agricultural production and protection by interacting with plants (Khodakovskaya et al. 2012; Giraldo et al. 2014). NPs have plant growth-promoting effects, which have vast applications in agriculture. Owing to the positive effects of NPs, they are called as “magic bullets,” which include nanopesticide, nanofertilizers, and herbicides which target particular cellular organelles in plant. The use of nanoparticles as fertilizer has innumerable opportunity to increase crop yield.

9.3 Role of Nanoparticles in Plant Growth and Development

Plants are crucial for all the communities as they are the primary producers and are responsible for the production of organic matter using the solar energy, which is important for other trophic groups (McKee and Filser 2016). Nanoparticles, based on their behavior and concentration, induce morphological and anatomical changes in plants, which may be positive or negative for their growth and development (Siddiqui et al. 2015). Once, plants get exposed to nanoparticles, these NPs penetrate the cell wall and then cross the intact cell membrane via pores (which indicate that uptake is size specific) and ultimately reaches the stele symplastically where distribution and translocation of nanoparticles is done by Xylem. NPs must integrate with apoplast of endodermis before reaching xylem (Aslani et al. 2014; Judy 2013; Ma et al. 2010; Rico et al. 2011).The effect of NPs on plants varies from species to species and plant to plant and effectiveness of NPs is dependent on its concentration which also varies from plants to plant. Plants require a number of macro and micro nutrients in different concentrations for their normal growth and development. These nutrients are generally present in the soil, but at times some of these nutrients are either present in lesser quantities or are not available to the plants. In order to replenish this nutrient deficit, different nanoparticles are being used (Table 9.1). Metal-based nanoparticles have enormous agricultural importance for their easy use and growth-enhancing property. For example, in soybean (*Glycine max*), a mixture of SiO_2 and TiO_2 nanoparticles enhances water- and fertilizer-absorbing abilities besides their utilization, which in turn accelerates its germination and growth. The mixture has also been reported to increase the activity of nitrate reductase and stimulation of antioxidant system in soybean (Lin and Xing 2007; Lu et al. 2002). Gold nanoparticles at concentration 0.013% (w/w) increased the ratio of shoot to root length in *Lactuca sativa* (Shah and Belozerova 2009). Various concentrations of gold NPs were tried on *Brassica juncea* cv. Pusa jaikisan; the rapid seed germination and increase in growth of seedling were observed. Seed yield, chlorophyll content, sugar content, and seed oil content also increased by application of 10 ppm concentration (except for sugar content which had a maximum at 25 ppm). It was suggested that the interference of these gold NPs in plant hormone action is responsible in growth profile changes of *Brassica* seedlings (Arora et al. 2012). *Brassica juncea*, when treated with silver nanoparticles (25 and 50 ppm), show increased shoot and root lengths (Sharma et al. 2012). Silver nanoparticles (AgNPs) at 13.5 mg/liter also caused root length increase in *Raphanus sativus* (Iram et al. 2014). Under in vitro conditions, silver NPs improved the growth by modulating the antioxidant status of 7-day-old *Brassica* seedlings (Sharma et al.

Table 9.1 Various types of nanoparticles and their role in plant growth and development

	Type	Main source	Concentration	Size of nanoparticle (nm)	Plant species	Significance	Reference
A. Macronutrients given as nanoparticles							
1.	Phosphorus	Hydroxyapatite	NA	16	Soybean (*Glycine max*)	Increased growth rate, seed yield, and biomass	Liu and Lal (2014)
2.	Calcium	$CaCO_3$	160 mg/L	20–80	Peanut (*Arachis hypogea*)	Increased seedling growth	Liu et al. (2005)
3.	Magnesium	Mg + Fe	0.5 g/L	NA	Black-eyed pea (*Vigna unguiculata*)	Increased seed weight and plant's photosynthetic activity	Delfani et al. (2014)
B. Micronutrients given as nanoparticles							
1.	Iron	Fe_3O_4	30, 45, and 60 mg/L	18.9–20.3	Soybean (*Glycine max*)	Increased chlorophyll content in subapical leaves	Ghafariyan et al. (2013)
		Fe_3O_4	30, 45, and 60 mg/L	18.9–20.3	Black-eyed pea (*Vigna unguiculata*)	Increased 1000 seed weight and number of pods/plant	Delfani et al. (2014)
2.	Manganese	Metallic Mn	0.05,0.1, 0.5, and 1.0 mg/L	20	Mung bean (*Vigna radiata*)	Increased root length, shoot length, dry weight, photosynthetic rate, and chlorophyll and carotenoid content	Pradhan et al. (2013)
3.	Zinc	ZnO	1-2000 mg/L	20	Mung bean (*Vigna radiata*), Chickpea (*Cicer arietinum*)	Increased root length, shoot length, and biomass	Dhoke et al. (2013)
		ZnO	1–1000 mg/L	20	Radish (*Raphanus sativus*), rapeseed (*Brassica napus*)	Root elongation	Lin and xing (2007)
		ZnO	400–800 mg/kg soil	10	Cucumber (*Cucumis sativus*)	Increased root dry mass, starch, and glutelins	Zhao et al. (2013)
		Mettalic Zn	1–2000 mg/L	35	Ryegrass (*Lolium pereme*)	Root elongation	Lin and xing (2007)

4	Copper	70% CuO + 30% Cu_2O	0.025,0.25, 0.5, and 5 g/L	30	Water seed (*Elodea densa* Planch)	Increased photosynthetic rate	Nekrasova et al. (2011)
		Metallic Cu	130 and 600 mg/kg soil	<50	Lettuce (*Lactuca sativa*)	Increased shoot/root ratio and increased total nitrogen and organic matter	Shah and Belozerova (2009)
5.	Molybdenum	Mo	8 mg/L	100–250	Chickpea (*Cicer arietinum*)	Increased nodule number/mass and increased activity of antioxidant enzymes	Tara et al. (2014)
C. Other metal-based nanoparticles							
1.	Titanium	TiO_2 anatase	2.5 g/L	5	Spinach (*Spinacia oleraceae*)	Increased biomass, nitrogen content, and chlorophyll content	Yang et al. (2007)
		TiO_2 anatase	10, 50, 100, 200, 500, 1000, and 2000 mg L^{-1}	5–10	Duckweed (Lemnoideae)	Increased root length, biomass, and chlorophyll content	Song et al. (2012)
2.	Gold	Au	80 µg/ml		*Arabidopsis thaliana*	Enhanced germination rate and seed yield, accelerated plant growth, and stimulated antioxidant activity	Ampleyeva et al. (2012)
3	Silicon	SiO_2	8 gL^{-1}		Tomato (*Lycopersicum esculentum*)	Seed germination Seedling fresh weight, seedling dry weight, and root and shoot lengths	Siddiqui and Al-Whaibi (2013)
		SiO_2	1 mM		Lentil (*Lens culinaris*)	Alleviate the adverse effect of salt stress and increase germination percentage, root and shoot length, and seedling weight	Janmohammadi et al. (2015)

(continued)

Table 9.1 (continued)

	Type	Main source	Concentration	Size of nanoparticle (nm)	Plant species	Significance	Reference
D. Carbon-based nanoparticles							
1.	CNTs		40 μg/mL		Tomato (*Lycopersicum esculentum)*	Germination, seedling growth	Morla et al. (2011)
		SWCNTs	9, 56, 315, and 1750 mg		Onion (*Allium cepa)*, cucumber (*Cucumis sativus)*	Root elongation	Canas et al. (2008)
		MWCNTs	25–100 μg/mL		Barley (*Hordeum vulgare* L.), soybean (*Glycine max*), maize (*Zea mays*)	Germination	Lahiani et al. (2013)
			50 and 200 μg/mL		Tomato (*Lycopersicon esculentum* Mill)	Height and number of flowers	Khodakovskaya et al. (2013)
			5 up to 500 μg/mL		Tobacco (*Nicotiana tabacum*)	Growth	Khodakovskaya et al. (2012)

2012). Application of AgNPs to soil increased maize plant biomass significantly (Sillen et al. 2015). An increase in plant height of *Borago* on the application of AgNPs was reported (Sah et al. 2011). Suitable concentration of nano-TiO_2 (mostly 0.25%) promoted photosynthesis and nitrogen metabolism in spinach resulting in improved growth (Gao et al. 2006; Hong et al. 2005; Yang et al. 2006).

9.3.1 NPs Have a Wide Range of Application in Different Plant Processes

CNTs in low doses can stimulate seed germination and plant growth. It was shown that an application of 2 g L^{-1} multi-walled CNTs increased the 5-day root elongation of germinated seeds of ryegrass and corn (Lin and Xing 2007). The root growth of germinated onion (*Allium cepa*) and cucumber seeds was enhanced by the exposure to single-walled CNTs at 0.16, 0.9, and 5 g L^{-1} (Canas et al. 2008). Both single-walled CNTs and multi-walled CNTs increased the seed germination percentage and enhanced seedling growth of tomato, soybean, and corn (Khodakovskaya et al. 2013; Lahiani et al. 2013; Villagarcia et al. 2012). It is proposed that surface charges of CNTs promote water uptake and utilization efficiency of the plant by positively affecting the expression and growth of water channel proteins in tomato plants (Khodakovskaya et al. 2013; Villagarcia et al. 2012).

9.3.2 Effect of NPs in Seed Germination

Nanoparticles have an extensive potential in uplifting agriculture and horticulture. The goal of nano-agriculture can be obtained by applying NPs, which can stimulate seed germination and enhance development of seedlings of valuable agricultural plant species. Due to the significant thickness of seed coat covering the whole seed, penetration of plant seeds could be more complicated as compared to plant cell walls, but it has been reported that different types of nanoparticles are able to penetrate plant cell walls and deliver nutrients (Liu et al. 2008; Serrato-Valenti et al. 2000). Various studies reported that SWCNTs in different concentrations can increase the germination rates in different plants like 10 mg L^{-1} SWCNTs for pepper (*Capsicum annuum*) and 30 mg L^{-1} of for salvia (*Salvia macrosiphon*) and tall fescue (*Festuca arundinacea*) (Pourkhaloee et al. 2011). Nanoparticles are also provided as nanofertilizers which are nanosize plant growth enhancers which supply one or more nutrients to the plants or facilitate the performance of conventional fertilizers. The nanofertilizers release nutrients on demand while preventing their premature conversion into nonabsorbable chemical/gaseous forms. This is achieved by preventing the interaction of nutrients with soil, water, and microorganisms.

9.3.3 Effect of NPs in Photosynthesis

Photosynthesis is a key process for plants on earth that changes light energy to chemical energy. Of the total radiations that fall on the earth, only small amount can be utilized by the plants in photosynthesis. Plants convert only 2–4% of the available energy in radiation in plant growth (Kirschbaum 2011). Different approaches of nanotechnology are applied in order to increase the efficacy of the plants. In the field of nano-biotechnology, researchers want to develop plants with better photosynthetic efficiency and biochemical sensing. Nanotubes (Nanobionics) are being used to increase the efficiency of photosynthesis and electron transport by manyfolds. The isolated chloroplast showed higher photosynthetic activity and electron transport rates than that of controls by single-walled carbon nanotubes (SWCNTs) (Giraldo et al. 2014). There are some nanoparticles which affect the photosynthetic properties directly. For example, the ability of mesoporous silica compound (SBA) to bind with photosystem II (PSII) suggests that PSII-SBA conjugate might have properties to develop photosensors and artificial photosynthetic system (Noji et al. 2011). Mesoporous silica is a mesoporous form of silica and a recent development in the field of nanotechnology. Other NPs enhance the activity of enzymes directly involved in photosynthesis. For example, SiO_2 NPs improve photosynthetic rate by improving the activity of carbonic anhydrase and synthesis of photosynthetic pigments (Siddiqui et al. 2014). Carbonic anhydrase supplies CO_2 to the Rubisco, which may improve photosynthesis (Siddiqui et al. 2012). Nanoparticles have a photocatalyzed characteristic, and some of the NPs improve the photosynthesis by acting as photocatalyst like nano-anatase TiO_2. Nano-anatase TiO_2 acts by several ways like by enhancing light absorbance, by increasing the transformation from light energy to chemical energy, or by inducing carbon dioxide assimilation. It has been found that nano-anatase TiO_2 enhances photosynthesis by activating Rubisco (complex of Rubisco and Rubisco activase) that promotes Rubisco carboxylation, thereby increasing growth of plants (Gao et al. 2006; Linglan et al. 2008). Nanobionics approach to engineered plants would enable new and advanced functional properties in photosynthetic organelles. Plant nanobionics is a field of bioengineering that alters or amplifies the functioning of tissues or organelle like chloroplast by simply inserting nanoparticles into the cells and chloroplasts of living plants. The long-term goal of the nanobionics is to create a wide array of wild-type plants capable of imaging objects in their environment, self-powering themselves as light sources and infrared communication devices, and also functioning as self-powered groundwater sensors (Ghorbanpour and Fahimirad 2017). TiO_2NPs protect chloroplast from aging for long-time illumination (Hong et al. 2005; Yang et al. 2006). The exogenous application of TiO_2NPs improves net photosynthetic rate, conductance to water, and transpiration rate in plants (Qi et al. 2013). According to Lei et al. (2007), nano-anatase promoted strongly whole-chain electron transport, photoreduction activity of photosystem II, and O_2-evolving and photophosphorylation activity of chlorophyll under both visible and ultraviolet light.

Table 9.2 Pesticidal effect against of different nanoparticles

Nanoparticle	Size (nm)	Plant	Pesticidal effect against	Reference
SiO_2	12	*Lactuca sativa*, *Oryza sativa*	*Sitophilus oryzae*	Shah and Belozerova (2009), Tan et al. 2012, Debnath et al. (2011)
Au	24	*Arabidopsis thaliana*, *Brassica juncea*, *Cucumis sativus*, *Lactuca sativa*	*Aspergillus flavus*, *Aspergillus niger*, *Puccinia gramini*, *E. coli*, *Staphylococcus aureus*	Jayaseelan et al. (2013), Smitha and Gopchandran (2013), Kumar et al. (2013), Arora et al. (2012), Barrena et al. (2009)
Ag	25	*Triticum aestivum*, *Brassica juncea*	*Rhipicephalus (Boophilus) microplus*, *Hippobosca maculatas*	Sharma et al. (2012), Santhoshkumar et al. (2012)
Cu	20–30	*Lactuca sativa*, *Vicia sativa*, *Helianthus annuus*	*Alternaria alternata*, *Aspergillus flavus*, *Fusarium solani*	Shah and Belozerova (2009)
CuO	25	*Triticum aestivum*	*Pythium* sp.	Zabrieski et al. (2015)
Fe_2O_3	10–50	*Arachis hypogaea*, *Triticum aestivum*	*Alternaria*, *Bipolaris*, *Fusarium* sp.	Rui et al. (2016), Khizhnyak et al. (2015)
TiO_2	160–220	*Spinacia oleracea*	*Rhipicephalus (Boophilus) microplus* (larve and adult)	Zheng et al. (2005), Hong et al. (2005)
P (hydroxyapatite)	10–40	*Glycine max*	*Aspergillus niger*	Liu et al. (2015).
$CuSO_4$	150	*Solanum lycopersicon* Mill	*Alternaria solani*, *Fusarium oxysporum*	Saharan et al. (2015)

9.3.4 Utilization of NPs in Disease Management

Due to the great variation in physiochemical properties and ultrasmall size of nanoparticles from their macroform, they are being used as phytopathogens, and application of nanotechnology in plant pathology is a novel approach. NPs possess a great potential for protecting food and agriculture products from bacteria, fungi, and virus (Table 9.2). Widespread bacterial and fungal pathogens spoil vegetables. The most common bacterial agents which attack most vegetables are *Erwinia carotovora*, *Pseudomonas* spp., *Corynebacterium*, and *Xanthomonas campestris*. Fungal pathogens causing spoilage of vegetables are species belonging to genera *Alternaria*, *Aspergillus*, *Cladosporium*, *Colletotrichum*, *Phomopsis*, *Fusarium*, *Penicillium*, *Phoma*, *Phytophthora*, *Pythium*, *Rhizopus* spp., *Botrytis cinerea*, *Ceratocystis fimbriata*, *Rhizoctonia solani*, *Sclerotinia sclerotiorum*, and some mildews. Some of these organisms are host specific, whereas others affect a wide variety of vegetables causing huge economic losses. Silver (Ag) ions cripple the enzyme in fungi and bacteria which metabolize oxygen to sustain life which leads to suffocation in fungi and bacteria, resulting in death (Alvarez-Puebla et al. 2004). Application of NPs along with the already existing protocols helps in improving plant protection (Abd-Elsalam et al. 2013; Kah et al. 2013; Li et al. 2007; Abd-Elsalam and Prasad 2018). Nanoparticles as nanopesticides also offer large specific surface area and hence increased affinity to the target (Jianhui et al. 2005). They involve either very small particles of pesticidal active ingredients or other small engineered structures with useful pesticidal properties (Bergeson 2010a). Nanopesticides can increase the dispersion and wettability of agricultural formulations (i.e., reduction in organic solvent runoff) and unwanted pesticide movement (Bergeson 2010b; Bhattacharyya et al. 2016). Several studies have shown that metal NPs are highly effective against plant pathogens, insects, and pests due to their smaller size and high reactivity, which may affect the activity of microorganisms (Kim et al. 1998). Silver as such don't possess antimicrobial properties, but NPs of silver act as antimicrobial agents. Silver nanoparticles show synergistic activity when combined with fluconazole disks and ketoconazole disks against *Phoma glomerata*, *Trichoderma* sp., *Aspergillus flavus*, *A. niger*, *A. tamarii*, *A. versicolor*, *Macrophomina phaseolina*, and *Penicillium* sp. (Jogee et al. 2017; Gajbhiye et al. 2009). Ag NPs show activity against pathogenic molds and yeasts such as *Aspergillus brasiliensis*, *Candida albicans*, *C. krusei*, *C. tropicalis*, and *C. glabrata* (Bryaskova et al. 2011)

9.4 Toxicity of Nanoparticles

There are both direct and indirect effects of nanoparticles on organisms (Fig. 9.2). Direct effects mainly are dependent on chemical composition and surface reactivity. NPs which have more surface area per mass are more biologically reactive when compared to large-sized particles of the same chemical composition (Oberdorster et al. 2005). This reactivity of NPs has impact on photosynthetic or respiratory processes; besides they might cause catalysis of redox reactions upon contact with organic molecules (Zhang 2003). Some of the NPs like fullerenes have photoinduced electron transfer capacity and thus can impact photosynthesis (Imahori et al. 2003). NPs are also known to show size-dependent toxicity, e.g., effects of alumina (Al_2O_3). NPs on root growth have been shown to be related to their size rather than their chemical composition (Yang and Watts 2005). Toxicity of TiO_2NPs to the green algae *Desmodesmus subspicatus* has been found to be dependent on the NPs' specific surface area, with the smallest particles showing more toxicity, whereas the larger ones caused less toxicity (Hund-Rinke and Simon 2006). Zn and ZnO NPs also show size-dependent toxicity by affecting growth in radish, rape, and ryegrass (Lin and Xing 2007). NPs act as physical barriers, release toxic ions (metal engineered NPs), produce of ROS, and may serve as pollutant carriers thus acting indirectly as toxins. For example, the accumulation of NPs on the surface of photosynthetic organisms may inhibit photosynthetic activity because of shading

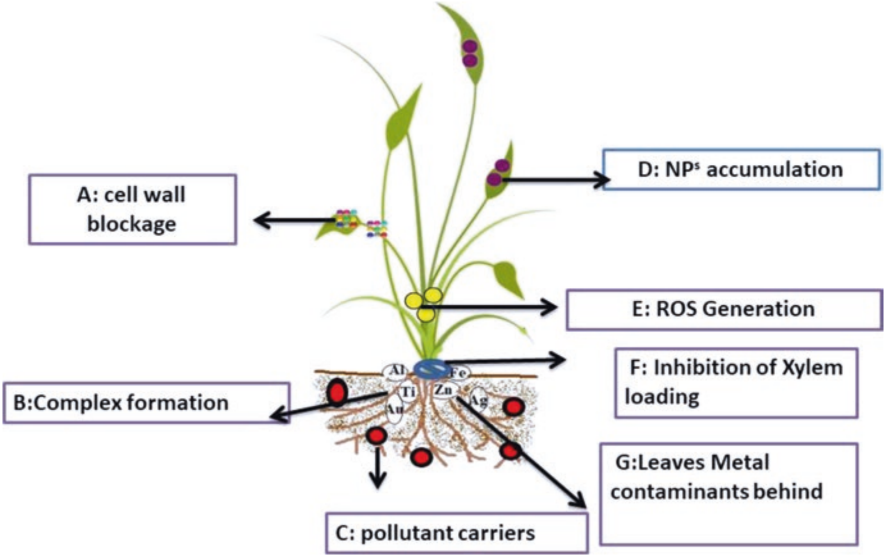

Fig. 9.2 Nanoparticle toxicity in plants. (A) Nanoparticles can cause cell wall blockage. (B) Macronutrients form complex with nanoparticles. (C) Nanoparticles serve as pollutant carriers, i.e., they can bind with heavy metals which are toxic to plants. (D) NPs accumulate on photosynthetic parts which results stomatal closure and halt transpiration and photosynthesis. (E) NPs are responsible for generation of Reactive Oxygen Species (ROS). (F) NPs can lead to inhibition of xylem loading and hence block the movement of water and nutrients. (G) NPs leave metal contaminants behind

effects, i.e., reduced light availability, acting indirectly as physical barrier. As a function of the tendency to aggregate and combine with other organic materials, NPs get adsorbed to algal cells (Chen and Elimele 2007). The fertilization of *Fucus serratus*, a marine seaweed, gets affected by aggregates of carbon black which gets bound to sperm cells (Fernandes et al. 2007). Similarly, NPs get adsorbed to the cell wall and thereby block the nutrient uptake and thus affect the growth and development.

9.5 Conclusion and Future Prospects

This chapter has focused on specific applications of nanoparticles in agriculture such as crop production and protection. Due to the incredible properties of nanoparticles like shape, size, surface features, dosage, etc., they possess the potential of converting poorly soluble, poorly absorbed, and labile biologically active substance into convenient deliverable substances. Nanoparticles can aid in plant growth and development and effective plant protection with reduced negative environmental impact. This chapter discusses the toxic effects of nanoparticles on plants with concerns regarding their use which are in favor of one process in plant while as might be adversely affecting other processes. At present, there is no clarity about the final fate of those nanoparticles that miss the targets and seep into fields. The fact that nanoparticles cannot be fully removed from human-consumed agricultural products poses another concern in using nanoparticles. All these issues must be studied for every individual type of nanoparticles before their introduction for real agricultural use.

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Chapter 10
Nanopesticide: Future Application of Nanomaterials in Plant Protection

Setyowati Retno Djiwanti and Suresh Kaushik

Contents

S. R. Djiwanti (✉)
Indonesian Agency for Agricultural Research and Development (IAARD), Indonesian Spice and Medicinal Crop Research Institute (ISMECRI), Plant Protection Division, West Java, Indonesia

S. Kaushik
Soil Science and Agricultural Chemistry, Indian Agricultural Research Institute, New Delhi, India

R. Prasad (ed.), *Plant Nanobionics*, Nanotechnology in the Life Sciences,
https://doi.org/10.1007/978-3-030-16379-2_10

10.1 Introduction

Pests and disease often limit agricultural production and have significant impact on farmers' incomes. The loss can occur on the crops in the field and in the storage. Farmers mostly use synthetic pesticides to manage pests to maximize crop yields and/or manage stored-product insect pests and disease, posing potential risks for workers, consumers, and the environments. It has been estimated that about 2.5 million tons of pesticides are used on crops each year and the worldwide damage caused by pesticides reaches $100 billion annually (Mohan et al. 2011). Furthermore, many of the chemical nematicides have been banned (91/414/EEC) or are under evaluation (20 09/1107/EU) by strict legislations in European Union countries (Ntalli et al. 2011).

For the above reasons, there is a need to search for cheaper, nonpersistent, and less toxic alternative control measures on crop pest insects and disease pathogens. The essential oils (EOs) extracted from plants are suitable as they are economically reasonable and have high activity in certain cases, and are also biodegradable (Silva et al. 2008; Sukumar et al. 1991). And also, a new approach by modern technology that plays an important and effective role in plant pests and disease control to avoid chemical pesticide hazards is nanotechnology. Nanotechnology has emerged as a promising area for innovative products, including pesticides. Nanotechnology offers great promise on the development of new formulations called nanoformulation, especially with nanoparticle application as an alternative to pesticides or assistant factor in preparation of pesticides (Martinelli et al. 2014; Abdellatif et al. 2016), as new formulations are able to improve the effectiveness and stability of botanical insecticides (Gogos et al. 2012; Scott and Chen 2012; Ghormade et al. 2011; Perlatti et al. 2013) and offer the ability to release the active compound to the target organism and then provide controlled release of the molecules at the site of action (Duran and Marcato 2013; Gogos et al. 2012; Perlatti et al. 2013; Prasad et al. 2019).

This chapter summarized the recent approach of nanotechnology in plant pest and disease management through developing nanopesticide and controlled release formulation of pesticides, and their strategic field application in minimizing the environmental impact. This review focuses on the enabling contribution of (1) nanomaterials to the use of metal as a pesticide active ingredient; (2) nanoemulsions to the use of EOs as natural pesticide agents, specifically addressing the formulation of stable EO nanoemulsions; and (3) small engineered structure as controlled release agent of agrochemical pesticidal properties and bioactive agent.

10.2 Developing Nanopesticide

10.2.1 Definition and Concept of Nanomaterials in Developing Nanopesticide

A nanomaterial is one millionth of a millimeter (mm) of materials that is engineered through nanotechnology manufacturing system. The term nanotechnology was described first by Professor Norio Taniguchi of Tokyo Science University in 1974 to illustrate precision manufacturing of materials at the nanometer level with the size of 1–100 nanometers (nm) (Taniguchi 1974). These materials display different properties from bulk materials due to their size. Nanomaterials show novel surface chemistry properties, physical strength, and distinct thermal, biological, electrical conductance, magnetism, and optical properties/effects associated with their atomic strength and are useful to enhance sensitivity, reduce response times, and improve detection limits and can be used in multiplexed systems (Johnston 2010; Merkt 2008). The nanoparticles (NPs) have a high surface to volume ratio that increases their reactivity and possible biochemical activity (Dubchak et al. 2010). Nanoparticles are of different shapes and many times smaller than bacterial cells. The particle size is even smaller than a virus particle like tomato mozaik virus (300 nm length and 10–18 nm diameter). Over many decades, nanotechnology and nanomaterials have been used as conductors and semiconductors, medical devices, sensors, coatings, catalytic agents, and also as pesticides (Bhattacharyya et al. 2010). Nanotechnology and nanomaterials are developing pesticides through nanoformulation technique.

10.2.2 Pesticide Nanoformulation

According to Athanassiou et al. (2018), nanoformulations are like other common pesticide formulations, they aid in increasing the apparent solubility of a poorly soluble active ingredient or in releasing the active ingredient in a slow or targeted manner, thus protecting the active ingredient against premature degradation. Pesticides developed from nanoformulation technique are called nanopesticides. Nanopesticides are prepared either by very small particles of pesticidal active ingredients or some other nanostructured molecules with pesticidal properties. Researchers have developed different types of nanopesticides like nanocapsulated formulations, nanoemulsion, nanogel, nanospheres, and metal and metal oxide nanoparticles (Kah and Hofmann 2014).

Merkt (2008) found that targeted nanoparticles often exhibit novel characteristics like extraordinary strength and more chemical reactivity and possess a high electrical conductivity. Nanomaterials used for formulating nanopesticides have desired properties such as biodegradability, solubility, permeability, and thermal stability (Bouwmeester et al. 2009). Targeted nanoparticles for pesticidal active ingredients often show a broad spectrum of activity against plant pest and disease pathogenic. Metal and plant essential oils/plant oils exhibit such broad-spectrum characteristics. Other pesticidal active ingredients targeted by nanoformulation recently being developed as nanopesticides are agrochemical pesticides and biopesticide organisms.

The applications of nanoemulsions in nanopesticide formulation and botanical pesticide formulation using plant essential oil for delivery of antimicrobials active/bioactive components have gained interest recently due to an extremely small droplet diameter in the range of 20–200 nm, high physical stability, high bioavailability, and optical transparency compared with other conventional emulsions (Solans et al. 2005; McClements 2012). According to Shafiq-un-Nabi et al. (2007) and Sakeena

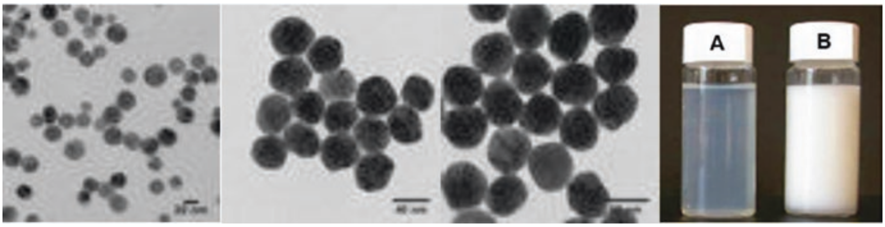

Fig. 10.1 Metal nanoparticles and essential oil nanoemulsion. Silver nanoparticles (left to right: 100 nm, 250 nm, 400 nm). (Oldenburg and Saunders 2018): (A) nanoemulsion, (B) macroemulsion. (Shafiq-un-Nabi et al. 2007)

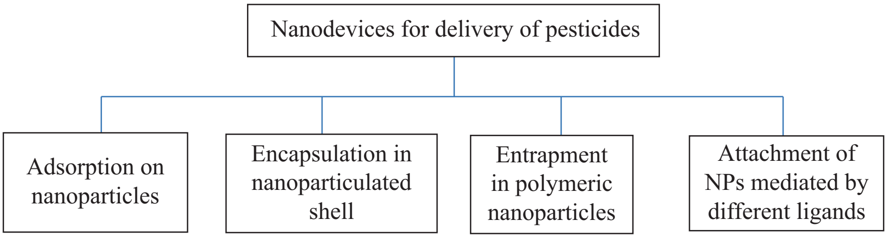

Fig. 10.2 Different nanodevices for delivery of pesticide. (Kaushik and Djiwanti 2017)

et al. (2011), nanoemulsions are clear, transparent, isotropic, and thermodynamically stable solutions of oils, surfactant, and cosurfactant with droplet size of less than 100 nm (Fig. 10.1). The surfactants are chosen from "Generally Regarded as Safe" category from FDA for use in food and pharmaceutical preparations. Other colloidal system devices, i.e., lipid carriers, including liposomes, solid lipid nanoparticles, and nanostructured lipid particles, may be used in essential oil nanoencapsulation. Nanoemulsions (NEs) were also developed to improve solubility, spreadability (better dispersion), and wettability, found helpful in less degradation and volatilization of active ingredient, and improve their bioavailability for a long time period, which implied to improve efficiency and reduction of effective pesticide concentration (Guillette and Iguchi 2012; Bergeson 2010a; Anton et al. 2008; Mason et al. 2006).

Nanopesticide formulations constitute the process and delivery methods of active ingredient into the nanomatrix. The process of absorption, attachment, encapsulation, or entrapment of the active ingredient into the nanomatrix occurs in nanopesticide formulations (Fig. 10.2). Nanoemulsions, nanoencapsulates, nanocontainers, and nanocages are some of the nanopesticide delivery methods which have been widely applied in nanoformulations (Bergeson 2010b).

Controlled release technology has emerged as an alternative approach with the promise to solve the problems accompanying the use of some agrochemicals, while avoiding possible side effects with others (Han et al. 2009). The ability to delay or control delivery of pesticides to the target organisms is achieved by these nanopesticide delivery methods (Singh et al. 2015). Nanoencapsulation of agrochemicals provides effective concentration of the active ingredient with high stability and site-targeted smart delivery with reduced collateral damage and less ecotoxicity (Nair and Kumar 2012). Nanoencapsulation and entrapment of agrochemicals pesticides and other active substances by using polymers, dendrimers, surface ionic attachments, and other mechanisms may be used in controlled and slow release of agrochemicals, which allows the slow uptake of active ingredients and in turn reduces the amount of agrochemical application by minimizing the input and waste (Chowdappa and Gowda 2013).

10.3 Metal-based Nanopesticide

Copper (Cu), mercury (Hg), zinc (Zn), chromium (Cr), nickel (Ni), cobalt (Co), tin (Sn), iron (Fe), titanium (Ti), magnesium (Mg), gold (Au), and silver (Ag) are the metals used as base for inorganic and organic fungicides. Among them, significant research and application have been done on silver and gold, against several plant pests and disease pathogens.

In the last decade, among nanostructures which possess and display variation in properties as compared to bulk metal, and due to their unique photocatalytic photothermal, optical, and electrical properties and stability, the silver and gold nanoparticles have gained much significance in research. Ultrasmall size and very high reactivity nanomaterials will affect the activity of pests and pathogens. Pesticides in nanosize can include either nano-/very small particles of pesticidal active ingredients or other nano-/small engineered structures with useful pesticidal properties (Bergeson 2010b). Important steps in metal-based nanoformulation are synthesis of metal nanoparticles or nano-/small engineered structures, characterization of the metal nanoparticles/nanomaterials, and exploring their antimicrobial activity against pests and disease pathogens.

10.3.1 Metal Nanoparticle Synthesis

The synthesis deals with the conversion of the matter of the macrosize into the particles of the nanosize, 1–100 nm. Metal nanoparticles could be synthesized by chemical, physical, and biological methods. Biosynthesis of particles at nanoscale using microorganisms and plants (including algae) has become popular recently due to the increase of the chemical, physical, and biological properties created by these method practices, in addition to their use as reducing and stabilizing agents (Abdellatif et al. 2016; Jain and Kothari 2014; Ahmed et al. 2015; Sharma et al. 2017; Mandal et al. 2006; Mohanpuria et al. 2007; Prasad et al. 2016). Microorganisms play an important role in diminishing the toxic metals by reduction of metal ions. Fungi have a number of advantages for NP synthesis in relation to other microbes and plant material. The use of fungi in the synthesis of NPs is potentially important since they produce large quantities of enzymes and are simpler to handle in the laboratory (Mandal et al. 2006, Mohanpuria et al. 2007; Prasad 2016, 2017; Prasad et al. 2018; Abdel-Aziz et al. 2018). A number of fungi, i.e., *Alternaria alternata*, *Fusarium oxysporium*, and *Amylomyces rouxii*, were screened to generate silver nanoparticles (AgNPs) (Gajbhiye et al. 2009; Musarrat et al. 2010; Al-Askar et al. 2013). Thakur and Shirkot (2017) reviewed various bacteria that have been reported with the ability to synthesize silver and gold metal nanoparticles [*Bacillus licheniformis*, *Bacillus subtilis* (culture supernatant), *Bacillus cereus*, *Bacillus* sp., *Bacillus flexus*, *Morganella* sp., *Escherichia coli*, *Proteus mirabilis*, *Corynebacterium* sp., *Staphylococcus aureus*, actinomycetes (*Thermomonospora* sp.)]. Biogold nanoparticle syntheses by various biological organisms including bacteria are becoming popular as these overcome the disadvantages (Zhang et al. 2016). Highly stable AuNPs of different sizes and shapes can be synthesized using bacteria, fungi, actinomycetes, and yeast. Ahmed et al. (2015) reviewed a plant diversity to be utilized toward a rapid and single protocol to produce silver nanoparticles and described their antimicrobial activities. Gholami-Shabani et al. (2017) reviewed about 130 more plant species extracts that could be used to synthesize metals at nanoscale and described their schematic protocol. Some plant species from aromatic herbs and spices, fruits, and algal (*Turbinaria turbinate*, *Ulva lactuca*) and pesticidal source plants effectively synthesized metals at nanoscales (1–100 nm). Now bioiron nanoparticles synthesized by various biological organisms such as bacteria, fungi, viruses, algae, and higher plants are becoming popular as these overcome the disadvantages of various physical and chemical methods (Bansal et al. 2014). Bacteria with their ability to reduce various metals grab target Fe^{2+} ions from the environment and convert these into FeO by iron reductase enzyme.

Green and biosynthesis of metal nanoparticles methods offer an easy, inexpensive, environmentally friendly, and appropriate setup for large-scale nanoparticles such as silver NP production compared with conventional chemical methods of production, in spite of increasing the antipathogenic activity (Hassan et al. 2016; Shankar et al. 2003). Induced systemic resistance was derived from *F. oxysporum*-biosynthesized AgNPs, because Nep1-like proteins secreted from *F. oxysporum* trigger plant defense responses and cell death (Veit et al. 2001). Combining green silver nanoparticle (GSN) with algae such as *T. turbinata* that supplements the GSN nematicidal effect may increase its applicability. Additionally, the mechanism in the nematicidal action of GSN also permits improvement of GSN effectiveness by adding natural compounds (i.e., algae formulations) (Abdellatif et al. 2016).

10.3.2 Mode of Action

Different types of inorganic nanomaterials like copper (Cu), zinc (Zn), titanium (Ti), magnesium (Mg), iron (Fe), gold (Au), and silver (Ag), aluminum (Al), and metal oxide-based polymers zinc oxide (ZnO) and titanium dioxide (TiO_2) have been developed for pests and disease management. DNA-tagged nanogold was effective to control the armyworm, *Spodoptera litura* (Chakravarthy et al. 2012a,

Table 10.1 Antimicrobial effect of metal nanoparticles on various plant pests, disease pathogens, and postharvest pests reported by researchers

Metal/metal oxide nanoparticles	Reducing and stabilizing agent	Efficacious pests and pathogens	References
Biogenic iron nanoformulations (70 nm)	Bacterial isolate (*Stenotrophomonas maltophilia* KBS 2.4) supernatant solution	*Meloidogyne incognita* in Okra	Sharma et al. (2017)
Biosilver nanoparticles	Fungus *Alternaria alternata*-mediated synthesis	*Phoma glomerata* of fungal pathogen of Ascochyta blight disease on pea	Gajbhiye et al. (2009)
Biosilver nanoparticles	Fungus *Fusarium oxysporium*	Antifungal activity (*Alternia alternata*, *Fusarium oxysporum*, and *Aspergillus flavus*)	Al-Askar et al. (2013)
Biosilver nanoparticles	Water extracts of the fungus *Amylomyces rouxii* strain KSU-09	Soil-borne fungus *Fusarium oxysporum*	Musarrat et al. (2010)
AgNPs	*Fusarium oxysporium* bioproduction	The antibacterial activity (*Erwinia carotovora*, *E. amylovora*, *P. wasabiae* Hf569027, *P. carotovorum atrosepticum* 1007, *D. chrysanthemi* Dsm4610, *P. wasabiae* 33, and *D. dadantii*)[54]	Al-Askar et al. (2013)
AgNPs (10–20 nm)	Aqueous leaf extract preparation biosynthesis-AgNPs	Sunhemp rosette virus (SHRV), on bean	Jain and Kothari (2014)
Green silver nanoparticles (8–19 nm, spherical shape)	Algal *Turbinaria turbinata* synthesized AgNP solution	*Meloidogyne javanica* in egg plant	Abdellatif et al. (2016)
Green silver nanoparticles	*Aristolochia indica* plant extract	Crop pest *Helicoverpa armigera*	Siva and Kumar (2015)
Ag and Zn nanoparticles	Chemical synthesis	*Aphis nerii* Boyer De Fonscolombe (Hemiptera: Aphididae)	Rouhani et al. (2012)
Al_2O_3 and TiO_2	Chemical synthesis	*Sitophilus oryzae* (store pest)	Sabbour (2012)
TiO_2	Photocatalysis	Bacterial pathogen *Xanthomonas perforans*	Paret et al. (2013)
AgNPs	Chemical synthesis	*Spodoptera litura*	Yasur and Usha Rani (2015)
Gold NPs	DNA-tagged nanogold	*Spodoptera litura* Fab. (Lepidoptera: Noctuidae)	Chakravarthy et al. (2012a, b)
Nanoparticles CdS, nano-Ag and nano-TiO_2 against	Chemical synthesis	*Spodoptera litura* (Fabricius) (Lepidoptera: Noctuidae)	Chakravarthy et al. (2012a, b)

(continued)

Table 10.1 (continued)

Metal/metal oxide nanoparticles	Reducing and stabilizing agent	Efficacious pests and pathogens	References
AgNPs	*Euphorbia prostrata*	Postharvest pest *Sitophilus oryzae*	Zahir et al. (2012)
	Avivennia marina	*Sitophilus oryzae*	Sankar and Abideen (2015)
Zinc oxide nanoparticles (ZnO NPs) (70 ± 15 nm)		Postharvest pathogenic fungi, *Botrytis cinerea*, and *Penicillium expansum*	Bryaskova et al. (2011)
Cu NPs		Four-order higher activity against bacterial blight *Xanthomonas axonopodis* pv. punicae on pomegranate at 10,000 times less concentration of recommended Cu	Mondal and Mani (2012)
$CuSo_4$ and $Na_2B_4O_7$ NPs		Rust disease of field peas	Singh et al. (2013)

2012b) (Table 10.1). An active preparation of FeNPs is well-known to possess nematicidal properties and thus used in fields of agriculture and horticulture (Sharma et al. 2017). The laboratory assays attested significant nematicidal effect of FeNP and the field evaluation demonstrated its benefits for mitigating damage caused by root-knot nematode. Biologically synthesized iron nanoparticles by a reaction of 2 mM $FeSO_4$ with 50 ml of selected bacterial isolate (*Stenotrophomonas maltophilia* KBS 2.4) supernatant solution were used as a potential nematicide in in vitro (>99% nematodes became inactive after 10 hrs) and in vivo experiments (88% of nematodes and root-knot numbers were reduced after 30–40 days of exposures) (Sharma et al. 2017).

However, silver nanoparticles have proved to be most effective as they exhibit potent antimicrobial efficacy against fungi, bacteria, virus, and parasitic nematodes. Silver nanoparticles are nanomaterials being applied as active ingredients in controlling plant pathogenic bacteria and fungi (Al-Askar et al. 2013; Musarrat et al. 2010; Gajbhiye et al. 2009) and their toxicity due to their induction of oxidative stress in the cells of targeted nematodes (Lim et al. 2012), due to affection in the function of membrane-bound enzymes in the respiratory chain to inhibit the oxygen metabolism leading to suffocation and subsequent cell death of bacteria and fungi (Puebla et al. 2004), and due to inhabiting replication of viral nucleic acid (Jain and Kothari 2014); AgNP has a microbial and nematicidal activity which may provide an alternative to high-risk chemical pesticides.

Review from some research results (Table 10.1) revealed that direct application of silver nanoparticles significantly suppressed the plant pests and disease pathogens such as fungi (i.e., *Alternia alternata*, *Fusarium oxysporum*, *Aspergillus fla-*

vus, *Phoma glomerata*), bacteria (i.e., *Erwinia carotovora*, *E. amylovora*, *P. wasabiae* Hf569027, *P. carotovorum atrosepticum* 1007, *D. chrysanthemi* Dsm4610, *P. wasabiae* 33, and *D. dadantii*), viruses (Sunhemp rosette virus (SHRV)), parasitic nematodes (i.e., *Meloidogyne incognita*, *M. javanica*), and crop pests (i.e., *Spodoptera litura*), including postharvest/stored-product pests (i.e., *Sitophilus oryzae*). This review indicated that silver nanoparticles have potential prospects and application in the management of plant pests and diseases.

Metal oxide NPs (Al_2O_3, TiO_2, ZnO) and $Na_2B_4O_7$ NPs showed insecticidal bioactivity and potential to use in managing stored-product pest (*Sitophilus oryzae*), crop pest (*Spodoptera litura*), bacterial pathogen *Xanthomonas perforans*, postharvest pathogenic fungi (*Botrytis cinerea*, *Penicillium expansum*), and rust disease of field peas (Table 10.1).

Nanoparticles possess distinct physical, biological, and chemical properties associated with their atomic strength (Merkt 2008). Due to their ultra submicroscopic size, nanoparticles gain the high degree of reactivity and sensitivity and thus have potential to prove very useful in controlling the pests and pathogens, as chemical and physical properties of nanoparticles vary greatly as compared to larger form.

Researchers have discussed and reviewed many modes of actions, but the exact mechanism by which silver NP control and prevent pests and disease pathogens is partially understood. Antimicrobial mechanisms were mostly studied and observed on bacterial pathogens. Basically, mode of toxicity of AgNPs is independent of silver ions but toxicity could be derived from a combination of silver nanoparticles and silver ions that are released during application of silver nanoparticles (Navarro et al. 2008; Asharani et al. 2008a). Small sizes of silver nanoparticles have the ability to pass through the membrane to interact with internal structures and become lodged within the membrane (Asharani et al. 2008b). Silver nanoparticles deposited in the membrane can affect the regulation of solute movements, exchange of proteins, as well as cell recognition. However, the mode of action of AgNPs against microbial pathogens is not very specific, and different mechanisms involve disrupting multiple cellular mechanisms, e.g., plasma membrane permeability, ATP synthesis, and response to oxidative stress in both eukaryotic and prokaryotic cells (Roh et al. 2009; Ahamed et al. 2010; Lim et al. 2012; Lara et al. 2011; Meyer et al. 2010; Sondi and Salopek-Sondi 2004; Morones et al. 2005; Lok et al. 2006; Choi and Hu 2008; Aziz et al. 2015, 2016). Subsequently, it leads to inhibition of respiration and other metabolic reactions as well as morphological and physical damages (Bragg and Rainnie 1974; Thurman and Gerba 1989). It was revealed that silver ions after penetrating the cell intercalate with bacterial DNA, consequently, inhibiting the proliferation and replication of the pathogen and ultimately killing the cell (Woo et al. 2009). Morones et al. (2005) observed that silver nanoparticles have impacts on the defense system of fungal pathogens in AgNP-treated cells.

The antimicrobial activity and property of the nanoparticle depend on the forms/shapes, size, and concentration of the nanoparticles. The silver nanoparticles with different shapes have different effects on bacterial cell (Rai et al. 2009). Truncated triangular nanoparticles reveal bacterial inhibition with silver content of 1.0 (one) µg, while spherical nanoparticles are needed with silver content of 12.5 µg, and the rod-shaped particles are needed with silver content in the range of 50–100 µg. Furthermore, the antimicrobial property of the silver nanoparticles is size and concentration dependent (Xia et al. 2016; Morones et al. 2005; Gavanji et al. 2012; Kim et al. 2012; Papp et al. 2010). Nanometer-sized silver possesses different properties due to morphological, structural, and physiological changes (Nel et al. 2003). The smaller silver nanoparticles have more significant antibacterial activity and more ability in DNA change. Silver ions release rate is a function of silver nanoparticle size (Oldenburg 2017). Generally, inhibition of plant pathogens is directly proportional to the concentration of AgNPs. Armstrong et al. (2013) reported that silver nanoparticles, like almost all nanoparticles, are potentially toxic beyond a certain concentration because the survival of the organism is compromised due to scores of pathophysiological abnormalities past that concentration. AgNP effect may be subtle and chronic at low concentrations applied in the field (Taha 2016). Toxicity of sub-lethal doses of AgNP to parasitic nematodes *M. incognita* could result in reproduction inhibition with 20, 40, and 50 ppm/ml of AgNP (Meyer et al. 2010; Taha 2016). However, in high concentration, nanosilver effect may cause toxicity to beneficial entomopathogenic nematodes, *Heterorhabditis indica*, *Steinernema arenarium* and *Steinernema abbasi* (Taha and Abo-Shady 2016), and *Caenorhabditis elegans* (Meyer et al. 2010; Lim et al. 2012). Syu et al. (2014) investigated the effects of the size and shape of AgNPs on growth, antimicrobial activity, and gene expression of *Arabidopsis* plant. Decahedral AgNPs (45 nm) exhibited the highest stimulation of root growth, while spherical ones (8 nm) did not stimulate root growth but induced uppermost levels of anthocyanin accumulation in plants. On the other hand, the highest antimicrobial activity was observed with triangular (47 nm) and spherical AgNPs. Moreover, AgNPs were found to activate *Arabidopsis* gene expression involved in cell proliferation, metabolism, and hormone signaling pathways. The toxic impact of AgNPs on plants, similarly to the effects of other metal NPs, is connected with their chemical composition enabling the release of toxic Ag^+ ions as well as with stress caused by some specific properties of these NPs, such as surface, size, and shape (Masarovičová and Kráľová 2013; Masarovičová et al. 2014).

10.3.3 Metal Nanoformulation

Silver-based organic and inorganic composites were developed for application against plant pest and disease pathogens (Table 10.2). Formulation stability is an important parameter for the biosafety of nanomaterials (Liu et al. 2008b). Some polymer and biopolymer stabilizers have been used in metal nanoformulation as stabilizer compounds. Hassan et al. (2016) used polyvinylpyrrolidone (PVP) as a stabilizer compound of silver nanoparticles against nematode *Meloidogyne incognita* on tomato. Cromwell et al. (2014) and Taha and Abo-Shady (2016) used starch

Table 10.2 Metal-based nanopesticide, their nanoformulation pesticidal, and antimicrobial activity

Metal and metal oxide nanoparticles	Nanoformulation method	Targeted pests and disease pathogens efficacious	References
Silver nanoparticles	Nanosized silica-silver	Bacterial pathogen *Pseudomonas syringae* and *Xanthomonas compestris* pv. *vesicatoria*	Park et al. (2006)
Silver nanoparticles (7–25 nm)	AgNP compound in colloidal suspension (7–25 nm particle size, 10,000 μL/mL silver content, pure water solvent)	Plant-pathogenic fungi on PDA (*Alternaria alternata*, *A. brassicicola*, *A. solani*, *Botrytis cinerea*, *Cladosporium cucumerinum*, *Corynespora cassiicola*, *Cylindrocarpon destructans*, *Didymella bryoniae*, *Fusarium oxysporum* f.sp. *cucumerinum*, *F. o*. f.sp. *lycopersici*, *F. solani*, *Fusarium* sp., *Glomerella cingulata*, *Monosporascus cannonballus*, *Pythium aphanidermatum*, *P. spinosum*, *Stemphylium lycopersici*)	Kim et al. (2012)
AgNPs (10–15 nm)	Chitosan–AgNp composite (size 10–15 nm)	Complete inhibition of conidial germination in *Colletotrichum gloeosporioides*	Chowdappa and Gowda (2013)
Silver nanoparticles (5 nm)	DNA-directed silver nanoparticles on graphene oxide (Ag@dsDNA@GO) composite	Xanthomonas *perforans* of tomato	Ocsoy et al. (2013)
Silver nanoparticles	AgNP was synthesized by a redox reaction of silver nitrate with sodium borohydride ($NaBH_4$) as a reducing agent using 0.2% starch (polymeric carbohydrate) as a stabilizer	In vitro study, J2 of *M. incognita* and *M. graminis* on turfgrass, reduced gall formation in the roots in 2 years without phytotoxicity	Cromwell et al. (2014)
Silver nanoparticles	Starch-stabilized Ag nanoparticles	*M. incognita*	Taha and Abo-Shady (2016)
Silver nanoparticles	Silver nanoparticles–PVP (polyvinylpyrrolidone) as stabilizer compound	*Meloidogyne incognita* on tomato	Hassan et al. (2016)
Ag+, Cu_2+, Zn_2+, Mn_2+,	Ag+, Cu_2+, Zn_2+, Mn_2+ loaded chitosan NPs	Antibacterial activity	Du et al. (2009)
Cu	Cu–chitosan NPs nanohydrogel	Antifungal pathogen *Fusarium graminearum*	Brunel et al. (2013)

(continued)

Table 10.2 (continued)

Metal and metal oxide nanoparticles	Nanoformulation method	Targeted pests and disease pathogens efficacious	References
Cu	Cu–chitosan NPs	Antifungal pathogen *Alternaria solani* and *Fusarium oxysporum*	Saharan et al. (2015)
Cu NPs	Soda-lime glass powder containing copper nanoparticle	Antimicrobial activity against Gram-positive, Gram-negative bacteria, yeast, and fungi	Esteban-Tejeda et al. (2009)
AgNP dust	AgNP dust stabilized with polyvinyl pyrrolidone	For control of castor semilooper, *Achaea janata* (L.) (Lepidoptera: Noctuidae), and the oriental leafworm moth, *Spodoptera litura* (F.) (Lepidoptera: Noctuidae) on *R. communis* leaves	Yasur and Usha Rani (2015)
Nanoalumina	Nanoalumina dust	Postharvest pests *Sitophilus oryzae* and *Rhyzopertha dominica*	Buteler et al. (2015)

as a stabilizer compound of silver nanoparticles against nematode *Meloidogyne* spp. Appropriate modification of chitosan nanomaterials by functionalizing them with metal compounds could significantly enhance their bioactivity toward plants through improvement of physical and chemical properties (Choudhary et al. 2017) (Table 10.2). Biopolymers such as starch, cellulose, alginate, chitin, and chitosan have been used for the development of new materials with environmental sustainability and desirable functionality (Babu et al. 2013).

Nanoform of copper (Cu) showed four order higher activity against bacterial blight on pomegranate at 10,000 times less concentration of recommended Cu (Mondal and Mani 2012). Titanium dioxide nanoparticles were also explored for bacterial spot disease of tomato and rose in pristine form or doped with zinc and silver (Paret et al. 2013). Alumina nanoparticles exhibited greater mortality against different postharvest pests (Buteler et al. 2015) (Table 10.2).

Other metal nanoformulations, such as Ag^{+}-, Cu^{2+}-, Zn^{2+}-, and Mn^{2+}- loaded chitosan nanoparticles, and Cu- and Zn-based chitosan NPs were found to possess broad-spectrum antimicrobial activity, act as plant defense booster, and enhance plant growth with regard to controlling plant diseases. Metals Cu and Zn have traditionally been used as components of agrochemicals. Cu and Zn, as components of nanoparticulate system, may reduce the risk of hazardous agrochemicals for crop improvement and protection. Due to high metal chelation ability of chitosan, metallic-based chitosan nanomaterials can be developed to fulfill antimicrobial action (antifungal activity and antibacterial activity (Saharan et al. 2013; Qi et al. 2004; Du et al. 2009; Ali et al. 2011), the deficiency of micronutrient/nanofertilizers (Corradini et al. 2010), and plant growth-promoting activity (Van et al. 2013; Saharan et al. 2016). As chitosan also has insecticidal properties (Sahab et al. 2015), metal-based chitosan NP composites will produce broad-spectrum microbial and insecticidal nanopesticides. Some researchers included Cu- and Zn-based chitosan NPs into agrochemical nanopesticides. However, as metals Cu, Zn, or Mn were not in the form of salts of metals, thus Cu- and Zn- or Ag- or Mn-based chitosan NPs may be included into metal-based nanopesticide.

Recently, considerable researches have been focused on various metal-based chitosan nanomaterials as potential antimicrobial agents. Nanochitosan acquired remarkable advantage over bulk chitosan due to large surface area and small size. Being nanosize of chitosan, it can easily interact with plant as well as microbial system that will lead to enhanced plant immune system, growth promotion, and antimicrobial activity (Van et al. 2013; Saharan and Pal 2016). More surface area and positively charged nanomaterials of Cu and Zn chitosan could interact easily to negatively charged cellular components of bacteria and fungi. This interaction provides an excellent antimicrobial activity. Cu-chitosan NPs exhibited higher antifungal activity compared to bulk chitosan, saponin, and $CuSO_4$ (Saharan et al. 2013). In another study, Cu-chitosan NPs are found to be effective against *Alternaria solani* and *Fusarium oxysporum* than the bulk chitosan and $CuSO_4$ (Saharan et al. 2015). Similarly, Zn-loaded chitosan NPs showed a wide spectrum of effective antimicrobial activities against various bacterial species including *E. coli*, *S. choleraesuis*, and *S. aureus*, which showed higher antibacterial activity than bulk chitosan, chitosan NPs, and Zn ions (Du et al. 2009). Similarly, for antifungal and antiviral activity, the negatively charged components of fungal and viral surfaces like protein and glycoprotein also interact with chitosan (Sudarshan et al. 1992). In general, Gram-negative bacteria were found to be more sensitive than Gram-positive bacteria.

It is observed that discharge of considerable amount of nanoparticles into environment due to increasing use of silver nanoparticles and widespread geographic distribution is increasing (Nam et al. 2014). Silver nanoparticle is now used in hydroponics systems and planter soils to eliminate unwanted microorganisms. As ultrasmall size nanoparticles have immense applications, the same characteristic is responsible for adverse effects on the environment, human beings, animals, and plants; thus some disadvantages and risks are involved in using nanoparticles (Khan and Rizvi 2014). All studies of toxicity on zebrafish and human cell indicated concern of potential risk (Nam et al. 2014; Verano-Braga et al. 2014; Ahamed et al. 2010; Johnston et al. 2010). Silver nanoparticle has been found to cause genotoxic, oxidative, inflammatory, cytotoxic consequences (Johnston et al. 2010). This finding indicated that production and field application of metal nanoparticles should be carried out with cautions and biosafety of metal nanoparticle-based pesticide is not yet accepted practically in plant protection area. It needs more research to evaluate the influence/impact of this new technology on all environmental components (Sharon et al. 2010). Several aspects of silver nanoparticles with relation to plants, viz., their half-life in soil, their toxicity effects on plants, and the optimum dosage for application in the field, need to be determined (Patel et al. 2014). However, to control the manufacturing and application of nanomaterials, several international programs, e.g., OECD (Organization for Economic Co-operation and Development), sponsorship program for the testing of manufactured nanomaterials to test nanoparticles, have been established (www.oecd.org/science/nanosafety/) (Nam et al. 2014)· Moreover, some eco-friendly, cheap technologies such as green and biosynthesis of nanoparticles and biomaterials for matrices in nanoformulation have been developed and should be supported in developing metal nanopesticide.

10.4 Essential Oil-based Nanopesticide

Phytochemicals extracted from different parts of plants such as alkaloids, flavonoids, essential oils, glycosides, limonoids, quassinoids, saponins, and phenolics become promising tools as fungicides, bactericides, and nematicides (Suruyavathana et al. 2010; Khalil 2014). Plant essential oils have been recognized as an important natural source of insecticide and pesticides and promising alternatives for chemical insecticides now (Isman 2006; Rajendran and Sriranjini 2008).

10.4.1 Plant Essential Oil

Essential oils (EOs) are a group of ethereal lipophilic compounds, extracted from herbs, spices, and aromatic plants such as thyme (thymol), oregano (carvacrol), and clove (eugenol), citronella grass (sitronellal dan geraniol), eucalyptus (eucalyptol), camphor (D-camphor, linalool, cineole), rosemary (1,8-cineole, camphor, β-myrcene, α-pinene, verbenone, borneol, camphene), and cinnamon (cinnamaldehyde) (Burt 2004). Essential oils contain large proportions of volatile terpenes and compounds such as terpenoids and phenolic compounds which have insecticidal, bactericidal, virucidal, fungicidal, antiparasitical, and nematicidal activities with the different mechanisms of action and other medicinal properties such as analgesic, sedative, anti-inflammatory, spasmolytic, and locally anaesthetic remedies (Elgengaihi et al. 2016; Fernandes et al. 2014; Lee et al. 2012; Chen et al. 2014; Bilia et al. 2014; Toure et al. 2007). These compounds involved in plants may act as repellents, attractants, hatching stimulants or inhibitors, as well as nematotoxicants (Chitwood 2002). Many plant essential oils show a broad spectrum of activity against plant pest insects, disease pathogens, and a range of stored-product pests and antivector activities and larvicidal properties (Mohan et al. 2011; Conti et al. 2010).

The exact mechanisms of antimicrobial activities of EOs are still not clear although several modes of actions have been proposed and studied (Lambert et al. 2001; Sikkema et al. 1994). A generalized model is related to the hydrophobic nature of EO components, which enables them to insert into the cell membrane, disturbing the structure and increasing its permeability and resulting in the leakage of cell contents such as ions, ATP, nucleic acids, and amino acids (Burt 2004).

Some essential oils such as clove oil, citronella grass oil, eucalyptus oil, camphor oil, and oregano oil showed fumigant activity and/or contact toxicity against post-harvest and/or crop pest and disease (pest insects, bacterial, fungal, viral pathogen, and parasitic nematodes) (Ho et al. 1994; Cimanga et al. 2002; Batish et al. 2006; Su et al. 2006; Liu et al. 2008a; Lee et al. 2012; Djiwanti and Supriadi 2012; Huang and Lakshman 2010; Wang et al. 2010; Prasad et al. 2010; Balfas and Mardiningsih 2016; Mariana and Noveriza 2013; Katooli et al. 2012; Patel and Jasrai 2015; Ravi et al. 2014; Laquale et al. 2018; Šegvic Klaric et al. 2007).

It has been reported that clove oil was successfully used as pesticide (Isman 2000; Jiang et al. 2012). Eugenol (4 allyl-2-methoxy phenol; $C_{10}H_{12}O_2$) is a major constituent of clove essential oil and is an organic phenol compound. In 1998, clove oil (CAS # 8000-34-8) as pesticide was registered under United States Environmental Protection Agency (USEPA). Also, clove oil is classified as a minimum-risk pesticide and is not subject to federal registration requirements because its active and inert ingredients are evidently safe for human use (USEPA 2011). All of these products have been approved for use in organic food production.

Phytochemicals like essential oils and secondary metabolites face problems of cost-effectiveness and stability (pesticidal activity). Essential oil from *Artemisia arborescens* L. faced the problem of instability during pesticidal activity against *Aphis gossipy* (citrus fruit pest), adult and young *Bemicia tabaci*, and *Lymantia dispar* (cork plant pest) (Lai et al. 2006). Neem oil has been reported to show antifeedant, repellent, insecticidal, grain protectant, and growth-inhibiting activities against these insects; because of having large droplet size, nonavailability of suitable spraying equipment at farmers' level, and phytotoxicity at higher doses, it did not show encouraging results for its commercial applications (Prakash and Rao 1997). EOs have poor water solubility and this is a technological problem for their application as pesticidal products. Also, the use of essential oils as fumigant agent in large scales encountered some problems such as low vapor pressure that could be solved using some formulations such as control released formulations (Rajendran and Sriranjini 2008).

Currently, there is a new trend in using the natural plant extracts as well as EOs as natural pesticides to control pests with nanoformulations, by encapsulation of bioactive compounds in aqueous solutions through the production of nanoemulsions (Duarte et al. 2015; Ebadollahi 2011).

10.4.2 Essential Oil Nanoformulation

The encapsulation of essentials oils using nanoemulsified systems has potential application in nanopesticide products for antimicrobial delivery systems providing control released manner. A variety of EOs delivery systems have been developed in two categories of nanocarriers, i.e., (1) polymeric nanoparticulate formulations, which resulted in significant improvement of the essential oil antimicrobial activity, and (2) lipid carriers, including liposomes, solid lipid nanoparticles, nanostructured lipid particles, and nanoemulsions (Bilia et al. 2014).

Nanoemulsions are colloidal nanodispersions of oil and water being thermodynamically stabilized by interfacial layer of surfactant/cosurfactant (Chen et al.

2006). EOs have to be associated or combined with surfactants in order to enhance the antimicrobial activities by increasing the solubility of EOs in the aqueous phase. Surfactants also prevent shear induced coalescence during emulsion process (Chen et al. 2006). Nanoemulsion consists of surfactant aggregates that are in the range of 1–100 nm. Nanoemulsions were characterized by droplet size, transmittance, and stability. In this nanotechnology, it is needed to develop nanoformulations with particle size ranging from 20 to 200 nm that improved insecticidal activity and emulsion stability (Hamdi et al. 2015).

Surfactants play a main role in lowering the surface tension between oil and water interfaces and are essential for stable droplet size. Most EO nanoemulsions are currently prepared with synthetic (nonionic) surfactants (Tween 80, Span® 80, and Polysorbate 80). Ionic (polymeric) surfactants are not generally preferred due to toxicological limitations (Garg and Kumar 2014; Gupta et al. 2016). Tween 80 is low molecular weight surfactant, has a high hydrophilic and lipophilic balance, and it is efficient in minimizing droplet size better than polymeric surfactants (Ghosh et al. 2013). Tween® 80 and Span® 80 are commonly used as safe surfactants because of their high degree of compatibility with other ingredients and low toxicity, Span® 80 as a viscous, lipophilic, emulsifying liquid agent. Tween® 80, hydrophilic in nature, is a derivative of Span® 80. Mixture of Span® 80 and Tween® 80 was used having stable nanoemulsion. These nonionic surfactants as uncharged molecules are also known as safe and biocompatible products; they are not affected by any pH changes of the mixture (Lv et al. 2014; Mahdi et al. 2011; Sagiri et al. 2012). Ionic (polymer) surfactants (e.g., sorbitan monoesters) are hydrophobic and tend formation of water-in-oil type. Sometimes, mixtures of both hydrophilic and hydrophobic surfactants are used for nanoemulsion formation. Lecithins, polaxamer, and polysorbates are some of the most preferred surfactants for use. Organic solvents such as propylene glycol, polyethylene glycol, ethanol, and glycerol are also generally preferred (Garg and Kumar 2014; Gupta et al. 2016). Molecular complexes such as cyclodextrin inclusion complexes also represent a valid strategy to increase water solubility, stability, and bioavailability and decrease volatility of essential oils (Bilia et al. 2014).

The common methods involved in nanoemulsion preparation include high energy methods (high pressure homogenization and ultrasonication) and low energy methods (phase inversion temperature and emulsion inversion point). The high-energy method utilizes mechanical devices to produce strong disruptive forces to break the oil and water phase to obtain nanoemulsions. The low-energy method utilizes the stored internal energy for the formation of small droplets. Emulsions are obtained by changing the process parameters like temperature, composition, and others that affect the hydrophilic–lipophilic balance (HLB) (Nirmala and Nagarajan 2017). However, each of these examples has certain limitations, e.g., high energy emulsification is used to prepare nanoemulsions and large quantity of surfactant required for formulating microemulsions. However, now some reports are available for the formation of essential oil nanoemulsion with low energy emulsification. Ultrasonication emulsification method has considerable advantages for production of clove oil nanoemulsion as a green pesticide with the nanoemulsion droplet size of 43 nm

(Shahavi et al. 2015). In preparation of nanoemulsion, Tween® 80/Span® 80 as nonionic surfactants via ultrasonic emulsification method was used.

10.4.3 Mode of Action

The nanoemulsion formulation of essential oils showed higher efficacy as pesticidal and antimicrobial. Nanoemulsion caused high mortality, and toxicity was increased by 35.6% compared to the EOs (Mossa et al. 2017). Regarding applications of essential oils in healthcare using nanoemulsions, the effect of rosemary oil was amplified more than 100-fold in 200 times lower than the concentration of the raw essential oil (https://www.doterra.com/US/en/blog/science-safety-physiology-nanoemulsion-essential-oils%202018). Some essential oil nanoformulations have been studied and assessed against some crop and storage pests and disease pathogens (Table 10.3).

In the current study, camphor nanoemulsion (oil-in-water) (5%) was prepared using Polysorbate 20 as a nonionic surfactant, camphor EO, and deionized water. Nanoemulsion of camphor EO (oil-in-water) (5%) with droplet diameter 99.0 nm was formulated by ultrasonic emulsification for 40 min using Polysorbate 20 as a nonionic surfactant, camphor EO, and deionized water. Nanoemulsion showed high insecticidal activity against wheat weevil, *Sitophilus granarius*, with LC_{50} 181.49 μg g^{-1}. From Gas Chromatography-Mass Spectrometry analysis, phytochemicals such as 1,8-cineole, β-cimene, D-limonene, α-pinen, and α-terpineol were found in camphor EO which could play a role as insecticidal activity. Camphor nanoemulsion did not show any effect on germination or seedling growth. Acute and sub-chronic toxicity studies showed no signs of toxicity or biochemical alterations in liver biomarkers of male rats (Mossa et al. 2017). Camphor leaves EO also had strong fumigant (LC_{50} 2.5 mg L^{-1}) and contact toxicity (LD_{50} 21.25 μg/adult) against *Lasioderma serricorne*. Camphor EO from stem barks, leaves, and fruits had highly fumigant and contact toxicity against *Tribolium castaneum* and *Lasioderma serricorne* (Gonzalez et al. 2014).

Nanoemulsion of eucalyptus essential oil on polyvinyl alcohol (PVA) pellet formulation with fumigant active ingredient had been developed. The pellet making chamber was completely sealed (Chiellini et al. 2003). Its water solubility, reactivity, and biodegradability make it a potentially useful material in biomedical, agricultural, and water treatment areas (Gohil et al. 2006). Insecticidal efficacy of produced pellets was investigated against adults (1–3 days old) of *Tribolium castaneum* (Herbst), *Callosobruchus maculatus* (F.), *Rhyzopertha dominica* (F.), *Oryzaephilus surinamensis* (L.), and *Sitophilus oryzae* (L.). A representative pesticide, NeemAzal (neem oil), was encapsulated into polyvinyl alcohol/alginate-montmorillonite (PVA/Alg-MMT) nanocomposite capsule beads, by cross-linking with glutaraldehyde. The addition of sodium MMT to these formulations was found to have a profound inhibitory effect on the release of NeemAzal and has the potential for controlled release of pesticide (Rashidzadeh et al. 2014) (Table 10.3).

Table 10.3 Some nanoformulations of essential oils reported effectively against plant pest and disease

Essential oils nanoemulsion	Nanoformulation loaded/ method	Pest and disease target	Reference
Eucalyptus EOs (1,8-cineole (eucalyptol)/fumigant toxicity	Nanoemulsion of eucalyptus essential oil on PVA pellet formulation with fumigant active ingredient	Storage pests *Tribolium castaneum* (Herbst), *Callosobruchus maculatus* (F.), *Rhyzopertha dominica* (F.), *Oryzaephilus surinamensis* (L.), and *Sitophilus oryzae* (L.)	Chiellini et al. (2003); Gohil et al. (2006)
Thyme essential oil (p-cymene, 1,8-cineole) and other thymol constituens)	Thyme oil-in-water nanoemulsions stabilized by a nonionic surfactant	Postharvest fungi: *Aspergillus*, *Penicillium*, *Alternaria*, *Cladosporium*, *Rhizopus*, *Trichoderma*	Šegvic Klaric et al. (2007)
Garlic essential oil	Polyethylene glycol	Postharvest pest *Tribolium castaneum*	Yang et al. (2009)
Artemisia arborescens L essential oil	*Artemisia arborescens* L essential oil-loaded solid lipid nanoparticles		Lai et al. (2006)
Citrus peel essential oil nanoformulations	Nanoformulations	Tomato borer, *Tuta absoluta*	Campolo et al. (2017)
Camphor (*Eucalyptus globulus*) essential oil (α-Pinene, (b) β-Cymene, (c) D-Limonene, (d) 1,8-Cineole, and (e) α-Terpineol)	Camphor essential oil nanoemulsion (droplet size 99.0 nm)	Insect stored grains wheat weevil, *Sitophilus granarius*	Mossa et al. (2017)
NeemAzal/neem oil (azadirachtin, nimbidin)	Encapsulated into polyvinyl alcohol/ alginate-montmorillonite (PVA/Alg-MMT) nanocomposite capsule beads by cross-linking with glutaraldehyde	Insecticide, nematicide	Rashidzadeh et al. (2014)

Liposomal encapsulation was also promising technology in essential oil nanoparticulate system. Liposomes are colloidal particles associated from amphiphilic lipids usually phospholipids as bilayer vesicles, which can be used to incorporate hydrophobic or hydrophilic bioactive components within the nonpolar regions and the interior aqueous core, respectively (McClements 2012a; São Pedro et al. 2013). Thymol, carvacrol, and their mixture all showed significantly enhanced antimicrobial activities after liposomal encapsulation (Liolios et al. 2009). Enhanced antimicrobial and antioxidant activities of EO from citrus lemon after encapsulation in liposomes were also reported (Gortzi et al. 2007). Eugenol loaded in nanoliposomes exhibited improved storage stability and sustained release but the antimicrobial activities of eugenol were reduced because the good protection of liposomal encapsulation also reduced the contact of antimicrobial with bacteria (Peng et al. 2015). Clove oil in liposomes showed sustained release of eugenol and maintained good quality and stability during storage (Akrachalanont 2008).

The green pesticide technology uses oil-in-water nanoemulsions as a nanopesticide delivery system to replace the traditional emulsifiable concentrates (oil). Nanoemulsion is used due to highly stable product for long duration. The main reasons to use oil in water as nanoemulsion are reducing the use of organic solvent and increasing the dispersity, wettability, and penetration properties of the droplets. Oil-in-water nanoemulsions are for the improvement of biological efficacy and reducing the dosage of pesticides (Shahavi et al. 2015); they would be a useful strategy in green pesticide technology. These green and nanopesticides are safe and low to mammalian toxicity and have many sites of toxic actions in pests, which lead to high selectivity and low resistance development (Ehsanfar and Modarres-Sanavy 2004; Elaissi et al. 2012).

10.5 Agrochemical and Bioactive Agent/Material-based Nanopesticide

Agrochemical nanoformulations may be developed by two pathways, directly processed into nanoparticles and using nanomaterials as carriers to formulate smart delivery systems or controlled release mechanisms (Cui et al. 2018), and the controlled use of biological active compound nanoformulation may be developed by using bionanomaterials as carriers to formulate smart delivery systems.

10.5.1 Agrochemical Pesticide Nanoformulations

Pesticides are still a component of integrated pest management and used in certain conditions. Problems in their applications are improper delivery of agrochemicals and management, only 0.1% of the chemicals used in crop protection reach the target pest while the rest are lost, and they enter the environment and may cause hazards to nontarget organisms, including humans (Pepper 2008). Safe application of conventional agrochemicals is a major concern.

Safe application of those chemicals is replaced by application of various nano-based formulations that are similar to conventional formulations developed with improved features of increased rate of solubility, stability, permeability, and biodegradability and decreased rate of agrochemical spreading with uniform dispersion (Kah et al. 2013; Kah 2015), recently called as controlled release technology. The composition of many conventional insecticides is mostly water soluble and requires a delivery system for their application in the field (Das et al. 2014). This involves formulating the pesticide with a carrier, such as lipid or polymer based (nanoemulsions), or other systems including silica and nanoclays.

Basically, the nanoformulations should degrade faster in the soil and slowly in plants with residue levels below the regulatory criteria in foodstuffs (Khan and Rizvi 2014). Due to better kinetic stability, smaller size, low viscosity, and optical transparency, nanoemulsions can serve as better pesticide delivery systems (Xu et al. 2010). Such formulations may greatly decrease the amount of pesticide concentration and associated environmental hazards. Nanopesticides shall reduce the rate of application because the quantity of the chemical actually being effective is at least 10–15 times smaller than that applied with classical formulations; hence much smaller than the normal amount could be required to achieve satisfactory control of the disease. The nanoemulsion, as a carrier for pesticide delivery, can improve the solubility and bioavailability of the active ingredients of the chemical. Since all the propagules/spores of a pathogen do not approach/invade the host at one time, rather they attack intermittently, hence persistence or slow/gradual release of active ingredient in the root zone shall enhance the effectiveness of the formulation (Khan et al. 2011). Thus, such nanoformulation pesticides may decrease adverse environmental and human effects as compared to classical pesticides. Shi et al. (2010) studied the toxicity of chlorfenapyr (nanopesticide) on mice. It was reported that the chlorfenapyr nanoformulation from 4.84 to 19.36 mg kg^{-1} was less toxic to mice than the common formulation.

Some agrochemical nanopesticides have shown more efficiency in controlling plant pest and disease (Table 10.4), and are used in nanoformulations. Some examples are given below

1. Imidacloprid nanocapsule and nanoparticle
2. Nanocapsule for carbaryl, itraconazole, bifenthrin, fipronil, and lansiumamide B
3. Insecticide-coated liposome of imidacloprid, thiamethoxam, carbofuran, thiram, β-cyfluthrin, and mancozeb
4. Carbofuran nanomicelle
5. Beta-cypermethrin nanogel
6. Imidacloprid or cyromazine nanogranule and nanoclay
7. Silica nanoparticle-controlled release of chlorfenapyr and nanocalcium carbonate and silica-controlled release of validamycin
8. Silica nanoparticle-coated 3 mercaptopropyltriethoxysilane
9. Imidacloprid or cyromazine nanogranule and nanoclay

Table 10.4 presents some controlled release formulations of agrochemical pesticides employing novel nano-ranged amphiphilic polymers. Polymer-based nanoformulations have been exploited for the encapsulation of most of the insecticides. Different polysaccharides (e.g., chitosan, alginates, starch) and polyesters (e.g., poly-ε-caprolactone, polyethylene glycol) have been considered for the synthesis of nanoinsecticides (Das et al. 2014). Liu et al. (2008a) studied that polymer stabilizers

Table 10.4 Some controlled release formulations of agrochemical pesticides and their bioactivity

Chemical pesticide	Nano/microencapsulation method	Bioactivity	Reference
Imidacloprid	Imidacloprid nanocapsule (lignin–polyethylene glycol–ethylcellulose copolymer) suspension	Insecticide	Flores-Cespedes et al. (2012)
Imidacloprid	Controlled release formulations of imidacloprid employing novel nano-ranged amphiphilic polymers (liposome)	Insecticide	Chhipa 2017b
Imidacloprid	SDS (sodium dodecyl sulfate) -modified silver/titanium dioxide (Ag/TiO$_2$) along with chitosan and alginate by microencapsulation technique to increase the photodegradation	The sodium dodecyl sulfate (SDS) can play a role to enhance the photodegradation of the NPs in soil	Guan et al. (2010)
Imidacloprid	Imidacloprid nanoparticle [chitosan–poly(lactide) copolymer]	Insecticide	Li et al. (2011)
Carbaryl	Insecticide nanocapsule (carboxymethylcellulos)		Isiklan (2004)
Itraconazole	Insecticide nanocapsule acrylic acid-buacrylate		Goldshtein et al. (2005)
Bifenthrin	Bifenthrin nanocapsule [synthetic polimers: polyvinylpyrrolidone (PVP), polyvinyl alcohol (PVA), and poly (acrylic acid)-b-poly(butyl acrylate) (PAA-b-PBA) and polyvinyl alcohol (PVOH)]	Insecticide	Liu et al. (2008a)
Thiamethoxam	Insecticide-coated liposome (polyethylene glycol polymer)	Insecticide	Wibowo et al. (2014)
Carbofuran	Insecticide-coated liposome [poly (ethylene glycol) polyvinyl pyrrolidone]	Systemic and contact insecticide, nematicide	Yin et al. (2012), Grillo et al. (2016)
Carbofuran	Carbofuran nanomicelle (polyethylene glycol dimethyl esters polymer)		Shakil et al. (2010)

(continued)

Table 10.4 (continued)

Chemical pesticide	Nano/microencapsulation method	Bioactivity	Reference
Thiram	Insecticide-coated liposome (polyethylene glycol polymer)	Fungicide, ectoparasiticide to prevent fungal diseases in seed and crops and similarly as a animal repellent to protect fruit trees and ornamentals from damage by rabbits, rodents and deer	Fraceto et al. (2016)
β-Cyfluthrin	Insecticide-coated liposome (polyethylene glycol polymer)	Pyrethroid insecticide (low aqueous solubility, semi-volatile) against pest *Callosobruchus maculatus*	Loha et al. (2012)
Mancozeb	Insecticide-coated liposome (polymeric nanoformulation)	Dithiocarbamate nonsystemic agricultural fungicide with multisite, protective action on contact	Amenta et al. (2015); Venugopal and Sainadh (2016)
Carbofuran	Carbofuran nanomicelle (polyethylene glycol dimethyl esters polymer)		Shakil et al. (2010)
Beta-cypermethrin	Beta-cypermethrin nanogel (methyl methacrylate and methacrylic acid with and without 2-hydroxy ethyl methacrylate crosslinkage)		Rudzinski et al. (2003)
Chlorfenapyr	Silica nanoparticle as controlled release	Twice insecticidal activity	Song et al. (2012)
Fipronil	Oilcore silica-shell nanocapsule for fipronil nanoemulsion	Insecticide	Wibowo et al. (2014); Gutierrez et al. (2008)
Lansiumamide B	Lansiumamide B biocompatible silica nanocapsules	Nematicidal activity	Yin et al. (2012)

(continued)

Table 10.4 (continued)

Chemical pesticide	Nano/microencapsulation method	Bioactivity	Reference
Validamycin	Nanosized calcium carbonate and porous silica as controlled release	More active for longer period fungicide *Rhizoctonia solani*	Qian et al. (2011)
3 mercaptopropyltriethoxysilane coated	Silica nanoparticles coated with 3 mercaptopropyltriethoxysilane	More efficient insecticide	Liu et al. (2006)
Metribuzin	Alginate controlled release formulations		Pepperman et al. (1991)
Aldicarb	Aldicarb nanogel (lignin)		Kok et al. (1999)
Imidacloprid or cyromazine	Imidacloprid or cyromazine nanogranule (lignin)		Fernandez-Perez et al. (2011); Ragaei and Sabry (2014)
Imidacloprid or cyromazine	Insecticide nanoclay (alginate-bentonite)		Fernandez-Perez et al. (2011); Ragaei and Sabry (2014)

like PVP, PVA, poly(acrylic acid)-b-poly(butyl acrylate) (PAA-b-PBA), and polyvinyl alcohol (PVOH) were able to use them in formulating a stable (bifenthrin) nanopesticide. Pepperman et al. (1991) have proved that biodegradable microbial polymers like polyhydroxyl alkanates were effective for controlled release of pesticides.

The controlled use of agrochemicals could be also possible by the development of smart delivery system using biomaterials. Encapsulation of various agrochemicals in chitosan, silica, alginate, and calcium carbonat is an option for controlled and sustained delivery (Choudhary et al. 2017; Song et al. 2012; Qian et al. 2011; Guan et al. 2010). Nanoformulations of silica nanocapsule for chlorfenapyr, fipronil nanoemulsion, lansiumamide B, and validamycin; imidacloprid–chitosan-poly(lactide) copolymer; and three mercaptopropyltriethoxysilane-coated silica nanoparticles showed higher insecticidal, nematicidal, and fungicidal activities (Table 10.4).

Biomaterials as components of nanoparticulate system may reduce the risk of hazardous agrochemicals for crop improvement and protection. Nanoparticles prepared from natural sources and biopolymers have some merits of biocompatibility and biodegradability. Khodakovsky et al. (2000) reported that when they planted tomato seeds in a soil that contained carbon nanotubes (CNTs), these CNTs could not only penetrate into the hard coat of germinating tomato seeds but also exerted a growth-enhancing effect. They envisaged that the enhanced growth was due to increased water uptake caused by penetration of the CNT. This could be an advantage for using CNT as a vehicle to deliver desired molecules such as chemicals or other pesticidal properties into the seeds during germination that can protect them from the diseases. Since it is growth promoting, it will not have any toxic or inhibiting or adverse effect on the plant. Carbon nanotubes are allotropes of carbon, whose nanostructure is cylindrical in shape.

However, ultrasmall-sized toxic pesticide materials, similar to metal nanoparticles, are also a big concern towards human health and environment, as their higher ability in contact to animal, aquatic biota and human in compared to conventional pesticides.

10.5.2 Bioactive Agent Nanoformulation

Biocontrol agents such as natural enemies of pests and pathogens also could play a role as pesticidal properties of biopesticide products (Bhattacharyya et al. 2016). There are some biological control agents such as entomopathogen, rhizobacteria, endophytic microbe, fungi (enthomopathogen), bacteria (rhizobacteria), viruses, and nematode (entomonematode) which are used against insect pests and disease pathogens. Mycopesticides (fungal biocontrol agents) are promising biological pesticides as there is no need of ingestion; instead, they act by contact, are very specific, and can be easily mass-produced (Baric et al. 2008). Microbial products such as enzymes, antibiotics, inhibitors, and toxins are also promising as biopesticides against plant pathogens and pests (Bhattacharyya et al. 2016).

Similarly, biopesticides developed from inorganic and organic minerals nanomaterials had been paid attention from researchers. Inorganic mineral such as amorphous nanosilica obtained from various sources such as phytoplankton, volcanic soil is used as a biopesticide useful against stored grain, fungal organism, and worms/nematode (Liu et al. 2008b); and organic mineral such as chitosan and its derivative (chitin) nanoparticle is used as a biopesticide useful against crop pests (Sahab et al. 2015). Silica nanoparticles were developed as active ingredients and as nanostructured silica as a stored pulse protector and showed insecticidal activity and potential to use in managing crop pest (*Spodoptera litura*) and stored-product pests/postharvest pests (i.e., *Sitophilus oryzae*, *Callosobruchus maculatus*) (Table 10.5). Bionanomaterial of nanodiatomaceous earth (DE) was found effective to manage postharvest pests, confused and red flour beetles *Tribolium confusum* and *Tribolium castaneum* (Sabbour and Abd El-Aziz 2015), and can be useful as biopesticide. Amorphous silica is considered to have low toxicity, but prolonged inhalation causes changes to the lungs (https://www.cdc.gov/niosh/pel88/68855-54.html). However, today's common DE formulations are safer to use, as they are predominantly made up of amorphous silica and contain little or no crystalline silica

Table 10.5 Some inorganic/organic minerals nanomaterial and their mode of action against pests

Inorganic minerals nanomaterials	Targeted pests and pathogens	References
SiNPs	*Spodoptera litura*	Debnath et al. (2011)
Silica NPs	*Sitophilus oryzae* (L.).	Debnath et al. (2012)
Silica nanoparticles (SNPs)	Reduction infestation of stored pulse beetle, *Callosobruchus maculatus* on seeds of *Cajanus cajan*, *Macrotyloma uniflorum*, *Vigna mungo*, *Vigna radiata*, *Cicer arietinum*, and *Vigna unguiculata*	Arumugam et al. (2015)
Nanostructured silica as a stored pulse protector	Bruchid beetle, *Callosobruchus maculatus* (Coleoptera: Bruchidae	Arumugam et al. (2015)
Nanodiatomaceous earth	Postharvest pests, confused and red flour beetles *Tribolium confusum* and *Tribolium castaneum*	Sabbour and Abd El-Aziz (2015)
Chitosan (CS)-g-poly (acrylic acid) PAA nanoparticles	*Aphis gossypii*	Sahab et al. (2015)
Chitosan nanoparticle-coated fungal metabolite	Crop pest *Spodoptera litura*	Chandra et al. (2013)

(Subramanyam and Roesli 2003). A chitin derivative (N-(2-chloro-6- fluorobenzyl-chitosan), chitosan, has also been found to show strong insecticidal activity in some plant pests (Qian et al. 2011; Liu et al. 2006).

Microbial-based and other biopesticide formulations need stabilization and directed delivery mechanism toward identified targets. Formulations prepared from organisms and/or biomaterials are usually susceptible to desiccation, ultraviolet light inactivation, or even heat. Nanoformulations may provide new ways to enhance the stability of these biological agents. The controlled use of biological active compounds (as same as of agrochemicals) could be possible by the development of smart delivery system using biomaterials. Chitosan and clay being biocompatible nanomaterials can be used as stabilizing and delivery agents and, hence, have potential applications in the development of biopesticide formulations. Chitosan nanoparticle-coated fungal metabolite (CNPCFM), uncoated fungal metabolite (UFM), and fungal spores (FS) of entomopathogenic fungi *Nomuraea rileyi* (F.) Samson were evaluated against pest *Spodoptera litura* (Chandra et al. 2013). Results showed that among the tested materials, CNPCFM was found to be more effective than UFM and FS. Chitosan itself has insecticidal properties/bioactivity, i.e., chitosan (CS)-g-poly(acrylic acid) (PAA) nanoparticles reduced egg laying of *Aphis gossypii* (20.9 ± 9.1 and 28.9 ± 9.2 eggs/female for laboratory and under semi-field conditions, respectively) than control (97.3 ± 4.9 and 90.3 ± 4.9 eggs/female for laboratory and under semi-field conditions, respectively) (Sahab et al. 2015). The use of chitosan NPs as stabilizer and delivery agent in biopesticide nanoformulation will improve their plant pest and disease effectivity and safety as well.

The exploration of inorganic/organic mineral (biomaterials) nanoparticles and nanobiopesticide bioactivity toward other disease pathogens and nematode suppression should be investigated, as their activity on these pathogens has been reported, and as nanostructure for controlled release of microbial-based and other biopesticide formulations. Chitosan, a hydrophilic biopolymer industrially obtained by *N*-deacetylation of chitin, can be applied as an antimicrobial agent against fungi, bacteria, and viruses and as an elicitor of plant defense mechanisms (Rabea et al. 2003).

10.6 Commercial Product and Uses of Nanopesticide

Plant protection products containing nanomaterials that alter the functionality or risk profile of active ingredients (nano-enabled pesticides) promise many benefits over conventional pesticide products, such as better targeting of pest species, increased efficacy, lower application rates, and enhanced environmental safety (Walker et al. 2017). Nanosilver is the most studied in suppression of pest and disease impact on crops. The advancement of silver nanomaterials manufacture especially in silver nanoformulation, were making them have already been in the market for several years apparently. Several approaches are being investigated continuously to develop silver nanoformulations to increase their antimicrobial activity, and biosafety as well.

Recently, one of the products of nanosilver-based formula is “Alstasan Silvox” nanosilver hydrogen peroxide under Chemtex Speciality Limited Company. The product was commercialized as a safe and an eco-friendly “biodegradable disinfectant” (www.silverhydrogenperoxide.com, accessed in 2018). However, the product was manufactured also for effective and efficient broad-spectrum fungicides, antibiotics/bactericides, virucides, and nematicides. The product can also be used in the prevention and treatment of various agricultural diseases like root-knot nematodes, bacterial blights, and powdery mildew. The product, owing to its nonfoaming nature, is suitable for both cleaning and disinfecting, effective over a large range of microorganisms, eco-friendly, biodegradable, colorless, odorless, noncarcinogenic and nonmutagenic in nature, with no danger of microbial resistance, nonpolluting, and nonstaining in nature, does not emit any harmful fumes (unlike chlorine, bromine, formalin, and aldehydes), can be used in multimedia sanitation (air, water, soil, surface), and stably works over a wide range of pH and temperature. This silver peroxide destroys biofilms; provides rapid sterilization unlike other traditional methods; is a cold sterilant; does not change/alter any physical properties of the medium; is nonflammable, minimizing transportation and storage risks; has high thermostability; maintains easy handling and dosing; is free of carcinogenic aldehydes; and has no gaps in efficacy. This silver peroxide works on a short contact time and provides long-lasting disinfection with no toxic residues. The product is claimed safe for human consumption upto a concentration of 25 ppm. This product is in transparent liquid form and can be applied by four different methods, namely, Clean-in-place (CIP) method, dip method, spray method, and fill and soak method.

In this product, the nanosilver has stabilizer function, activator function, and oligodynamic action of the hydrogen peroxide (chemical naturally used as an antiseptic).

Nanoformulation of metal such as silver has a broad spectrum of antimicrobial activity and has been broadly applied as an active disinfecting and sterilization agent and in various fields such as water preservation, food and beverage storage, pharmaceutical, cosmetics, treatment of various human diseases, and agriculture; it would appear that their manufactured product is categorized as safe with broad utility application and cannot be categorized as an agro-nanopesticide only. Even in this product, the nanosilver has been applied as a stabilizer and activator and has oligodynamic action of the hydrogen peroxide. With all those characteristics described above, this nanosilver product seems to meet the criteria of desirable and ideal for its safe, efficient, and effective applications in agriculture. According to Khot et al. (2012) and Sangeetha et al. (2017), the advancement of nanomaterials with intense dispersion and interaction between the fluid and solid phases, with well-understood toxicodynamics and toxic kinetics, biodegradability in soil and environment, less toxicity and more photogenerativity, and smart and stable application in agriculture sector, would be desirable and ideal for their efficient and effective applications in agriculture.

Eventhough the duration or expiration of the long-term effect of the nanosilver (in the product) was undetermined and its long time of higher reactivity of nanosilver exposure by continuous application requires consideration of a bioaccumulation risk assessment, this nanosilver product offers effective and efficient broad-spectrum nanopesticides against plant pest and disease. However, this product shown that developing metal-based nanopesticide, is creating and designing the nanoformulation contained nanometal as pesticidal ingredient or as stabilizer and activator of the formula product.

Another nanopesticide product is nanochemical pesticide. One of the first nanoindustrial applications is the development of nanochemical pesticides (or nanopesticides) which contain nanoscale chemical toxins (Kuzma and Verhage 2006). Leading agrochemical companies developing nano-based pesticides are BASF, Bayer Crop Science, Monsanto, and Syngenta. However, the marketing of smart pesticides is currently constricted, especially through environmental groups/risk assessors opposing their introduction or potential risks associated with nanoscale materials, because the impacts of nanoparticles on the environment and human health are still largely unknown and unpredictable (Annex E 2018, http://www.nanotechproject.org/). Some of the nanopesticides issued in the market recently are mentioned in Table 10.6.

Table 10.6 Nano-based product on the market (Annex E 2018, http://www.nanotechproject.org/)

Company	Product	Mechanism
Syngenta	PRIMO Maxx and KARATE ZEON	Inhibit neural system
Nano Green	Nano Green	Attack respiratory apparatus
Agro Nano-technology Corp	Nano Gro	Mimics stress conditions, increasing crop activity and yield

10.7 Future Prospects and Challenges of Nanopesticide Formulation and Application in Plant Pest and Disease Management

Nanomaterials give plant pest- and disease pathogen-targeted applications in plant protection through nanopesticide formulation of (1) nanoparticles (metal, EOs, agrochemicals), as an alternative pesticidal active ingredient to conventional pesticides, and (2) nanostructures providing pesticidal ingredient (agrochemicals, bioactive agent, EOs, metals) as controlled release mediator. Potential pesticidal ingredient-targeted applications are metal nanoparticles (silver and gold), essential oil nanoemulsion (clove, citronella grass, eucalyptus, camphor, thyme, *Monarda* spp.), agrochemicals (toxic pesticide), and bioactive agents (microorganisms, biomaterials, microbial products).

Nanomaterials and nanoencapsulation were solutions of the problem associated with pesticidal ingredients of metal, essential oil, agrochemicals, and bioactive agent and their application. The bulk metals have low antimicrobial and insecticidal effect. Silver nanoparticles, which have a high surface area and high fraction of surface atoms, have high antimicrobial effect as compared to the bulk silver (Patel et al. 2014). Chemical pesticides are ineffective to solve the problem of nematodes, as nematode population increased several months after the nematicidal is used (Thakur and Shirkot 2017), and of devastating disease pathogens such as viruses and bacteria. Controlled release technology from nanocarrier of nano-based formulations has emerged as an alternative approach with the promise to solve the problems accompanying the use of some agrochemicals while avoiding possible side effects with others (Han et al. 2009). Small engineered structure which provides pesticidal properties has shown slow degradation and controlled release of active ingredient for a long time period, making them environmentally safe and less toxic in comparison to chemical pesticide (Chhipa 2017a). The ability to delay or control delivery of pesticides to the target organisms is achieved by these nanopesticide delivery methods (Singh et al. 2015). Without encapsulation, EOs face the problem of instability during pesticidal activity, nonavailability of suitable spraying equipment at farmers' level since EOs have large droplet size, and low vapor pressure when used as fumigant agent in large scales. Nanoemulsions or nanoencapsulation of essential oil could solve the problem of water solubility and low vapor pressure, respectively. Nanoformulations may enhance the stability of these biological agents and biomaterials from desiccation, UV light inactivation, or heat stimuli. The controlled use of biological active compounds (as same as of agrochemicals) could be possible by the development of smart delivery system using nano-biomaterials. In order to keep the residue level below the critical limits as permissible by the regulatory criteria in foodstuffs, the nanoformulation should be degraded fast in the soil but slowly in plants (Khan and Rizvi 2014). These nanostructures have shown slow degradation and controlled release of active ingredients for a long time period in plants.

At present there is growing interest to utilize antifungal properties of AgNPs for plant disease management (Karimi et al. 2012; Aziz et al. 2016), because well-dispersed and stabilized AgNP solution can act as excellent fungicide due to good adhesion on bacterial and fungal cell surface (Kim et al. 2008), and so contribute to healthy plant growth. Metal nanoparticles offer a lot of potentials to effectively control pest population through their targeted approach; nanoparticles mediate higher penetration of active ingredients with a minimum concentration of chemicals used, as they penetrate easily through the cell wall and produce maximum effect (Thakur and Shirkot 2017). The nanotechnology has the immense potential prospect of applications in agriculture and plant pest management in particular direct application of nanoparticles to soil or seed or foliage to protect plants from different types of pathogen invasion by suppressing them as by the chemical methods (Thakur and Shirkot 2017). Silver nanoparticle is now used in hydroponics systems and planter soils to eliminate unwanted microorganisms. Using nanopesticides will contribute to effective and efficient spraying and, thus, decrease splash losses which are often evident with conventional pesticide and EOs spraying, since the droplet size is diminished also by this nanoformulation system (Bergeson 2010a). Moreover, silver is an excellent plant growth stimulator (Oldenburg 2017). Silver nanoparticles have merits over common chemical antimicrobial agents causing multidrug resistance (Guzman et al. 2009). Nanosilver-based compounds give promising broad-spectrum pesticides, as silver metallic nanoparticles exhibited bactericidal, fungicidal, virucidal, nematicidal, and insecticidal activities (Park et al. 2006; Jo et al. 2009; El-Shazly et al. 2017; Abbassy et al. 2017; Siva and Kumar 2015; Sankar and Abideen 2015; Sharma et al. 2017). Further these nanoparticles are free of toxic chemicals and hence are compatible with biological entities and safer to use. Moreover, AgNP may provide an additional benefit of managing multiple plant pathogens, as complex diseases often occur in the field. These effects may be due to its mode of action being not specific but associated with multiple cellular mechanisms. For this reason, AgNP is a wide-spectrum antimicrobial agent capable of affecting plant-pathogenic fungi and bacteria (Park et al. 2006; Jo et al. 2009). For example, it is possible that AgNP has an antifungal effect on several root-associated fungal pathogens (e.g., *Gaeumannomyces graminis* and *Rhizoctonia solani*). Pathogens treated with AgNP may become more tolerant to root-knot nematode damage because of some protection from additional stress by these other pathogens (Taha 2016).

From the viewpoint of the advantage of silver nanoparticles, nanopesticides offer promising higher effectiveness and safety and could be alternative to conventional pesticide. However, controversion of their biosafety to ecosystem had been addressed to their field application. The discharge of considerable amount of nanoparticles in the environment observed due to the increasing use of silver nanoparticles and the widespread geographic distribution is increasing (Nam et al. 2014). The AgNP antimicrobial activity is not specific and has higher reactivity; thus its mode of action could come in contact with plants, soil, and aquatic biota including fish, animals, and human beings and affect adversely the beneficial microorganisms. Colman et al. (2013) found that nanosilver treatment led to changes in microbial community composition, biomass, extracellular enzyme activity, and affected some ground plant species.

Since the mechanism of metal nanoparticle (e.g., AgNPs) toxicity remains undetermined, the use of AgNP-based pesticides may cause contamination in soil and water due to longer persistence, enhanced transport, and higher reactivity of nanoparticles (Khan and Rizvi 2014). Biodegradation of pesticides/nanopesticide is very important to remove the toxic compounds from the natural ecosystem. The application of silver and agrochemical-based nanoparticle product should be followed with soil and water remediation measurements (which usually applied for conventional chemical pesticides) to minimize the adverse effect of toxic NPs. Pesticide-contaminated soil and water are generally treated using phytoremediation, biodegradation, photochemical processes, and oxidation processes. Some literatures revealed that both chemical and biological nanomaterials also have a substantial role in crop protection as in irrigation water filtration and remediation of harmful pesticides (Patil et al. 2016). Iron nanoparticles occupy an important place among nanomaterials due to their enormous applications in environmental remediation and waste water treatment (Ali et al. 2016). Pesticides like chlorpyrifos and atrazine can be degraded using nanosized zerovalent iron. Similarly, some pesticide residues can also be photocatalytically decomposed using TiO_2 doped with Fe_2O_3 either incorporated into the pesticide formulations or sprayed directly on crops (Sasson et al. 2007). Iron oxide was a catalyst and adsorbent for natural and synthetic micropollutants (Xu et al. 2012; Rajabi et al. 2012). A potential bioremediation treatment is slowly gaining popularity. Some plant species have shown capability to accumulate heavy metals and other toxic subtances. The essential oil plant, citronella grass, showed ability in phytoremediation for the decontamination of metal-polluted soil (Handique and Handique 2009). Biochars also have shown ability to alleviate the soil function and decrease the biomass emission, binded carbon, and heavy metal substances (Juhaeti et al. 2005). Ramadass and Thiagarajan (2017) reviewed the microbes which play a major and important role in biodegradation. Common genera of bacteria such as *Bacillus*, *Pseudomonas*, *Flavobacterium*, *Sphingomonas*, *Brevibacterium*, and *Burkholderia* possess the inherent ability to utilize specific chemical groups in the pesticides as their sole source of either carbon and/or nitrogen and consequently achieve their conversion into nontoxic end products. Then, applied nanopesticide (of metal and agrochemical) as a component of integrated pest management (IPM) concept, which consequently lowers the volume of nanopesticide that will be applied, may minimize volume and spread of such nanopesticide, consequently lowering the impact on the environment.

Essential oils and bioactive agent-based nanopesticides were practically accepted as effective and safe nanopesticides. EOs-based nanopesticides are considered active, safe, and alternative to synthetic pesticides to control pest and disease pathogens, including storage pests, without producing adverse effects on seed germination and ecosystem (Khan and Rizvi 2014; Williams 2002; Dhekney et al.

2007). These oils have broad spectrum of pesticidal and insecticidal activities against many pests and disease pathogens due to the presence of many active components including volatile subtances, which had different sites and mechanisms of toxic action from highly fumigant and contact toxicity against crop pest and storage pests. One bioactive agent such as chitosan is few of the promising candidates in the future for nanopesticide formulation as alternative safe and effective pesticidal active ingredients, and or the nanostructure for controlled release delivery system of pesticidal ingredients, due to its unique properties such as abundance, biocompatibility, biodegradability, hydrophilicity, safety, and Nontoxicity. These bioactive agents have been used in several applications including antifungal activity (Saharan et al. 2013), antibacterial activity (Qi et al. 2004; Du et al. 2009; Ali et al. 2011), plant growth-promoting activity (Van et al. 2013; Saharan et al. 2015, 2016), and nanofertilizers (Corradini et al. 2010).

Great efforts are required in the commercialization of nanomaterials for agricultural applications (i.e., metal, agrochemicals), which require proper protection needs, testing priorities, risk assessment, and regulatory guidance at the global level (Chen and Yada 2011). Otherwise, the development and commercialization of essential oil and bioactive agent-based nanopesticides as green pesticides are prospects and challenges in future research and industry. The plant-based pesticides are in high demand, because they are sustainable in the environment and they are safe and are also pleasant to use (Maia and Moore 2011). The wide availability of essential oils from the flavor and fragrance industries, well received by consumers for use against home and garden pests, proves effective in agricultural situations for organic food production, and the allowed component of IPM has made it possible to fast track the commercialization of essential oil-based pesticides (Mohan et al. 2011). However, much work is needed to prepare effective, low-cost, and scalable nanoemulsions for nanopesticide application. The efficacy of EOs is greatly affected by many factors, such as plant's ripeness period, cultivation area, and essential oil distillation method/technology; different results can be observed (Ozdemir and Gozel 2017). In nanoformulations, nanoparticles prepared from natural sources (silica, chitosan, clay) and biopolymers have some merits of biocompatibility and biodegradability.

10.8 Conclusion and Suggestion

Developing nanopesticides includes developing application of nanomaterials as pesticidal active agents and as nanocarriers for developing delivery systems, improving conventional pesticide and bioactive agent nanoformulations. Nanomaterial applications in pesticide formulation increased their efficacy, efficiency, stability, durability, solubility, and targeted delivery, and controlled release rates of pesticidal agent, leading to protection against their adverse effect to environment.

Some potential green technologies and biomaterials useful for preparation of effective and safe pesticidal ingredients and structures of pesticidal nanoformulations should be considered and supported by researchers and the industry in the future design and fabrication of new metal, essential oils, agrochemicals, and bioactive agent-based nanopesticides. Future silver and metal nanopesticide manufacturing should consider size and concentration of nanoparticles, which are effective to pests and pathogens but less toxic to nontarget organisms. Future studies on EOs pesticide nanoformulation could focus on determining GAP (Good Agricultural Practice) of EOs plants, their postharvest measures, and distillation method in order to obtain highly active ingredient content and effective and efficient scalable nanoemulsions for application.

Nanopesticides significantly affect pest and disease pathogen suppression because of their specific physical and chemical properties and being environmentally safe and less toxic in comparison to excess use of agrochemical pesticides. However, their undetermined long-term effect of ultrasmall size of metal and agrochemicals, and as some product of their formula increased; its long-term exposed field and water are better being ameliorated through, i.e., ameliorant/bio-ameliorant filter, phytoremediation plants, and their application as component of IPM concept.

Strategic application and research of bioremediation plants and microorganisms, along with determination of the biodegradation rate of contaminants/pollutans, including exploration of new and improved nanostructures and nanomaterials for safe, effective, and efficient nanopesticide formulation, may support mitigation and suppression of possible adverse effects of harmful metal and agrochemical nanopesticides and environmental protection in the future.

Since the environmental fate of nanometal and agrochemical pesticide remains undetermined, utility of nanopesticide is a matter of choice for the government and/or farmer/consumer considering the harmful effects in the ecosystem and human health. However, in the future, nanopesticide safe use uniform should be considered and specifically designed as nanopesticide differ from conventional pesticides.

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Chapter 11
Nanotechnology: An Emerging Tool for Management of Biotic Stresses in Plants

Monika Hajong, Nongthombam Olivia Devi, Manashi Debbarma, and Dipali Majumder

Contents

M. Hajong · N. O. Devi · M. Debbarma · D. Majumder (✉)
School of Crop Protection, College of Post-Graduate Studies,
Central Agricultural University (Imphal), Umiam, Meghalaya, India

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11.1 Introduction

Biotic stresses caused by fungi, bacteria, viruses, viroids, phytoplasma, nematodes, insects, and weeds are major constraints for crop production. Crop losses due to pests and diseases are the major threat for farming community and to food security worldwide (Pandey et al. 2017). Crop yield losses due to biotic stresses range from 20% to 40% or even more than 50% in certain cases (Pestovsky and Martinez-Antonio 2017). The estimated crop losses due to biotic stresses amount for approximately 2000 billion dollars per year (Oluwaseun and Sarin 2017) worldwide. The status of global food security, i.e., the balance between growing demand for food for increasing world population and global agricultural output, combined with discrepancies between supply and demand for agricultural items at different level (regional, national, and international) is alarming (Savary et al. 2012). Timely and accurate diagnosis of plant diseases and management strategies undertaken in right time helps to minimize the yield loss of the crops.

Rapid plant disease diagnosis techniques with high sensitivity and accuracy are essential to prevent disease spread over large area with minimal loss to crop yield and food quality assurance (Kashyap et al. 2016). Conventional methods of detection of plant pathogens are time-consuming and less reliable and require complex sample handling. Although immunological and molecular (nucleic acid based) techniques are in advance stage, they still have some issues that are related to rapidity and signal strength (Kashyap et al. 2016).

The term nanotechnology was first used and coined by Taniguchi (1974). The prefix "nano" is a Greek word which means "dwarf" (Nikalje 2015). Nanotechnology is the art and science of manipulating matter at the nanoscale size (1–100 nm or 1.0×10^{-9} m) to create new and unique NMs with enormous potential to change the conventional practices (Chinnamuthu and Boopathi 2009). Nanoscale materials showed very unusual physical, chemical, and biological properties that are completely different from their bulk and individual molecules (Li et al. 2001). The size, shape, ratio of surface to volume, crystal phase, and chemical composition are key parameters which define many outstanding properties of these NMs which are relevant for their application in agriculture. Nanotechnology combines solid-state physics, chemistry, chemical engineering, biochemistry, biophysics, and materials science (Abobatta 2018).

Nanoimaging, nanopore DNA sequencing tools, biosensor, QDs, and nanostructured platforms have the potential to enhance sensitivity, specificity, and speed of detection and thereby facilitate high-throughput analysis, which can be used for high-quality monitoring and crop protection (Mohammad et al. 2014). The miRNA based nanotechnology can be explored for detection and management of crop diseases (Chaudhary et al. 2018). Integration of nanotechnology-based approaches in agriculture has great potential to cope up with global challenges for food production or security, sustainability, and climate change (Prasad et al. 2014, 2017; Mishra et al. 2017).

Crop protection is the major key for sustainable crop production, especially under adverse environmental conditions (Mohammad et al. 2014). Global pesticide consumption to combat the loss due to pest and diseases constitutes about millions of tonnes per year (Joginder et al. 2017). Indiscriminate use of agrochemicals has led to several problems such as development of new races resistant to fungicides, unwanted side effects on beneficial organisms, residual toxicity in human food, animal feed, ecosystem disruption, environmental pollution, and decline in soil fertility (Gopal et al. 2012; Chowdappa and Gowda 2013; Joginder et al. 2017). The hazardous consequences of these synthetic chemicals against pest and diseases have been a major hindrance in achieving food safety and crop production under sustainable agriculture (Joginder et al. 2017). Nanotechnology has diverse applications in all stages of production, processing, storing, packaging, and transport of agricultural products (Mousavi and Rezaei 2011). Moreover, in recent years nanotechnology has been increasingly applied for the development of novel antimicrobial products (Banik and Sharma 2011; Ocsoy et al. 2013).

Nanotechnology has been considered as an additional technology which could help in meeting the global demands for sustainable agriculture. Application of nanotechnology in crop protection holds a significant promise in pest and disease management either by controlled delivery of functional molecules or as diagnostic tool for disease detection (Sharon et al. 2010; Chowdappa and Gowda 2013; Prasad et al. 2014, 2017; Bhattacharyya et al. 2016; Ismail et al. 2017; Gupta et al. 2018). In this chapter we have highlighted different types of NPs, their mode of action, some of the most promising and successful applications of nanotechnology in diagnosis and management of biotic stresses as technological boost for the improvement of agriculture in a cost-effective and environmentally friendly way. Finally we also overviewed the potential risks and limitations of application of NMs in agriculture for crop protection.

11.2 Important Nanoparticles Used in Plant Protection and Their Synthesis

A wide range of materials are used to manufacture various NPs like organic (chitosan, proteins, liposomes, and aptamers) and inorganic [silver (Ag), gold (Au), platinum (Pt), aluminum oxide (Al_2O_3), ferric oxide (Fe_2O_3), cerium dioxide (CeO_2), graphene, silica (SiO_2), and zinc oxide (ZnO)]. Other materials are also used such as ceramics, chitosan, polymers, dendrimers, and emulsions. Carbon nanomaterials (CNMs) such as single-walled carbon nanotubes (SWCNTs), multi-walled carbon nanotubes (MWCNTs),and grapheme are also being used in synthesis of NPs.

11.3 Synthesis of Nanoparticles

Before discussing the potential role of various NPs against biotic stresses in crop protection, one must first address the issues related to NMs synthesis. The reason behind this is to highlight the several steps involved during the production of NPs by which by-products and impurities can contaminate the final formulation and cause negative impacts on the receiving plant system (Petersen et al. 2014). Due to wide range applications of NPs in different fields of science and technology, different methods have been designed for their synthesis. Generally, NPs are synthesized by a variety of chemical and physical methods which are quite expensive and pose harmful effect to human health and environment (Ahmed and Ikram 2015). Therefore, a number of recent approaches seek more "eco-friendly" platforms and high efficiency such as biosynthesis using plant extracts, enzymes, and microorganisms (Bansal et al. 2014; Haleemkhan et al. 2015; Kuppusamy et al. 2016; Prasad 2014; Prasad et al. 2016). Generally, there are two approaches involved in the syntheses of NPs, i.e., "top to bottom" approach or "bottom to up" approach. The top to bottom approach reduces the size of large structure to smallest structure, whereas the bottom to up approach involves changing individual atoms and molecules into nanostructures. NP synthesis is not a simple process and hence requires specific skill and facilities. Characterization of NPs after synthesis is another important step that ascertains the attainment of desired particle size and their relative uniformity.

Biological agents such as plants and microbes have advantages over conventional chemical methods which associated with ecotoxicity (Chowdappa and Gowda 2013). The biological methods used for the synthesis of NPs include both extracellular and intracellular methods as shown in Table 11.1. Plant contains abundant natural compounds such as alkaloids, flavonoids, saponins, steroids, tannins, and other nutritional compounds. Table 11.2 shows important NP synthesis by plant extract. Plant extracts are considered as cost-effective, environment-friendly, and efficient alternative for the large-scale synthesis of NPs (Khatoon et al. 2017).

Synthesis of NPs with virus-like particles was not so common. Dujardin et al. (2003) reported the use of wild-type and recombinant *Tobacco mosaic virus* (TMV) for manufacturing metal nanoparticles (Pt, Au, or Ag). Synthesis of iron oxide and iron-platinum NP from *Brome mosaic virus* (BMV) and *Cowpea mosaic virus* (CMV) were also reported (Huang et al. 2007; Shah et al. 2009).

11.3.1 Application of Nanotechnology

11.3.1.1 Role of Nanotechnology in Detection and Diagnosis of Biotic Stresses in Plants

Early diagnosis of biotic stresses especially plant diseases is necessary for proper disease management and to prevent epidemic diseases. Nanotechnology helps in developing detection techniques which are simple and accurate, take less time, and do

Table 11.1 Microbes used in biosynthesis of nanoparticles

NPs	Microbes	Synthesis location	Methods	References
	Fungi			
Ag	*Fusarium oxysporum*	Extracellular	Reduction	Duran et al. (2005)
Ag	*Aspergillus fumigatus*	Extracellular	Reduction	Bhainsa and D'Souza (2006)
Au	*Verticillium* sp.	Intracellular	Reduction	Ramanathan et al. (2013)
Cadmium sulfide (CdS)	*F. oxysporum*	Extracellular	Enzyme mediated	Rai et al. (2009)
CdS	*Schizosaccharomyces pombe*	Intracellular		Kowshik et al. (2002)
Pt	*Neurospora crassa*	Extracellular	Reduction	Sanghi and Verma (2009)
	Bacteria			
Ag	*Bacillus thuringiensis* (Bt)	Crystal spore	Reduction	Jain and Kothari (2014)
Ag	*Enterobacter cloacae*	Extracellular	Reduction	Kalimuthu et al. (2008)
Ag	*B. subtilis*	Extracellular	Reduction	Saifuddin et al. (2009)
Au	*Pseudomonas aeruginosa*	Extracellular	Reduction	Narayanan and Sakthivel (2010)
Palladium (Pd) and Pt	*Escherichia coli*	Extracellular	Reduction	Deplanche et al. (2010)

Table 11.2 Biosynthesis of nanoparticles via different plants and their applications

NPs	Plants	Findings	References
Ag	*Croton sparsiflorus*	Effective against *Staphylococcus aureus*, *E. coli*, and *B. subtilis*	Kathiravan et al. (2015)
Ag	*Olea europaea*	Effective against drug resistance bacterial isolates	Khalil et al. (2014)
Silver nitrate ($AgNO_3$)	*Solanum torvum*	*P. aeruginosa*, *S. aureus*, *Aspergillus flavus*, and *A. niger*	Govindaraju et al. (2010)
$AgNO_3$	*Argemone mexicana*	*E. coli*, *P. aeruginosa*, and *A. flavus*	Singh et al. (2010)
Copper oxide (CuO)	*Phyllanthus amarus*	More effective than rifampicin against *B. subtilis*	Acharyulu et al. (2014)
Spherical and hexagonal ZnO	*Parthenium hysterophorus* L.	*A. flavus* and *A. niger*	Rajiv et al. (2013)
TiO_2	*Psidium guajava*	*Aeromonas hydrophila, Proteus mirabilis*, *E. coli*, *S. aureus*, and *P. aeruginosa*	Santhoshkumar et al. (2014)
ZnO	*Moringa oleifera*	*S. aureus*, *B. subtilis*, *P. aeruginosa*, *P. mirabilis*, *E. coli*, and fungal strains such as *Candida albicans* and *C. tropicalis*	Elumalai et al. (2015)
ZnO	*Camellia sinensis*	Antimicrobial activity	Senthilkumar and Sivakumar (2014)

not require any complicated techniques for operation. Nanophytopathology is a science which uses nanotechnology for detecting, diagnosing, and controlling plant diseases and their pathogens at an early stage (Hussain 2017). Nanotechnological tools such as nanobiosensors, nanofabrication, nanobarcodes, and other portable diagnostic systems help in diagnosing different plant diseases. Furthermore, nanodiagnostic kits can easily and quickly detect potential plant pathogens and thereby prevent the epidemic diseases. Nanomolecular techniques are used in monitoring and understanding the plant-microbe interactions, pathogen population genetics, and gene transfer between pathogens and host. Various NPs and QDs are used in fast detection of virus (Yao et al. 2009), fungi (Chartuprayoon et al. 2010), and bacteria (Boonham et al. 2008) as a biological marker with extreme accuracy. Use of important NPs and nanodevices in detection and diagnosis of plant diseases are discussed below.

11.3.1.2 Nanoparticles

NPs have a large surface to volume ratio, chemically alterable physical properties, strong affinity to target particularly proteins (AuNPs), enhanced or delayed particles (Sharon et al. 2010). Baac et al. (2006) used surface plasmon resonance (SPR) technique a form of NP-based sensor to directly detect an intact form of insect pathogen: the baculovirus, *Autographa californica* multiple nuclear polyhedrosis virus (AcMNPV). Yao et al. (2009) detected *Xanthomonas axonopodis* pv. *vesicatoria* (bacterial spot) in Solanaceous crops by using fluorescent SiO_2 NPs in combination with antibodies.

11.3.1.3 Nanoscale Biosensors

Plant disease forecasting aimed to forecast the chances or severity of plant diseases and nanosensors are used to improve pathogen detection. Bionanosensor significantly reduced response time to discover potential disease problems and increased sensitivity to detect pathogens. Nanoscale biosensors are utilized to detect and quantify minute amounts of biotic stresses such as viruses, bacteria, fungi, toxins, and other biohazardous substances in the environment. The major roles of these devices are to increase the use of autonomous sensors linked to global positioning system (GPS) for real-time monitoring. Otles and Yalcin (2010) reported NPs like carbon nanotubes (CNTs), dendrimers, superparamagnetic NPs, QDs, and metallic NPs (Au, SiO_2, and other noble metal NPs) used in the development of nanobiosensors. Nanosensors can detect mycotoxin which is a toxic secondary metabolites produced by fungi like *Aspergillus*, *Penicillium*, *Rhizopus*, *Alternaria*, and *Fusarium*. The nanoscale biosensor can also aid in precision farming and enhance productivity through better fertilization management, reduced input cost, and environment safety (Duhan et al. 2017).

11.3.1.4 Quantum Dots

QDs are nanocrystals having semiconductor properties. These are basically NPs that fluoresce when excited by a light source. QDs are used as inorganic fluorophores which can detect nucleic acid concentration due to its unique physical properties like narrow emission peak and longer fluorescence lifespan. With the help of a single excitation light source, QDs can be excited to all colors due to their broad absorption spectra (Warad et al. 2004). Their applications in medical science to detect specific biological markers are quite promising, but their use in plant pathology is limited. Synthesis of highly fluorescent cadmium telluride quantum dots (CdTeQDs) was achieved when *F. oxysporum* isolates were reacted with a mixture of Cadmium chloride ($CdCl_2$) and Tellurium dichloride ($TeCl_2$) at ambient conditions (Jain 2003). A QDs-fluorescence resonance energy transfer (FRET)-based sensor to detect witches' broom disease of lime caused by *Phytoplasma aurantifolia* was also developed. Detection of *Polymyxa betae* (Keskin), a vector of *Beet Necrotic Yellow Vein Virus* (BNYVV), was successfully done by QDs-FRET-based sensor.

11.3.1.5 Nanobarcodes

A bio-barcoded DNA (b-DNA) or NP-based barcode is an ultrasensitive method of amplification and detection of nucleic acids by tagging the pathogen. The concept of bio-barcode assay is unique and used as a potential alternative to the polymerase chain reaction (PCR) technique. But these devices can detect limited pathogens. Nanobarcodes are used in detection of pathogen DNA by developing a multiplexed diagnostic kit in order (Li et al. 2005). Bio-barcoded DNA tests employ oligonucleotide-modified magnetic AuNPs for signal amplification and for simple separation of a target protein from the sample (Goluch et al. 2006). Eastman et al. (2006) developed a QD nanobarcode-based microbead random array platform for accurate and reproducible gene expression profiling in a high-throughput and also used in detection of plant pathogen.

11.3.1.6 Nano Diagnostic Kit

These diagnostic kits are simple and robust which can be easily carried to the field and detect the pathogens at field level. Lattanzio et al. (2012) used multiplex dipstick immunoassay, a kind of nanodiagnostic kit for semiquantitative determination of *Fusarium* mycotoxins, viz., zearalenone, T-2, and HT-2 toxins, deoxynivalenol, and fumonisins in wheat, oats, and maize.

11.3.1.7 Nanofabrication

Nanofabrication is a nanodiagnostic imaging tool which can visualize plant tissue and cells for early diagnosis and detection of plant diseases (Rosen et al. 2011). This tool works by modulating the physical and chemical properties of NPs, which enhanced the contrast, imaging time, tissue specificity, and signal strength. Meng et al. (2005) reported the use of nanofabrication techniques in creating artificial plant parts such as stomata and xylem vessel.

11.3.1.8 Nanopore Sequencing System

Nanopore sequencing, also known as the fourth-generation DNA or next-generation sequencing technology equipment, has the potential of analyzing the entire genome in minutes instead of hour. It reduced the cost and time for pathogen identification. It is based on the application of an external voltage that causes electrolyte ions in a solution to move from one side of a nanopore to another electrophoretically. Badial et al. (2018) reported that a portable nanopore-based massively parallel sequencing technology can detect unsuspected viral and bacterial pathogens in plants and insect tissues. This approach of nanopore sequencing can also determine the major components of the insect vector's microbiome and the specific strain of small-genome, high-titer pathogens. The major drawback of such next-generation sequencing is that they require more expensive equipment with complicated data processing and sample preparation (Wight et al. 2016).

11.3.1.9 Nanoparticles in MicroRNA Detection

The miRNA-based technologies with unique features are promising tool in detecting and combating plant diseases. The miRNA is a small noncoding endogenous RNA molecule (about 18–23 nucleotides), which plays a key role in regulatory functions responsible for gene expression in plants and animals. Therefore, it is a powerful tool for controlling various epidemics in plants (Chaudhary et al. 2018).

Precise and sensitive assessment of miRNA acts as biomarkers which lead to early and correct diagnosis of plant diseases (Degliangeli et al. 2014). Generally, miRNA detection is based on real-time reverse transcription polymerase chain reaction (qRT-PCR) and microarrays. Nanotechnology is the right choice to make sensitive and precise alternatives for miRNA sensing as these detection techniques are prone to error. The artificial miRNA (amiRNA) technology can target endogenous miRNA precursors to give a small RNA guiding gene silencing in plants (Parizotto et al. 2004; Schwab et al. 2006). Oligonucleotide substitutions which mimic the intact secondary structure of endogenous miRNA precursors lead to targeted silencing of desired gene (Ai et al. 2011). Expression of a miRNA in transgenic *Arabidopsis* showed resistance to plant viruses such as *Turnip yellow mosaic virus* (TYMV) and *Turnip mosaic virus* (TMV).

11.3.2 Role of Nanotechnology in Plant Disease Management

To tackle the excessive usage of pesticides nanotechnology can tackle such problems which are eco-friendly and safe to the environment. The NPs can apply directly into the soil, seed, or foliage to protect the plants from invading pathogen. They directly affect the pathogens and these NPs also used in the formulation of pesticide (Khan and Rizvi 2014). Nanotechnology has many potential uses in plant disease management in different ways and is an emerging approach that may prove very effective in future for farm applications (Abd-Elsalam and Prasad 2018). Some of the NPs involved in plant disease management are given below.

11.3.2.1 Silver Nanoparticles

The Ag NP is the most studied and utilized NP since the use of nanosized Ag particles as antimicrobial agents have become more widespread. Ag NPs have broad-spectrum, strong inhibitory, and multiple modes of antimicrobial activity (You et al. 2012). They are less toxic to humans and animals than synthetic fungicides. Therefore, it is used mostly for controlling various plant pathogens as compared with commercially used fungicides. But its application against plant viruses has not been explored much. Lower concentrations of Ag NPs are sufficient for microbial control since NPs efficiently penetrate into microbial cells (Samuel and Guggenbichler 2004). The antimicrobial effect of Ag in unicellular microorganisms is thought to be brought about by enzyme inactivation (Kim et al. 1998) and affects biochemical processes in the microorganisms (Prameela 2017).

11.3.2.2 Silica Nanoparticles

Silicon induces the plant's own defense mechanisms (Remus-Borel et al. 2005; Fauteux et al. 2006) by increasing disease and stress resistance in plants (Brecht et al. 2004). SiO_2 NPs can deliver DNA and chemicals into plants, thus, creating a powerful new tool for targeted delivery into plant cells by offering the possibility of genetic manipulation of plants. They have regularly arranged pores which increase the surface area of the NPs (Wang et al. 2002). Mode of action of SiO_2 NPs in agricultural formulations is taken over from pharmaceutical applications, where mesoporous SiO_2 NPs are used as controlled release carriers in drug delivery (Chen et al. 2004). Torney et al. (2007) showed the application of SiO_2 NPs in the target-specific delivery of proteins, nucleotides, and chemicals in plant biotechnology by using a honeycomb mesoporous SiO_2 NP system with 3 nm pores can transport DNA and chemicals into isolated plant cells and intact leaves.

11.3.2.3 Copper Nanoparticles

Cu plays an important role in the prevention and treatment of a large variety of plant diseases especially in vineyards and organic farming (Borkow and Gabbay 2005). Cu-based chemicals are effectively used as antimicrobials in agriculture. However, with respect to its nanoparticulate form, there have been a limited number of studies especially in the area to control plant diseases. Cu-based fungicides generate highly reactive hydroxyl radicals which can damage lipids, proteins, DNA, and other biomolecules. Banik and Luque (2017) used Cu NPs against plant pathogenic fungi, oomycete, bacteria, beneficial microbes *Trichoderma harzianum* and *Rhizobium* spp. and reported that integration of Cu NPs with non-nano Cu like copper oxychloride (COC) caused growth inhibition of *Phytophthora cinnamomi*, *A. alternata* and *P. syringae*. They also found that Cu NPs were not biocidal against *Rhizobium* spp. and *T. harzianum* indicating its potential use in the agroecosystem.

11.3.2.4 Zinc Oxide Nanoparticles

ZnO NPs increased plant growth, development, and enhanced resistance by inducing reactive oxygen species (ROS) generation, which can lead to cell death when the antioxidative capacity of the cell is exceeded. ZnO NPs are used as bactericides and fungicides in agricultural and food safety applications. They have shown much better antimicrobial activity than large Zn particles, since the small size <100 nm and the high surface-to-volume ratio of NPs allow better interaction with bacteria (Xie et al. 2011). Nano ZnO supplemented with Murashige and Skoog (MS) media improved tolerance to biotic stress by promoting somatic embryogenesis, shooting, regeneration of plantlets, and also induced proline synthesis and the activity of superoxide dismutase, catalase, and peroxidase (Helaly et al. 2014).

11.3.2.5 Chitosan-based Nanoparticles

Chitosan is a natural polysaccharide of β-1-4 linked *N*-acetyl-ᴅ-glucosamine and ᴅ-glucosamine. Chitosan has various applications in biology due to its biodegradable, nontoxic, and antifungal properties. To avoid the harmful effect of synthetic chemicals, chitosan and chitosan NPs are found to be more effective against many pathogens and reduce their spread and enhance plant defenses. Fragments from chitosan are known to have eliciting activities leading to a variety of defense responses in host plants in response to microbial infections, including the accumulation of phytoalexins, pathogen-related (PR) proteins and proteinase inhibitors, lignin synthesis, and callose formation (El-Hadrami et al. 2010). Chitosan NP is a positive modulator of innate immune responses in plants (Chandra et al. 2015). Chitosan NPs' treatment leaves produced significant improvement in the plant's innate immune response through induction of defense enzyme activity, upregulation of defense-related genes including that of several antioxidant enzymes, as well as the elevation of the levels of total phenolic and increase in nitric oxide (NO). Chitosan NPs may be used as a more effective phytosanitary or disease control agent compared to natural chitosan for sustainable organic cultivation.

Plant-parasitic nematodes are important agricultural pests, and their control measures depend upon the use of highly toxic nematicides which are harmful to the environment (Bhau et al. 2016). NPs have shown to be an effective nematicide against many plant-parasitic nematodes as they have multisite mode of action. Au and Ag NPs possess nematicidal activity which provides an alternative to high-risk synthetic nematicides or inconsistent biological control agents (Thakur and Shirkot 2017). Silver NPs when used along with chemicals like nematicides, their efficiency increased significantly.

11.3.3 Role of Nanotechnology in Insect Pest Management

Pesticides cause adverse effects on human health, environment, and pollinating insects. Due to extensive use of conventional insecticides resulted into development of resistance pests, nanopesticide came as an alternative method having enhanced property and reduced the quantity of insecticide application compared to conventional insecticide. NMs can be used in the preparation of new formulations like pesticides, insecticides, and insect repellents (Gajbhiye et al. 2009). Wang et al. (2014a, b) reported the use of Porous Hollow Silica NPs (PHSNPs) loaded with validamycin as efficient hydrophilic delivery system of water-soluble pesticide for its controlled release.

11.3.4 Role of Nanotechnology in Weed Management

Weeds are the biggest threat in agriculture and result in a decline of crop yield due to use of nutrients by the weeds which otherwise were available to the crop plants. Commercial herbicides are designed to control weed plants but when sprayed have a chance of damaging crop plants, decreasing soil fertility, and creating soil pollution. Nanoherbicides under development in the current decade could be a new strategy to address all the problems caused by the conventional herbicides (Abigail and Chidambaram 2017). Nanoherbicide used for early weed control could reduce the herbicide resistance potential. Nanoherbicide, after entering the root system of the weed and gets translocated, inhibits the glycolysis of the plant root system starvation of the plant and thus kills it. Luque and Rubiales (2009) reported the use of nanoencapsulation to control parasitic plants by killing systematically at lower doses. Nanoherbicide also helps in detoxification of residue herbicide, for example, CarboxyMethly Cellulose NPs detoxified 88% of Atrazine (Satapanajaru et al. 2008). Table 11.3 shows the role of different NPs against various biotic stresses.

Table 11.3 Role of different nanoparticles against various biotic stresses in plants

Nanoparticles	Biotic stresses	Reference
	Fungi	
Ag	*A. alternata*, *Sclerotinia sclerotiorum*, *Macrophomina phaseolina*, *Rhizoctonia solani*, *Botrytis cinerea*, and *C. lunata*	Krishnaraj et al. (2012)
Ag	*Sphaerotheca pannosa* var. *rosae*	Kim et al. (2008)
Ag	*A. flavus* and *Fusarium solani*	Gallardo et al. (2016)
SiO_2	*F. oxysporum* and *A. niger*	Suriyaprabha et al. (2013)
Zn	*B. cinerea* and *Penicillium expansum*	He et al. (2011)
ZnO	*A. niger and F. oxysporum*	Patra et al. (2012)
Chitosan and Ag	*A. alternata*	Ahmed (2017)
Ag	*Bipolaris sorokiniana* and *Magnaporthe grisea*	Jo et al. 2009
ZnO and magnesium oxide (MgO)	*A. alternata, F. oxysporum*, *Rhizopus stolonifer*, and *Mucor plumbeus*	Wani and Shah (2012)
	Bacteria	
Ag	*E. coli, P. aeruginosa*, and *S. aureus*	Guzman et al. (2012)
Zn	*P. aeruginosa*	Jayaseelan et al. (2012)
CuO	*E. coli*, *P. aeruginosa*, *B. subtilis*, and *S. aureus*	Azam et al. (2012)
DNA-directed Ag	*Xanthomonas perforans*	Ocsoy et al. (2013)
	Virus	
Ag	*Sunhemp rosette virus* (SHRV)	Jain and Kothari (2014)
Au	*Barley yellow mosaic virus* (BYMV)	Alkubaisi et al. (2015)
	Insect pests	
Nanostructured Alumina N	*Sitophilus oryzae* L. and *Rhyzopertha dominica*	Stadler et al. (2010)
Ag NPs, TiO_2, ZnO, and Al_2O_3	*Sitophilus oryzae* and Grasserie disease in silkworm (caused by *Bombyx mori* and baculovirus BmNPV (*B. mori* nuclear polyhedrosis virus)	Goswami et al. (2010)
SiO_2	*Spodoptera littoralis*	Helaly et al. (2016)
Chitosan NPs coated fungal metabolite	*Aphis gossypii*	Chandra et al. (2013)
Chitosan	*Callosobruchus maculatus*	Sahab et al. (2015)
Ag and Zn	*Aphis nerii*	Rouhani et al. (2012)
	Weeds	
Ag	*Lemna minor*	Gubbins et al. (2011)
Ag NPs chitosan encapsulated paraquat	*Eichhornia crassipes*	Namasivayam et al. (2014)
CuO	*Lolium perenne* and *Lolium rigidum*	Atha et al. (2012)

(continued)

Table 11.3 (continued)

Nanoparticles	Biotic stresses	Reference
Poly(ε caprolactone) (PCL) nanocapsule of atrazine	*Amaranthus viridis* and *Biden spilosa*	Sousa et al. (2018)
	Nematode	
TiO_2, ZnO, Al_2O_3, and Ag	*Caenorhabditis elegans*	Roh et al. (2009), Wang et al. (2009)
Ag, SiO_2, and TiO_2	*Meloidogyne incognita*	Ardakani (2013)
Ag NP	*M. incognita*	Cromwell et al. (2014)
SiO_2	*C. elegans*	Pluskota et al. (2009), Acosta et al. (2018)

11.3.5 Role of NPs on Plant Growth Enhancement

NMs and their various formulations have great potential as novel tool for crop growth and development (Selva Preetha and Balakrishnan 2017) which improves the existing crop management practices. From the various reports, it was found that nanofertilizers (NFs) significantly influenced the seed germination and seedling growth. Due to easy penetration of NF into the seed thereby, availability of nutrient to the growing seedling also increased, resulting into healthy and more shoot and root length. But if the concentration is more than the optimum doses it may inhibit the germination and seedling growth of the plant. Therefore, NPs have both positive and negative effects on the plant (Nadi et al. 2013). The efficacy of NPs can be determined by their size, surface covering, chemical composition, and reactivity (Khodakovskaya et al. 2012) and depends on their concentration which varies from plants to plants (Table 11.4).

The impacts of using NPs in plants are as shown in Tables 11.4 and 11.5. In most of the studies NPs showed negative impact at higher concentration, whereas Mahmoodzadeh et al. (2013) reported that in *Brassica napus*, TiO_2 NPs up to 2000 ppm concentration increased seed germination and seedling vigor. Shah and Belozerova (2009) studied the effect of metal NPs such as silicon (Si), Pd, Au, and copper (Cu) on seed germination of lettuce. They observed that NPs showed positive effects of Pd and Au at lower concentration, Si and Cu at higher concentration, and Au and Cu in combined mixture.

Table 11.4 Effects of NPs on growth and development of various crop plants

Nanoparticles	Optimum concentration	Plant	Effects	References
Ag	10–30 μg/mL	*Boswellia ovalifoliolata*	Increased germination and seedling growth	Savithramma et al. (2012)
MWCNTs	40 μg/mL	*Solanum lycopersicum*	Uptake nutrients, i.e., K, Ca, Fe, Mn, and Zn	Tiwari et al. (2013)
Nanoanatase TiO_2	0.25%	*Spinacia oleracea*	Induction in enzyme activity	Yang et al. (2006)
CNTs	75 wt% CNTs	*Medicago saliva* and *Triticum aestivum*	Root elongation	Miralles et al. (2012)
Water soluble carbon nanotubes (wsCNTs)	6.0 μg/mL	*Cicer arietinum*	Growth rate	Tripathi et al. (2011)
Sulfur	500, 1000, 2000, and 4000 ppm	*Vigna radiata*	Dry weight	Patra et al. (2013)
nZVI (nanoscale Zero-valent iron particles) iron oxide NPs	Iron 0.5 g/L	*Arabidopsis thaliana*	Root elongation	Kim et al. (2014)
Alumina NPs	10 mg/L	*Lemna minor*	Increased in root length	Juhel et al. (2011)
Cerium oxide (CeO_2)	500, 1000, 2000, 4000 mg/L	*Zea mays*, *Medicago sativa* and *G. max*	Increased root and stem growth	Lopez-Moreno et al. (2010)
Iron oxide	50 ppm	*Vigna radiate*	Enhancement in biomass	Dhoke et al. (2013)
Cobalt oxide (Co_3O_4)	5 g/L	*Raphanus sativus*	Increased root growth	Wu et al. (2012)
CuO	500 mg/kg	*Triticum aestivum*	Biomass increased	Dimkpa et al. 2012
TiO_2	1000 mg/L	*T. aestivum*	Chlorophyll content increased	Mahmoodzadeh et al. (2013)
TiO_2	0.05–0.2 g/L	*S. lycopersicum*	Increased net photosynthetic rate and enhanced H_2O conductance	Qi et al. (2013)
ZnO	1.5 ppm	*C. arietinum*	Shoot and dry weight increased	Burman et al. (2013)
ZnO	400 mg/kg	*Cucumis sativus* fruit	Micronutrients (Cu, Mn, and Zn)	Zhao et al. (2014)
ZnO	10 mg/L	*Cyamopsis tetragonoloba*	Significantly increased plant biomass, shoot length, root length, and root area	Raliya and Tarafdar (2013)

(continued)

Table 11.4 (continued)

Nanoparticles	Optimum concentration	Plant	Effects	References
Carbon based grapheme NPs	At lower doses	*Coriandrum sativam* and *Allium sativum*	Trigger physiological processes and acting as growth regulators	Chakravarty et al. (2015)

Table 11.5 Inhibitory effect of nanoparticles on various crop plants

NPs (size)	Conc.	Plant studied	Impact	References
Ag NPs (10 nm)	0.2, 0.5, and 3 mg/L	*A. thaliana*	Inhibit root growth, decrease in chlorophyll “a” and “b” and hence total chlorophyll	Qian et al. (2013)
CuO (<50 nm)	2.5, 10, 50, 100, and 1000 mg/L	*Oryza sativa*	NPs accumulate in chloroplast	Costa and Sharma (2016)
ZnO (15.37 nm)	100, 200 μM	*T. aestivum*	Photosynthetic efficiency is reduced and inhibit antioxidant activity	Tripathi et al. (2017)
Cu NPs (around 20 nm)	200, 400, 600, 800, and 1000 mg/L	*Phaseolus radiates* and *T. aestivum*	Seedling and shoot growth decreased with an increase in NP concentration, roots were more effected than the shoot	Lee et al. (2008)
TiO_2 NP (15 nm)	100 mg/L	*Linum usitatissimum*	Root biomass and root length reduced	Clement et al. (2013)
CeO_2 (10 ± 3.2 nm)	100 and 500 mg/L	Transgenic cotton (Bt-29317) Conventional cotton (Jihe 321)	Destruction of vascular bundles, levels of Zn, Mg, Fe, and P in xylem sap was reduced and conventional cotton was more sustainable to CeO_2 NP stress in comparison to transgenic cotton	Nhan et al. (2015)
NiO (23.34 nm)	25, 50, 100, 250, 500, 1000, 2000 mg/L	*S. lycopersicum*	Apoptosis in tomato root cells	Faisal et al. (2013)
Al (18), ZnO (20), Zn (35), Al_2O_3 (60 nm)	2000 mg/L	*Raphanus Raphanistrum* spp. *sativus*, *Brassica napus*, *Lolium perenne*, *Lactuca sativa*, *Zea mays*, *C. sativus*	Phytotoxic effect with 2000 mg/L	Lin and Xing (2007)

(continued)

Table 11.5 (continued)

NPs (size)	Conc.	Plant studied	Impact	References
Ag NP	750 and 1500 mg L-1 1500 mg L-1	Lolium and *Linum usitatissimum* *Hordeum vulgare* L.	Complete inhibition of ryegrass germination Only 13% reduction	El-Temsah and Joner (2012)
Fe_3O_4 (17.7 ± 3.9 nm)	20, 50, 100 mg/L	*Z. mays*	Germination index decreases with 100 mg/L treatment	Li et al. (2016)

11.4 Mechanism of NPs-Plant Interaction Against Biotic Stresses

From the various scientific studies, it was found that most of the NPs are toxic to plants at high concentration. Therefore, to make clear the toxic effect of different NPs and their uptake and translocation by plant into different tissues are needed. Based on their transportation, properties and reactivity, NPs will interfere with different metabolic activity.

11.4.1 Uptake and Translocation of NPs

The uptake efficiency of NPs and their effects on the growth and metabolic functions vary among plants. For the uptake and translocation of NPs, in a plant has to pass through a various chemical and physiological barriers. Cell wall is the first barrier of NPs to cross, when it comes in contact with plant. Cell walls (plants) composed of cellulose that permits the entry of smaller particles like NPs and restricting the larger one. Kurepa et al. (2010) reported that NPs can also induce the formation of larger pores in cell wall which further facilitate the entry of larger NPs. Generally, NPs enter plant tissue either through root or aboveground parts like root junctions and wounds and then move through apoplastic and symplastic pathways to the xylem, crossing the endodermis and then moving to the rest of the plant through the vascular bundles. This type of transport was reported in mesoporous silica NPs (Sun et al. 2014) and SiO_2 NPs (Le et al. 2014). NPs also transported inside the cells through endocytosis (Blechinger et al. 2013) or through pores or channels, as in the case of TiO_2 NPs (Gao et al. 2008). ZnO NPs barely move beyond the endodermis but absorbed from the root nutrient solution by the root and internally transported by the apoplastic and symplastic pathways (Lin and Xing 2008).

The mathematical model proposed by Wong et al. (2016) indicates lipid exchange mechanism for NP transport inside the plant cells. They indicated that size, magnitude, and zeta potentials determined the transport of NPs inside the plant system. NPs when present at higher concentrations damage the plant cell wall and plasma membrane, thereby penetrating it and interacting with different plant's normal processes (Mirzajani et al. 2013).

11.4.2 *Mechanisms of Nanoparticles-Plant Interaction in Response to Biotic Stresses*

NPs interfere with plant physiological and metabolic functions directly or indirectly in several ways, by providing micronutrients (Liu and Lal 2015), gene regulation (Nair and Chung 2014), or interfering with different oxidative processes which results in oxidative burst. There are many possible mechanisms but the real mechanism of NPs in plants against biotic stresses is not very well known (Panacek et al. 2006). Following few possible mechanisms were reported by several workers.

11.4.3 *Direct Attachment of NPs with Plant Pathogens*

Ag NPs directly attached to the spores of *F. oxysporum* to penetrate the cell membranes to kill the fungal spores (Abkhoo and Panjehkeh 2017) and disturb their permeability and respiration (Panacek et al. 2006). The binding of NPs to the bacteria depends on surface area available for interaction. Smaller particles with larger surface area available for interaction will give more bactericidal effect than the larger particles (Panacek et al. 2006). Ag NPs were also found inside the bacterial and fungal cell, causing DNA damage. Cai et al. (2018) observed direct attachment of Magnesium oxide nanoparticles (MgO NPs) to the surfaces of the *Ralstonia solanacearum* cells. Ag NP-treated fungal hyphae were seriously damaged on hyphal walls which result into plasmolysis of hyphae (Min et al. 2009).

Wang et al. (2014a) reported the three steps antifungal mechanism of carbon nanomaterials (CNMs), i.e., (i) NPs deposit on surface of the *F. graminearum* spores, and (ii) water uptake was inhibited and (iii) then plasmolysis of spores. The well-dispersed CNMs, graphene oxide (GO) wrap on spores, and cluster of reduced graphene oxide (rGO) was also detected beside the *F. graminearum* spores. But the mechanism of CNMs that inhibit water uptake inside the spores is not yet clear. But it may be due to high CNM concentrations that water uptake and spore development could be prevented due to increased blockage of water channels imposed by surface-adsorbed CNMs.

11.4.3.1 ROS Production (Destructive or Signaling Role)

It was observed that NPs when present in excess result into ROS production and interfere with the oxidative mechanism and electron transport chain of chloroplast and mitochondria (Jiang et al. 2014; Cvjetko et al. 2017). Several reports have shown an increase in lipid peroxidation, protein modifications, and DNA damage in plants-NP interaction (Van Breusegem and Dat 2006; Atha et al. 2012). ZnO and Ag NPs generate ROS, the primary cause for the antimicrobial activity (Hwang et al. 2012*;* Xue et al. 2014). Zinc nitrate-derived nano-ZnO against *A. fumigatus* showed hydroxyl- and superoxide radicals-mediated fungal cell wall deformity and death due to high energy transfer (Patra and Goswami 2012). Zheng et al. (2005) reported the seed treatment of TiO_2 NPs increased 45% increment in chlorophyll “a” in spinach. They observed that this was due to the increase in inorganic nutrients absorption that enhanced the utilization of organic substance and quenching of oxygen-free radicals.

The indication of NPs influence the hormonal balance in plants was observed by increased cytokinin level in *Capsicum annuum* as a response to Ag NP stress and a decreased indole-3-acetic acid (IAA) and abscisic acid (ABA) in cotton in response to CuO NP, thereby affecting the plant metabolism. Hence, conclusion was drawn that the toxic effect of NPs in the plant was mainly through ROS production.

In spite of destructive activity of ROS, it also has a signaling role in a variety of cellular processes including tolerance to environmental stresses (Sharma et al. 2012a, b). This dual role of ROS depends on the equilibrium between ROS production and scavenging. Therefore, plant cells developed a strong antioxidant mechanism to precisely control the ROS level. This antioxidant mechanism produces enzymatic (catalase, guaiacol peroxidase, and superoxide dismutase) and nonenzymatic (ascorbate, carotenoids, glutathione, tocopherols, and phenolics) molecules (Sharma et al. 2012b). Therefore, to cope up with the plants under stress increases the production of antioxidant molecules (Rastogi and Pospisil 2010; Sharma et al. 2012b). This mechanism was reported by several workers (Faisal et al. 2013; Jiang et al. 2014; Costa and Sharma 2016) who confirm the regulation of antioxidant system as a response to NP-plant interaction. If increased ROS production cannot control by this antioxidant, then ROS will oxidized the cell macromolecules and ultimately plants will be death due to apoptosis or necrosis (Sharma et al. 2012b; Faisal et al. 2013). Induction of defense phenomenon was induced like expression of resistance genes (Van Aken 2015), accumulation of proteins, defensive metabolites, and enzymatic and nonenzymatic antioxidants (Jiang et al. 2012), when the level of oxidative stress does not exceed the toxic threshold. Corral-Diaz et al. (2014) also reported increased accumulation of antioxidants in plants in response to CeO_2 NP. Though the exact mechanism of plant-NPs interaction is not understood, the possible mechanism is induced.

11.4.3.2 Other Mechanisms

Ocsoy et al. (2013) observed that Ag^+ ions when bind to cysteine-containing proteins on plasma membranes caused physiological and biochemical damage. Ag NPs penetrated and damaged the cell membrane on plant pathogenic fungi, hence reducing the infection (Jo et al. 2009). Lamsal et al. (2011) reported disease suppression by Ag NPs through resistance mechanisms. He et al. (2011) reported ZnO NPs caused systemic disruption of cellular function of *B. cinerea* and *Penicillium expansum*, resulting into hyphal malformation and fungal death. Various NPs were observed to decay membrane potential, decreased ATPase activity at the cellular level. Inactivation of cell wall thiol groups of fungal cell wall by Ag ions resulted into disruption of transmembrane, electron transport chain, and energy metabolism. Other mechanisms like mutations in fungal DNA, dissociation of enzyme complexes, reduction in membrane permeability and cell lysis (Velmurugan et al. 2009). Ag NPs' toxicity to nematode is due to disruption of cellular mechanism and severely affects the ATP synthesis, membrane permeability, oxidative stress induction, and increased formation of ROS (Ahamed et al. 2010; Lim et al. 2012). SiO_2 NPs induce accumulation of insoluble ubiquitinated proteins and nuclear amyloid and reduce the pharyngeal pumping resulting in premature aging of *Caenorhabditis elegans* (Scharf et al. 2013).

Li et al. (2017) reported the expression of stress response genes such as glutathione S-transferase (*Shgst*1) and superoxide dismutase 2 (*ShSOD*2) induced in the *Sclerotinia homoeocarpa* on exposure to the Ag NPs and ZnO. A significant increase in the nucleic acid contents of fungal hyphae was also observed. They also observed that a zinc transporter (*Shzrt*1) helps in accumulating and Ag NPs into *S. homoeocarpa* cell. Abnormal expression of several water channel genes, *LeAqp2*, in tomato plants induced by MWCNTs (Khodakovskaya et al. 2011).

11.4.3.3 Mechanisms of NPs-Insect Interaction

The insect pests used the cuticular lipids to protect their water barrier and thereby preventing death from desiccation. When nanosilica is applied as insecticide into the plant surface, insect pests die due to particles absorbed into the cuticular lipids by physisorption (Barik et al. 2008). Aluminosilicate in nanotube can stick to plant surfaces and surface hair of insect pests; thereby physiological functions were disturbed (Patil 2009). Nanosilica also affects the feeding preference of the *S. littoralis* and increases the resistance of tomato plants. It also affects the biological parameters of the insect such as longevity and nymph production, thus reducing the reproductive potential (El-bendary and El-Helaly 2013).

From the various studies discussed above, and in the literature in general, the antimicrobial mechanism of NPs was often unclear. The possible mechanisms may not operate separately but more than one mechanism can occur simultaneously.

11.5 Types of Nanoformulation Used in Plant Protection

Significant differences exist between nanotechnology-based and conventional formulations, because of their size and surface characteristics. Pesticide nanodelivery techniques such as nanoencapsulates, nanocages, and nanocontainers, being more efficient lead to less pesticide release in environment including quick pesticide degradation in soil (Sadurni et al. 2005). Certain properties of these NMs, such as their ability to dissolve in water more effectively and higher stability, are designed to increase the potential of these pesticides. Nanoformulations are regarded as excellent agrochemicals enhancing the bioefficacy of pesticides with a good shelf life. There are different types of nanoformulations that can be used for agrochemicals like nanogel, nanoemulsions, nanoencapsulations, nanosuspensions, and others.

11.5.1 Nanogel

Nanogels may be defined as nanosized hydrogel systems which are either copolymerized or monomeric. They are also highly cross-linked systems in nature containing polymer systems (Phillips et al. 2010). The need for developing nanogel systems has proved to be potential for delivering active ingredients in controlled, sustained, and targetable manner due to sudden outbreak in the field of nanotechnology. Initially, the gels have come across as semisolid formulations with three-dimensional organic systems encompassing fluids and drugs. The importance of nanosized microgel and hydrogel has begun due to specific delivery system anticipation. Nanogels are classical formulations and can change variably to provide a three-dimensional structure, by varying solvent quality and splitting the volume fraction (Kageyama et al. 2008).

11.5.2 Nanoemulsions

The nanoemulsion formulations have characteristic features like low viscosity, good stability, dispersity, and transparent properties making them beneficial in various fields like pharma and food industries, cosmetic, and agrochemical formulations (Nair et al. 2010). They have a particle size less than 200 nm, making the systems transparent and kinetically stable. Pesticides formulated with nanoemulsions are rather more environmentally friendly, cost-effective, and economically viable as compared to microemulsions and surfactants due to their low-surfactant concentration (Hazra et al. 2013). Nanoemulsions are produced by application of low-energy emulsification methods, and the energy stored could promote smaller sized NPs for longer life (Lim et al. 2011). Nanoemulsions are water or oil-based, containing uniform suspensions of pesticidal NPs, along with many potential applications for controlling disease and pest. Due to its low surface tension, nanoemulsions show greater stability and increased covering in leaves (Gogoi et al. 2009). The main advantages are solubilization of hydrophobic pesticides, no precipitation, increased stability, and improved uptake but are broadly developed for poorly water-soluble one.

11.5.3 Nanoencapsulation

Delivery of these pesticides depends on specific conditions, such as moisture and temperature. Nanoencapsulation techniques provide both inherent and altered pesticides to control the release and successive availability of pesticides to the crops (Eerikainen et al. 2003). Nanoencapsulated pesticides enable small amount of pesticides to be used efficiently over a given period of time interval allowing them to withstand the severe environmental processes that help to eradicate conventionally applied pesticides, i.e., evaporation and photolytic, leaching, hydrolytic, and microbial degradation.

11.5.4 Nanosuspensions

It is submicron colloidal dispersion of pesticides consisting of pure particles stabilized by surfactants. Problems related with distribution of poor water soluble pesticide and lipid-soluble pesticides can be resolved by using nanosuspension formulation. Nanosuspensions are prepared for the compounds that are insoluble in water but are soluble in oil. Conventionally, the pesticides are formulated in liposome emulsion systems that are insoluble in water but soluble in oil phase system. Since these lipidic formulation approaches are not applicable to all pesticides, nanosuspensions are preferred in this case. Similarly, when pesticides are insoluble in both water and organic media, these suspensions are used as a formulation approach, instead of using lipidic systems.

11.6 Polymer-based Nanoformulations

The first formulation containing polymers is prepared for controlled release of biocides since the early 1970s. Polymeric nanoformulations are preferred by researchers rather than compared to commercial formulations due to their expression of higher efficacy of the encapsulated ingredient in insecticidal property. The most important characteristics of polymeric nanoformulation are slow release, low solubility of the encapsulated insecticide, and protection against degradation making them first option for nanoencapsulation. Due to abovementioned features, polymeric nanoinsecticides can be used for practical application with large potential. A new concept of hybrid nanoformulation (encapsulation of liposome coating or nanoemulsion) has been proposed for the controlled release of some insecticides. Most of the nanoinsecticides have been constructed for slow release along with persistence in the environment, in order to assure efficacy. Therefore, it is necessary to inspect the environmental fate processes for both nanoformulated insecticides and nanocarriers. So, given below different pesticide formulations:

11.6.1 Fungicide Formulation

Polyethylene glycol has been used to trap mancozeb to form a nanopesticide formulation. Mancozeb is a nonsystemic fungicide. It has both antifungal and antibacterial activities against *C. albicans* and *S. aureus*, respectively (Venugopal and Sainadh 2016). Carbendazim is a systemic benzimidazole fungicide and amphiphilic-based copolymer which has been used to achieve controlled release of this fungicide formulation. Slow release of active ingredients compared to commercial 50% WP is focused here which also reduces the need for further applications. It effectively controls the pathogen *R. solani*, which affects the rice plant (Mondal et al. 2017). Lower concentration of 0.5 and 1 ppm of carbendazim controls the plant pathogen *F. oxysporum* and *A. parasiticus*. A product named as Nano green was reported to eliminate blast disease (*M. grisea*) from infected rice plant and it was prepared by mixing several bio-based chemicals.

11.6.2 Insecticide Formulation

Insecticide beta-cypermethrin can be added into nanoemulsions thereby showing uniform distribution and stability. It comes under hydrophobic pyrethroids group of insecticide. Pesticide solubility is very necessary in diluted forms of emulsions (Du et al. 2016). When compared to commercial formulations, beta-cypermethrin displays good dispersion in the nanoemulsion formulations (Wang et al. 2007). Insecticide imidacloprid formulation shows fine bioefficacy. It is able to attain controlled release of the insecticide and control the soybean pest thereby increasing yield of plant (Adak et al. 2012). Mixed formulation of imidacloprid and carbofuran can manage insects such as *A. gossypii* which is widely distributed affecting many agricultural crops like pumpkin, cotton, citrus, etc. The formulation shows better control when compared to the commercial one (Amini Jam et al. 2014). Nanoformulation of controlled release etofenprox controls *S. litura* as it increases the availability of active ingredient and avoids the loss of insecticide (Hwang et al. 2011). Novaluron is a chemical along with insect growth regulator which is less toxic to the environment and also to the nontarget organisms. When added to the microemulsion novaluron becomes organic solvent-free, which makes it able to control pests (Elek et al. 2010). The organophosphate group in triazofos acts as insecticide, nematicide, and acaricide. It is highly flammable and toxic. Due to its poor solubility in water, the chemical is used in microemulsion system. It prevents the hydrolysis of pesticide in an alkaline condition which is better compared to acidic condition in the nanoemulsion form (Song et al. 2009).

11.6.3 Herbicide Formulation

Glyphosate belongs to hydrophilic organophosphorous group of herbicide. Initially, glyphosate isopropyl amine is combined with the emulsion formulation which is further diluted to form a nanoformulation. Preemulsion form which is nanoformulated has a long shelf life and potent ability to deliver the glyphosate isopropyl amine herbicide to control the weeds, viz., *Eleusine indica* commonly known as Indian goose grass (Jiang et al. 2011). Lower amounts of surfactant reduce the environment toxicity as compared to commercial pesticide formulations (Jiang et al. 2011; Piscureanu et al. 2001). The herbicide pretilachlor is used as encapsulated monolithic dispersions to control the weed *E. crusgalli* by incorporating in microemulsions. The emulsion is much better as it has low particle size. Even after further dilution of the emulsion formulation, the particle size is maintained in the nanoscale range. It shows a long shelf life for more than a year, due to its low droplet size (Goswami et al. 2010). Metribuzin is a most commonly used herbicide and it is highly soluble in water which results in groundwater contamination. Sepiolite gel ensures controlled release of the herbicide as it is able to entrap the metribuzin (Maqueda et al. 2009).

11.7 Smart Delivery System of Nanoformulation

Smart delivery of agrochemicals such as fertilizers and pesticides is an important condition of application in agriculture. Nanoformulations showed controlled release of agrochemicals, site-targeted delivery, reduction in toxicity, and enhanced nutrient application of delivered fertilizers (Cui et al. 2010; Bhattacharyya et al. 2016; Prasad et al. 2019). Agrochemicals are traditionally applied to crops by spraying or broadcasting methods. Very less concentration of chemicals reaches the target site of crops, which is much below the minimum effective concentration required. Hence, repeated application is required to have an effective control which results in causing some unfavorable effects such as soil and water pollution. Large-scale use of agrochemicals affects normal flora and fauna causing environmental pollution. Thus, to avoid repeated application of chemicals with safe and easy mode of delivery, nanoencapsulated agrochemicals should be designed in such a way that they possess all necessary properties such as effective concentration (high solubility, stability, and effectiveness), time-controlled release in response to certain stimuli, enhanced targeted activity, and less ecotoxicity (Boehm et al. 2003).

Nanotechnology has possible prospects of use in different ways for managing diseases and pests. When NPs are applied directly in soil, their effects on nontarget organisms will be of great significance especially the mineral solubilizing microorganisms. Second, carbon tubes and cups are used as carrier in pheromones, systemic acquired resistance (SAR)-inducing chemicals, polyamine synthesis inhibitors, and also concentrated active ingredients of pesticides for their controlled release especially under flooded conditions (Khan et al. 2014). Application of herbicides with inadequate soil moisture may lead to loss as vapor, especially in rainfed areas; therefore, herbicides cannot be applied in advance anticipating rainfall. The competing weed along with crops is expected to get nourished by the controlled release of encapsulated herbicides (Chinnamuthu and Boopathi 2009).

11.7.1 In Vitro Methods of Application

11.7.1.1 Aeroponics

Weathers and Zobel (1992) first reported this method. In this method, plant roots are suspended in air and the nutrient solution is sprayed continuously. The gaseous environment around the roots can be controlled through this method. However, the use of aeroponics is not widespread as it requires a high level of nutrients to sustain rapid plant growth.

11.7.1.2 Hydroponics

This technique was first introduced from dissolved inorganic salts by Gericke (1937). This technique is also known as “solution culture” as the plants are grown without soil, viz., plants along with their roots immersed in a liquid nutrient solution. Some of the factors that need to be focused while using this method of nutrient delivery are volumes of nutrient solution, maintenance of oxygen demands and pH. Sand and gravel as supporting materials are also employed in certain commercial application. In this case, nutrient solution is flushed out from one end and old solution is removed from the other end. This method has demerits such as frequent pathogen attack and high moisture rates which may result in over wilting of soil-based plants.

11.7.2 In Vivo Methods of Application

11.7.2.1 Soil Application

Soil application using agrochemicals is the most common method of nutrient supplement. The factors that need to be focused while choosing this agrochemicals application method are how long will the fertilizer last in the soil, soil texture, soil salinity, and plant sensitivities to salts, salt content, and pH of the amendment. It is well known that adsorption of mineral nutrients are affected by negative soil particles. Most agricultural soil has small anion exchange capacity as compared to cation exchange capacity.

Nitrate remains mobile in the soil solution and is receptive to leaching by water moving through the soil, among anions. Phosphate ions bind to soil particles having aluminum or iron since the positively charged Fe^{2+}, Fe^{3+}, and Al^{3+} have OH^{-} group that exchanges with phosphate. Thereby, phosphate can be tightly bound, showing its mobility and availability in soil limiting the growth of plant (Taiz and Zeiger 2010).

11.7.2.2 Foliar Application

Liquid fertilizers are directly sprayed onto the leaves in this method. It is usually used for the supply of trace elements. This method of application during the rapid growth phase can reduce the time lag between application and uptake by plant. It can also avoid the problem of restricted uptake of a nutrient from soil. Uptake of iron, manganese, and Cu may be more cost-effective with this method when compared to soil application method where they get adsorbed on soil particles showing less availability to root system (Taiz and Zeiger 2010). Foliar application method has advantage if it is used for nanofertilizers as stomata and leaf epidermal cells are extensively involved in nutrient uptake. But application protocol should be standardized to minimize damage in the leaves. Demerit of this method is that spraying should be done in specific time (morning and evening) as the stomata open during these time periods only. Another demerit is if inappropriate concentration of chemical fertilizer is applied there is a possibility of plant damage.

11.8 Limitations and Potential Risks of Nanotechnology

In spite of having wide range application of nanotechnology, it may pose negative effects on the environment, ecosystem, and humans. Various limitations and potential risks associated with releasing NMs into the environment are given below:

- Use of NMs in agriculture, water, and food may have hazards for human, environment, animals, and plants (Gruere et al. 2011). NPs may threaten free living nitrogen-fixing bacteria and disturb natural symbiotic relationships. Chemical hazards on plants after treatment with high concentration of NPs like Ag NPs generate free radicals in living tissue leading in DNA damage.
- Limitation of large-scale manufacturing and effectiveness of NMs application in agriculture (Chowdappa and Gowda 2013).
- Loss of jobs in traditional farming and manufacturing industry
- Commercialization of NMs for agricultural applications requires efforts and knowledge on proper protection needs, testing priorities, risk assessment, and regulatory guidance (Chen and Yada 2011).
- Airborne nanopesticides may be deposited on leaves and floral parts of plants which may plug stomata and creating a physical toxic barrier on stigma preventing pollen germination and tube penetration into stigma.

- The NPs can cause phytotoxicity and may enter the vascular tissue of plants and impair translocation of water, minerals, and photosynthates.
- The NPs may get inhaled by the human beings and animals deep into lungs resulting into various ill effects and disorders.
- Nanopesticides may contaminate soil and water bodies due to enhanced transport, longer persistence, and higher reactivity of the particles. Some NPs may also be transferred through food webs (Pestovsky and Martinez-Antonio 2017).

11.9 Future Prospects

The potential role of nanotechnology in all research fields cannot be overlooked. But certain constraints and negative impact of nanotechnological interventions in agricultural sector must be taken seriously. So, there is an urgent effort required in forwarding and developing the futuristic researches depending on the knowledge gaps. Likewise following points will highlight on important future research on nanotechnology:

(i) One must search a way so that the risks associated with the use of NPs can be reduced. Only NP synthesis with few application methodologies with limited resources cannot accept in agricultural sector. Therefore, all the scientific researchers should work together to improve the future research with more realistic approach.
(ii) Study of concentration of NPs to be applied in soil system is one of the important prospect, so that accurate and nontoxic dose of NPs can be applied properly.
(iii) So, there is urgent need of synthesis of NPs with eco-friendly approaches which include microbes and plants, as they provide lesser or no toxicity to the environment.

11.10 Conclusion

Nanotechnology is emerging out as the greatest potential tool of twenty-first-century agriculture and expected to become a driving economic force in the near future to feed increasing world population in the next decades by combating with biotic stresses. The technology has already been explored much for detection of animal and human pathogen, but for plant pathogens nanotechnological application is still in its infancy.

In spite of multifaceted application of nanotechnology in agriculture, it may pose detrimental effects on the environment, ecosystem, soil health, and humans. Metal NPs of Cu, TiO_2, SiO_2, and Co have a toxic and inflammatory effect on certain cells.

Researchers must always remember the potential adverse effects of nanoformulation like phytotoxicity at high concentration and toxicity for nontargeted organisms irrespective of the chemical nature of NPs. Therefore, nanotechnological progress must be viewed with caution and dealt accordingly. Nanoformulation with "smart" delivery is an environment-friendly option to be used for plant disease management. Nanosensors can be linked to GPS for real-time monitoring of diseases and crop health. Application of green chemistry in synthesis of NMs by using living cells and plant extracts has reduced the use of toxic solvents and thereby ensures ecoprotection. Increasing trend on bionanotechnological studies on physiology of host-pathogen and disease diagnosis will help in formulation of novel strategies for disease management. Controlled application of nanotechnology-based methods will open opportunities for developing new materials that will enhance ability to develop faster, sensitive, and more reliable analytical systems. Future nanophytopathological research must be directed to understand the molecular mechanism of plant-NP interaction and in the area of remediation of NP from cultivated soil and wastewater. Specific nanodevices and DNA nanodevices could allow accurate, rapid tracking, detection, and diagnosis of plant pathogens at the early stages of disease development. Nanophytopathology is an interesting field of research, which needs deeper investigation to make it safer and environment-friendly tool for crop protection.

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Chapter 12

Plant Nanobionics: Application of Nanobiosensors in Plant Biology

Monica Butnariu and Alina Butu

Contents

M. Butnariu (✉)
Chemistry & Biochemistry Discipline, Banat's University of Agricultural Sciences and Veterinary Medicine "King Michael I of Romania" from Timisoara, Calea Aradului, Timisoara, Romania

A. Butu
National Institute of Research and Development for Biological Sciences, Splaiul Independentei, Bucharest, Romania

R. Prasad (ed.), *Plant Nanobionics*, Nanotechnology in the Life Sciences,
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12.1 Introduction

Plants are a fascinating research topic if we relate to environmental stress. Because they are physically stuck in specific spots, the plants have to handle in that site, regardless of the environmental conditions. Moving to another place is not an option. But what plants can do is to modify the internal "environment," and plants are "true masters" of manipulating their metabolism to deal with environmental disturbances. This feature is one of the reasons why plants are useful in various research; we can rely on them as "sensitive indicators" of environmental changes, even in completely new environments. In the absence of normal conditions, plants cannot use the classical pathways of metabolism, so they need to identify other solutions. This is what happens when plants adjust their metabolism for regulating gene activation, thus producing more or less proteins that are useful or not in the new environmental conditions. The different parts of the plant come with their own genetic regulation strategies.

A number of genes that are involved in the creation and remodeling of cell walls are activated differently in growing plants. Other genes with a role in identifying light, which are normally active on the leaves, are active at the root level. In leaves, many genes associated with transmission of hormonal information are suppressed, and genes associated with insect protection are more active. These trends are also seen in the (higher) number of proteins involved in message transmission, cell wall metabolism, and plant protection. These patterns of gene and protein functioning indicate that in unfavorable conditions, the plants respond by weakening the cell walls and creating new ways to understand the environment. It is possible to monitor changes in the genes in real time by labelling certain proteins with fluorescent elements. Plants modified with fluorescent proteins can give useful information about how they respond to the environment. These modified plants act as biological sensors (NBSs).

Specialized cameras and microscopes allow us to monitor how the plant uses these fluorescent proteins (Hamers et al. 2014). Chemical or biological NBS functions on the principle of signal emission (voltage or electrical, photonic) in response to a chemical reaction involve a chemical or biological receptor, R (macrocyclic ligand, antibody enzyme), that binds to a specific target molecule of a sample to be studied, the analyte, A.

Signal transmission is achieved by coupling with a transducer T that interfaces NBS processes with the processing–transform unit in a measurable signal. Analysis of signals in plant nanobionics aims at processing signals recorded by measurements in order to extract the maximum of useful information for diagnostics and

Table 12.1 Common applications of chemo and NBSs

Applications	Examples
Automobiles	The fuel supply control, monitoring the noxious and gas emissions
Defense	Military applications, countermeasures in biological and chemical weapons
Aeronautical industry	Air quality monitoring systems in airplane cabin
Chemical industry	Emission monitoring systems for toxic gases, material testing
Civilian security	Gas detection
Environment, environmental protection	Detection of pollutants in air, water, and soil, BOD, detergents
Plant nanobionics	In vivo/in vitro evaluation, determination of gas concentration
Customs control	Detection of illegal, dangerous substances, drugs, explosives, radioactive substances
Agriculture, agrochemistry, green chemistry and sustainable technology, organometallics, inorganic materials and nanoparticles, pharmacognosy, medicinal chemistry and drug synthesis, flow chemistry, organic photo chemistry, etc.	Determination of chemical composition of raw and elaborated sap, level of degradation, pH detection, herbicides, pesticides, etc.

monitoring. An NBS is a measurement tool for physiological measures which transforms them into measurable signals. As shown in Table 12.1, there are many areas with important applications for chemical and biological sensors, from continuous monitoring of chemical processes to plant nanobionics (He et al. 2016).

Nanotechnology is the ability to build objects by assembling atoms at a time in well-defined sequences. With the tools provided by nanotechnology, genetic engineering, and proteomics, “bottom-up” objects can be built, meaning assembling atoms and molecules into structures. To do this, other types of nanometer-sized instruments and devices are needed. To make macroscopic objects, billions of these small devices (assemblies) are needed. To reproduce these types of tools, we need a self-replication method or replication tools (replicators).

Essential components in a sensory structure have unique meanings due to miniaturization and large-scale integration into integrated circuits, making themselves chips with a strong interfacing of the analyte–receiver reaction processes. By consensus it has been established that the term should be reserved for use as a sensor that incorporates biological elements such as enzymes, antibodies, nucleic acids, microorganisms, or cells. Table 12.1 shows the interferences of the NBS chemosensor applications during their evolution.

NBSs will be defined as a compact analytical device incorporating a biologic sensing element or biologic derivative integrated with a physicochemical transducer. The goal of NBSs is to produce an analog or digital electronic signal that is proportional to the concentration of a single analyte or a group of analytes.

These devices are mostly used in genetic engineering in agriculture, where it is necessary to know the mechanisms of reaction and the affinity of enzymes and microorganisms for different substrates of interest and signaling molecules. A biochip is a device that contains a structure of individual sensory elements (NBSs) interconnected by functions and recognition specifications, integrated on a chip. The number of NBSs on a chip may be of the order of 10^6 units. In this degree of integration, a set of distinct tests can be performed extremely quickly and efficiently. In contrast to microchips, biochips are not electronic structures (they contain different electronic structures coupled to nanobiosensory elements). Each NBS can be thought of as a "microreactor" that performs a specific chemical reaction with an analyte. NBSs from biochips can be designed to detect a wide variety of analytes, including DNA, antibodies, proteins, and biomolecules. The advantages are multiple: sensors can be produced in batches or sequences that can be assembled in parallel or serial, providing a high manufacturing yield; sensors can be assembled on very small areas with reduced distances between them; 3D structures can be generated providing high signals besides 2D structures; any type of biochemical reaction may be incorporated; NBSs can be produced separately and subsequently assembled according to the specificity and nature of the application.

The important features regardless of industry or technology are selectivity, sensitivity, and stability in the design of sensory systems integrated with structures and arrangements of sensory elements (Wan Salim et al. 2013). One of the integrated systems including rotational aseptic sampling is a robotic fluid and reusable electrodes formed by ink-jet printing injection system.

The system contains an enzyme electrode with immobilized GOx in gel, and the detection of hydrogen peroxide is carried out on a rhodinised carbon electrode (Rh coating). Although the enzyme electrode has stability and efficiency characteristics, the problem of automated sample monitoring and sampling in an integrated system requires multiparameter optimization due to reciprocal interferences. There is a requirement on specific domains (environment and genetic engineering) of highly performing integrated systems that work in in vivo conditions, such as dialysis, the use of biointerfaces, evanescent techniques, and atomic force microscopy to grasp in the depth of the biological phenomena (identifying and understanding the interaction of proteins). The in vivo exploitation of detection systems for both glucose and lactate was confirmed by the efficacy of using phospholipid copolymers and improving hemocompatibility.

Immunosensors provide an example for the development of integrated systems where microseparations, chromatographic methods, and electrochemical couplings with optical detectors are incorporated, which ultimately lead to a miniaturized system. There are examples where the level of integration and miniaturization becomes more pronounced (DNA–nanotube or biochips–biointerfaces). NBSs are expected to be widely used in plant nanobionics where physiological/biochemical parameters should be identified.

Advanced ink-jet technology has developed methods for analyzing nanoliter fractions on a three-dimensional NBS surface at a speed of 6 m/s. It is expected to produce one million NBSs/cm^2 areas using photolithography, contact fingerprinting or self-assembling techniques, and adsorption/desorption under the laser beam that allows "writing" proteins on the surface to be analyzed with great precision. Laser techniques, MAPLE (*Matrix Assisted Pulsed Laser Evaporation*) or DW (*Direct Writing*) approached for immobilizing biological materials on substrates, are in the laboratory stage but have prospects for use as molecular imprinting methods (Potocký et al. 2014).

12.1.1 Sensitivity

Whether NBSs are individuals, in integrated systems, or areas of NBSs, all are characterized by unique parameters such as sensitivity and detection limit for a range of analytes. Trace detection of various analytes (indicators, additives, contaminants) with sufficient sensitivity and safety is the basic criteria of an NBS to be used. The detection limit in the laboratory is pushed to an atom when the atomic force microscopy is used. Thus, the enzymatic electrodes, studied and continuously perfected, use palliative such as concentrating the analyte of interest, which leads to major design and miniaturization difficulties.

NBSs for phenol vapors were identified, where the phenoloxidase was immobilized on a glycerol gel with a range of interdigitated electrodes. Phenol vapors are directly partitioned into the gel and oxidized to quinone. Signal amplification was improved by redox amplification of the quinone/catechol couple to obtain a reasonable sensitivity resulting in a detection limit of 30 ppb phenol. This principle can be extended to other carbon compounds up to the ppt (parts per trillion) limits. DNA structures have been studied as potential receptors.

Sandwich structures of liquid crystal dispersions and DNA-polycation complexes have been studied with relatively good success in identifying different analytes. The polycation with the role to maintain structural integrity of DNA and DNA-protamine complexes allows detection of hydrolysis of the trypsin enzyme to the detection limit of 10^{-14} M.

Elimination of the polycation leads to an increase in the distance between the two DNA strands resulting in the appearance of an intensive band in the circular dichroism spectrum due to the texture modification (Espinoza et al. 2014).

12.1.2 Stability

From a practical standpoint, the disadvantage is their inherent instability. Different strategies have been approached to improve longevity and preserve the structure of biological receptors. Immobilization in matrices by sol–gel technique for glucose NBSs is one of the strategies; fluorescence indicators are used: hexahydrate chloride (2,2′-bipyridyl) ruthenium (II) and 1-hydroxypyrene-3,6,8 trisulfonic acid.

In addition to the optical property improvement of the gel, the stability of the GOX enzyme has also improved. Other examples are the case of monooxygenase used in hydrocarbon detection; detection of organic halides with metalloporphyrins; and detection of carbon tetrachloride, haloalkane (perchloroethylene), and insecticides (DDT) (Kazakova et al. 2013).

12.1.3 Selectivity

Improving the selectivity of an NBS can be approached on two levels: through direct transducer–biological receiver interfacing to reduce interference and new receptors with improved affinity or new affinity capabilities. Selectivity is a key parameter that requires the performance of an NBS. Pyrroloquinoline is used as a mediator in a glucose oxidase enzyme electrode for the measurement of glucose in the raw or elaborated cavity.

Alternatively, the electrocatalytic detection of the reaction products resulting from the enzymatic reactions can be improved by chemically modified electrodes such as rhodinised electrodes or hexacyanoferrate modified carbon electrodes. Prussian blue is used to modify the electrode surface at amperometric detection of oxygenated water at both oxidation and reduction potentials for the enzyme electrode in lactate and glucose detection.

One solution is to identify redox centers of the enzyme via a molecular wire to perform the electron transfer to the electrode (enzymes linked by molecular wires), but the concerns have focused on immobilized mediators on different polymer chains. Molecular wires are regarded as intermediates in long-range electron transfer, consisting of two pyridine groups linked by thiophenes with different lengths. Such wires can be used in conjunction with self-assembly techniques to produce an isolated electrode that transfers electrons to predetermined molecular pathways (Jones et al. 2013).

12.2 The Biological Components of Nanobiosensors (NBSs)

An ideal NBS is a device that will detect an “analyte,” the subject under analysis and which is present in a given sample. Most samples also contain other analytes which may interfere with the NBS response. It must have a specific selectivity to identify the target analyte. It is necessary to design NBSs with selectivity for an analyte with the ability to discriminate the interferences produced by the other components in the analyzed sample.

Specific identification and selectivity capacity are the key components of molecular recognition. Molecular recognition is accomplished by the sensor component of a host molecule (*host–chemoreceptor*) that binds selectively to the “guest” target molecule/guest molecule that needs to be identified. For each “host–guest” system, there is a specific chemical reaction from the multitude of possible reaction channels. When the host–guest response was identified, the host molecule is immobilized/incorporated into NBSs, typically on a transducer-contacting membrane/contact electrode. Finally, a way to signal that the bindings/recognition event has occurred (transducer to transducer) has to be found (Rodríguez–Sevilla et al. 2014).

12.2.1 Principles of Molecular Recognition

One of the requirements for molecular recognition is the existence of groups or centers with specific reactivity in the host molecule that can “close” or bind ions, atoms, molecules, and biomolecules. All living organisms use enzymes, which are proteins that contain “pockets,” active centers, designed to recognize a specific analyte. This means that only a specific analyte is able to enter the enzyme pocket. Enzymes can be used in NBSs as host receptors with molecular recognition capability but are unstable. To design host molecules that can be used in an NBS, the following criteria are considered: the host molecule must be stable under the conditions in which it is to be used, must be able to selectively bind the analyte in the sample, must be able to be immobilized in a film/membrane that is in contact with the sample, must signal that a host–host binding response has occurred, and must ideally release the analyte after detection so the host is free to be reusable. Biological receptors include antibodies, membrane receptors, signaling molecules, enzymes, ribosomes, lectins, phytohormones, etc.

They bind analytes using “lock-and-key” molecular recognition mechanisms (key–lock, identification–immobilization). Biological receptors are not practical solutions for many applications because the specificity, sensitivity, and stability cannot be optimized. Artificial receivers are immobilization environments that can be optimized by molecular design for any type of application. Synthetic receptor design and synthesis are based on tools developed by proteomics and genetic engineering, producing recognition components that can respond to the occurrence and identification of metabolic deficiencies in plant nanobionics.

There are platforms and areas of artificial receptors based on combinatorial mathematical techniques, interface biology, and surface chemistry. They have induced the development of various artificial receptor environments with rapid and diversified selection for any target analyte. The current technique for producing synthetic receptors is called CARA (combinatorial array of receptor analysis) (Fang et al. 2015).

Supramolecular chemistry has developed a wide range of synthetic macrocycles. The most common feature for macrocycle classes is that they contain cavities that act as host pockets for guest molecules. The selectivity of the hosts can be done in “read mode” by varying the size of the preformed cavities. 12-crown-4 has a small cavity ideal for the binding of small ions such as Li^+, while 18-crown-6 has a large cavity that fits better with larger ions such as K^+.

The size of the cavities is important for the selectivity of the host, but the question remains what attracts an ion or molecule into a preformed cavity and which factors stabilize the host–guest complex. In enzymes, weak noncovalent interactions (hydrogen bonding, electrostatics, dipole–dipole, van der Waals, etc.) are used to link the guest into the enzyme pocket (interactions stabilize host–guest interaction). Macrocycles contain polar functionalities, capable of interacting with guests via hydrogen bonding, electrostatic interactions, and dipole–dipole interactions. It is desirable that bonding in the cavity is not strong, because it is important that the analyte, the guest, is released from the host after it has been detected and measured. Crown ethers and calixarene are ideal for bonding metal cations, based on the size of their cavity, but also on the high density of electrons present on the oxygen atoms in the cavity. The base compound selectively binds Li^+ to other metallic cations; the modified version of the base macrocycle has a good selectivity for Na^+. By synthetic modification it is possible to increase the capacity of the host cavity, and new functionalities can be introduced that will favor the binding of specific molecules and ions (da Silva et al. 2013).

Other modified calixarenes, which demonstrate this principle, are the group of tetraphosphine oxide of the calix[4]arene. By changing binding groups on the same template, calix[4]arene from esters in phosphorus hydrogen oxides selectivity changes from Na^+ to Ca^{2+}.

By increasing the number of repeatable units in esters and phosphorus hydrogen oxides at six, the cavity increases, and the selectivity changes in favor of the higher Cs^+ and Pb^{2+} cations, respectively. Some host compounds have been developed for the selective detection of low molecular weight compounds. An example involves the use of the tetra (S-propanol) calix[4]arena containing four lateral chiral halves for selective differentiation of the phenylalanyl enantiomers. Other techniques of supramolecular chemistry may be involved in the synthesis of synthetic receptors that simulate the properties of enzymes. The basic structures that can be modified are porphyrins, semiconductor polymers of the tetrathiafulvalene (TTF) class, and PPVs. Other patterns can be considered modified polysaccharides. A linear archetype is the polyanilines containing the two types of redox states (Meyer et al. 2007).

12.2.2 Molecular Basics of Ag–Ab Interaction

Among the multiple NBS classifications, bioaffinity has a range of applications, and antigen–antibody interactions (Ag–Ab) play a role and are considered to be an instrument in the development of molecular recognition principles. In vivo Ag–Ab interactions are reversible. Factors that condition the Ag–Ab interaction are the structural complementarity between the antigenic determinant and the antibody combining site; this is the exclusive factor of the specificity of the reaction; the structural complementarity involves the conformational adaptation of the two reacting groups and was conceived in structural terms on the key–lock principle; the chemical complementarity of the reaction groups is the consequence of structural complementarity and signifies the entry into action of intermolecular forces that stabilize and consolidate the interaction of the two groups.

The formation of intermolecular bonds requires the existence of atomic groups sufficiently close to the two molecules. The distance between them is inversely proportional to the degree of complementarity. Although structural complementarity is not strictly obligatory, higher spatial matching is more conducive to interaction. It is expressed by the congruent of contact surfaces that provide intermolecular attraction forces that stabilize the complex.

The Ag–Ab interaction involves the following types of noncovalent bonds: H bonds, electrostatic forces, van der Waals linkages, and hydrophobic bonds. All are nonspecific forces of low value and their nature makes the reaction reversible. H bonds form when two atoms share an atomic H nucleus (one proton). The common proton is found between two atoms of N or O or between N and O. The H nucleus is covalently bonded to one of the two atoms (N or O). The H bond has a binding energy of 3–7 kcal/mol.

Intermolecular forces are involved in Ag–Ab complex formation. The action of these forces requires close contact between the two reaction groups. The H bonds result from the formation of an H bridge between two nearby atoms.

The electrostatic forces are due to the attraction of the ionic groups with opposite charges located at the periphery of the two protein chains. The van der Waals forces result from the interaction between different electron clouds, represented in the form of oscillating dipoles.

The van der Waals relationships, the weakest interaction forces, are active at very small distances between the reaction groups. The binding energy is 1–2 kcal/mol. Van der Waals' links are not based on a permanent separation of electrical charges but on their fluctuations induced by the proximity of molecules. At intermolecular distance, instantaneous electric fields are formed, with a polarizing effect on neighboring molecules.

Between the nearby atoms, there is a mutual attraction force induced by fluctuating dipole load, which a dipole induces in the neighboring dipole (dispersion forces). Their intensity depends on the distance between the groups involved and is inversely proportional to the seventh power of the distance. Their value is optimal at 1–2 Å.

Hydrophobic bonds, which can contribute with half of the Ag–Ab binding force, are produced by the association of nonpolar and hydrophobic groups, whereby water molecules are excluded. The optimum distance between the reactive groups varies with the type of bond.

The electrostatic forces (coulomb or ionic) are the result of the attraction between atoms or groups of atoms with the opposite electric charge located on the two reacting groups: between a cation (Na^+) and an anion (Cl^-) or between COO^- and NH^{3+} (Agrawal et al. 2012).

The binding energy of these forces is significant at very small (less than 100 Å) distances from the reaction groups. Exact juxtaposition of ions favors the action of these forces. The binding energy is 5 kcal/mol and varies inversely with the square of the distance between the two reaction groups ($1/d^2$). Hydrophobic (or a polar) linkages occur between nonpolar (nonionized) groups in aqueous solutions and are the consequence of the tendency to exclude the ordered molecule of water molecules between the antigen and antibody molecules.

These linkages are favored by amino acids with a polar group that tends to associate, reducing the number of water molecules in their vicinity. By removing the water molecules between the reaction groups, the distance between the active sites decreases much, and the value of the stabilizing forces increases. Taken each one on their own, space complementarity or intermolecular forces are not sufficient to form stable relationships.

For the stability of the Ag–Ab interaction, both conditions are required. The higher the binding energy of the reactants, the stable the Ag–Ab complexes. The interaction of the antigen- and antibody-reactive groups is defined by two parameters: the affinity and avidity of the antibodies. Measurement of antibody affinity can be achieved by dialysis at equilibrium. The Ag–Ab interaction is reversible. Within the dialysis bag, the hapten is partially free and partially bound to the antibodies, depending on the affinity of the antibodies. Through the membrane of the dialysis bag, only the free hapten can be diffused, and its external concentration will equal the concentration of the free hapten inside the bag (Kersten and Feilner 2007).

Measurement of the concentration of the hapten in the dialysis bag allows for the calculation of the amount of antibody-bound hapten. The constant renewal of the buffer results in total dissociation and loss of hapten in the dialysis bag, which indicates the reversible nature of Ag–Ab binding. Affinity of antibodies measures the binding force between an antigenic determinant and the complementary binding site of a specific antibody. Affinity is the result of attraction and rejection forces that mediate the interaction of the two reactants.

The strength of these interactions is measured in the reaction between a monovalent antigen (hapten) and specific antibodies. A high affinity interaction requires perfect complementary structures, while the imperfect complementarity of the reaction groups causes a low affinity, since the attraction forces are active only at very small distances and are diminished by the rejection forces.

Complexes formed by antibodies with high affinity are rapidly eliminated from the circulation without adverse effects on renal function. The Ag–Ab interaction is permanently characterized by the formation and cancellation of various types of intermolecular bonds. In vivo, probably all Ag–Ab reactions are reversible, but secondary in vitro reactions (agglutination, precipitation), under the conditions of reagent balance, are irreversible (Sakamoto et al. 2018).

It is essential that the host–guest binding event (the receptor–analyte interaction, R–A) is detected. It is thus necessary to have a way of identifying and transducing the signal from the receptor–analyte interaction to the outside to be processed. It is generally defined as a transducer. The transducer must be in contact with the receiver or the diaphragm that immobilized the handset. Electrode and interfacial interactions are determinant in capturing the signal from an R–A interaction and transforming it into an electrical or photonic signal. There are ways of identifying the R–A event, collecting the signal and transducing it as an external signal. The way of identifying the signals and their transduction defines the type of NBSs.

This means immobilizing the receiver on an electrochemical transducer that measures a current (amperometric method) or a voltage (potentiometric) between two electrodes. If R is immobilized on an optical component, then we will define optical NBSs (optical fiber, fluorescence, absorption, surface plasmon resonance (SPR)). For detection, at most electrochemical NBSs, it is necessary for the membranes containing the host molecule to be placed on a surface of an electrode that leads to an electrochemical response to the binding of the guest.

The approach works well when target analysts are loaded species such as metal cations. Neutral molecules cannot be detected from the point of view of electrochemical transduction, so the optical detection methods have been successfully used. A chiral host in calixarene contains naphthyl, fluorescent units. Upon binding to the guest, fluorescence is attenuated as a result of interaction between the naphthyl–phenyl groups in the host or analyte. The fluorescence attenuation is proportional to the concentration of the analyte. Optical methods are used because they offer greater sensitivity than electrochemical techniques. In the absence of the guest analyte, this compound does not exhibit fluorescence because the pyrenyl substituent cannot come in contact with the adjacent nitrophenyl substituent (and the fluorescence attenuation occurs due to their interaction).

However, in the presence of Na^+ ions, fluorescence is observed, because the Na^+ ion enters the cavity and binds to the oxygen in the phenoxy and carbonyl groups in the host. This binding induces a more rigid conformation by removing the nitrophenyl groups of pyrene to prevent fluorescence attenuation (Gaggeri et al. 2012).

12.2.3 Types of Biological Components

NBS is a bioelectronic analysis system that combines a transducer with a biological component that is in a specific interdependence. NBSs use biological systems with different levels of recognition of the substances to be determined. The first step in this interaction is the formation of the specific complex of the biologically active, immobilized substance R (the receptor, the substrate with the sensitive biological component) with the analyte A (often defined as the chemical signal). Table 12.2 summarizes specific patterns of NBSs in relation to the nature of the receptor and the chemical/biochemical signal.

There are two general classes of NBSs that are based on the bioaffinity response between R and A that alters the distribution of electrical charges that can be measured with specific transducers or consuming the substrate by a specific reaction. The biological constituent of the molecular recognition element (R) is represented by various active species that can be enzymes or enzymatic systems, antibodies (Ab) or antigens (Ag), receptors, populations of bacteria or eukaryotic cells, tissue fragments, and sometimes even signaling molecules. Analytes or substances that can be analyzed (A) are glucose or other sugars, amino acids, alcohols, lipids, and nucleotides.

Table 12.2 Specific schemes for designing an NBS in relation to the nature of the receptor and the chemical/biochemical signal

1. Nanobiosensors of bioaffinity $A + R \rightarrow AR$ Changing the electron density	
R Receiver	Chemical response A
1. Dye	1. Proteins
2. Lectin	2. Saccharides
3. Apoenzyme	3. Glycoproteins
4. Antibody	4. Inhibitive substrate
5. Transport system	5. Prosthetic group
	6. Antigen
	7. Hormone
	8. Analog substrate
2. Metabolic nanobiosensors $A + R \rightarrow AR \rightarrow P + R$ Consumption of substrate and product formation	
R Receiver	Chemical response A
1. Enzymes	1. Substrate
2. Microorganisms	2. Cofactor
3. Microbes	3. Inhibitive
4. Striped tissue	4. Activator
	5. Enzyme activity

They can be identified by their specific interaction, or their concentration can be measured by various methods. Both R and A represent distinct molecular species with high macromolecular specialization (antibodies, antigens, enzymes, receptors, etc.) or are complex systems (cells, tissues, etc.) (Kersten and Feilner 2007). After the active biological component, they can be grouped as follows:

- Enzymatic NBSs: Enzymes are energy proteins characterized by their catalytic function. Modified substrate molecules lead to oxidation, reduction, and hydrolysis reactions that can be measured by enzymatic NBSs. Enzymatic NBSs produce a linear response depending on the substrate concentration.
- Immunosensors: Antibodies are glycoproteins produced by the immune system when an external substance, antigen, is involved. It is theoretically possible to produce antibodies without identifying an antigen. An immunosensor is a high sensitivity NBS. The principle of operation is based on the Ag–Ab interaction of molecular recognition.
- NBSs with receptors: The regularity of biological processes is ensured by high sensitivity molecular processes based on the specialization of structural proteins (receptors) capable of recognizing a number of physiological signals. This is the case for neurotransmitters, whose action is mediated through the presence of receptors in the plasma membrane, in sites or cell targets. Activation of the bio-

logically active site is via the ion channels. The acetylcholine receptor is the first known receptor in neurotransmitting phenomena.

- NBSs based on cells or tissues: Measurement of molecular species is not limited to interaction with the compounds to be analyzed; the transformations that occur can be measured as resulting products. It is desirable to operate with cell populations whose major metabolic pathways are known. Relevant is NBSs' L-arginine, which associates populations of bacterial cells of *Streptococcus faecium* in combination with an ammonia electrode. Arginine is metabolized by microorganisms. It is difficult to obtain complex reactions outside the cellular structures. Similar to the use of cell populations as sensitive elements, fragments or parts of plant tissues may be used. The advantage is greater because there is no extra effort to keep the cells viable in a natural arrangement. For adenosine NBSs, a tissue biosensitive element has been proposed. For dopamine NBSs, specialists have focused on the pulp of banana fruit, considering that it has remarkable biocatalytic properties.
- NBSs with redox proteins: The redox proteins are involved in biochemical processes such as cellular respiration and photosynthesis reaction (Kersten and Feilner 2007).

NBS catalysts use enzymes, microorganisms, or cells to catalyze a reaction with a target substance. NBSs own an affinity on using antibodies, receptors, and nucleic acids that bind to a target substance.

Reactions are quantified by electrochemical, optical, evanescence transducers, etc.

The main types of known redox proteins are cytochromes, containing iron in the prosthetic group, and cytochrome "c" is involved in the transfer of electrons into mitochondria; ferredoxins contain iron and sulfur ions in dimeric combinations of chloroplasts (2Fe–2S) ferredoxin and tetrameric combinations of bacterial ferredoxin 2 (2Fe–2S) involved in photosynthesis and transfer of fixed nitrogen ions, respectively; blue proteins contain copper linked to the smallest cysteine residue involved in a tetrahedral structure such as plastocyanin and azurin that mediates electron transfer in photosynthesis and possibly in nitrite reduction; flavoproteins, containing a prosthetic group and an organic conjugate, are involved in the transfer of proteins such as flavotoxins (Agrawal et al. 2012). These proteins play a role in nature, due to the location on their surface of the redox centers. The subtle architecture of molecules offers selectivity and specificity to these molecules in their interaction with other proteins or enzymes, such as the cytochrome c structure. Porphyrin iron (heme) is located at the center of the molecule and is well covered or hidden, being exposed to solvents in a small proportion of 0.06% of the total molecular surface.

From those presented above and from Table 12.2, we can see that NBSs can be classified into two groups according to the biological component.

The protein has a positive potential of +9 mV due to excess lysinic base debris. There is a 324 Debye dipole moment, which produces an imbalance in the spatial distribution of the acidic chain balance. A number of lysine residues are distributed around the solvent to which the center of the heme that interacts with the redox proteins is exposed (Nelsen et al. 1990).

12.3 Integration of Biological Components into NBSs

NBSs are classified in three generations. At the first-generation sensors, the biocatalyst is attached to the surface of the membrane, and then this arrangement is fixed to the surface of the transducer. The adsorption or covalent attachment of the biologically active component to the surface of the transducer allows the elimination of the semipermeable membrane, which is the second generation. The direct linking of the biocatalyst to the electronic device that translates and amplifies the signal, such as the compact transistor, is the basis of the third-generation NBS miniaturization. Depending on the nature of the immobilization and the interaction between the three components, the A–R membrane contact with the electrodes to the transducer, and the processes in the NBSs have evolved over a generation.

First, the specificity and selectivity are dominated by the biological component and are directly related to its nature: enzymes, antibodies, and microorganisms. The specificity derives from the binding of the analyte to the biological component used as the receptor. At the base of this dominant sequence is the A–R biochemical reaction and the collision process between A and R. Second, the transport of the analyte to and through the surface considered to R is also an important factor. This process is related to the transport of a physical size through typical diffusion, migration, and convection mechanisms. Third, the NBS signal is dependent on the A–R reaction assumed to be at a constant speed.

Transient states and biochemical pseudo-equilibrium conditions are dominated by the reaction kinetics, the nature of the transport, which in turn is coupled with the immobilized A–R interface substrate reactions. Even in the case of a real equilibrium, the reaction speed near the steady state will be important in determining the response time. The kinetics of these processes require additional conditions (Agrawal et al. 2012).

The new types of nanoscale materials with different levels of biocompatibility, the new generation of biocompound cells based on a better understanding of metabolism, the manipulation of information stored at the molecular level all have led to a generation of NBSs with a high level of integration. Molecular information initially stored in the base molecular components can be expressed directly to a higher level called "supramolecular" where interactions between molecules are performed by preestablished algorithms, leading to adaptive, functional, and intelligent materials. Materials are built on conceptional, supramolecular, and combinatorial principles. Separation, storage, and detection techniques are developed using "biomimetic" membranes that function according to biological models or precise physicochemical principles (Li et al. 2014).

12.4 NBSs Based on DNA, Nanotubes, and Semiconductor Polymers

Electrochemical NBS with DNA is the result of medical diagnosis requirements to quickly and accurately determine the segments of a DNA sequence. Results from genetics, molecular biology, and nanotechnology have led to one of the most accurate detection methods: electrochemical NBSs with DNA (combining the principle of NBS ISFET with molecular wires from nanotubes). The operating principle consists of collecting the signal between two electrodes—one working electrode and another reference electrode. The auxiliary electrodes have a specified role in their turn. The sensing mechanism consists in modifying the *I*–*V* characteristic (current–voltage) in the presence of a target molecule. Carbon nanotubes are exceptional for the work electrode with high electron transfer velocity and excellent spatial resolution. Target in NBS DNA is an unknown sequence of DNA (or oligonucleotides) attached by functionalization to the carboxyl or amino CNT groups. Researchers reported the developing plants' ability to capture 30% more energy by implanting carbon nanotubes into chloroplasts and plant organisms where photosynthesis takes place. They managed to modify plants so as to detect nitric oxide by implanting another type of carbon nanotubes. "The plants are suitable for the role of a technological platform. They heal themselves, they are durable, they resist the harsh environments and they have their own sources of energy and water." The transformation of plants to photon devices, with own energy, such as explosive detectors or chemical weapons, is expected (Panchal and Upadhyay 2014).

External or surface electrodes are metal electrodes that contact the NBSs' bioactive component either directly (dry or solid electrodes) or through an electrolyte solution (liquid electrodes). Solid or dry electrodes are made in silver, platinum, gold, and nickel. Internal electrodes are made of thin wires made of durable metal: stainless steel, platinum, and tungsten. The active part of the electrode can be covered with a metallic conductor layer (gold, silver) and the inactive one with an insulating layer (polymer/thin film). NBSs' active contact surfaces are large in size compared to cell sizes and are used for extracellular recordings.

Microelectrodes are internal electrodes, but they are built to measure potentials in direct contact with the receiver in NBSs. The contact surface with R is micronized. Microelectrodes can be solid, compounds which can be achieved by depositing a conductive layer (platinum, gold) on a glass support having a particularly thin peak, and another constructive variant consists of inserting a metallic or carbon fiber conductor into an epoxy resin support mixed with a conductive paste; they are used in cellular samples and consist of a glass pipette having a micronized tip filled with an electrolytic solution containing potassium chloride. In the electrolyte solution, a conducting wire is immersed to pick up the electrical potential (Wu et al. 2014).

12.4.1 The Gold Electrode

It was thought that it is not possible to transfer electrons directly between the electrode and the proteins due to their distortion. Several practical considerations have led to the conclusion that the active center of the heme is irreversibly adsorbed when resulting in protein denaturation in contact with the electrode. Changing the surface of the gold electrode by surface adsorption of 4,4′-bipyridyl resulted in the modification of the electrode surface configuration for interaction with cytochrome "c." 4,4′ Bipyridyl is not an electroactive substance in the potential region and therefore does not play a role as a mediator. This electrochemical addition was possible due to the quasireversible binding of cytochrome "c" to the modified gold electrode with 4.4′ bipyridyl, thereby resulting in the hydrogen linkages in the lysine residues to bound to the nitrogen of the pyridyl which modified the surface of the electrode. Transmutation through complex protein electrode rapidly directs the transfer of electrons, which is accomplished by the following scheme: cytochrome diffusion "c" on the electrode, protein binding on the surface, electron transfer, and protein desorption. Following this process, more than 60 surface changes were possible for electrochemistry of proteins and the gold electrode. Using a bifunctional reagent (X-Y), wherein the X group is the N, P or S bonded electrode and the Y group, which must be bonded "represent also examples of patterns developed" (Agrawal et al. 2012).

12.4.2 Graphite Electrode

Electrochemistry of proteins has been extended to the carbon electrode. Pyrolytic carbon–graphite forms, vitreous carbon and mesocarbon, are structures in which graphene plans are arranged in ABABA hexagonal mesh or disordered in different turbulent forms. The base graphene plan is hydrophobic, but existing or induced defects lead to free C–C bonds, and there is an increase in C–O linkages by oxidation. The direct electrochemistry of positively charged proteins can therefore be performed on the edges of the graphite plans of the carbon electrode. The direct transfer of electrons to negatively charged proteins, such as plastocyanin with graphite electrode (edges or plane edges), can be aided with Mn, Ca, Cr complex cations complexed with amino compounds, Cr $(Am6)^{3+}$, used as promoters of reactions. In this context, the promoters are inactive redox species in solutions but allow the transfer of electrons to the redox proteins. Microminiaturized electrodes have specific advantages among which we mention the improvement of polarization and contact with biological material at the active sites.

Specificity and selectivity depend on the NBS receptor biological component and its affinity for the analyte. Affinity is a specific feature of enzymes, antibiotics, and receptors being used in functions in living organisms. Affinity is based on the chemical coupling between a component and its complementary partner. In the case of high-affinity components, the diffusion process is rapid, leading to the formation of the Ag–Ab type of complex. The association reaction specific to molecular recognition will be characterized by the first-order response rate constant. In NBS measurements it is essential to consider the concentration of a constant component and other variables. The results of electrochemistry of proteins have been extended to amino acids and peptides (Barroso et al. 2015).

12.4.3 Kinetics of **Enzymes** *Used in NBSs*

The addition of enzymes to solutions containing substrate molecules is the essential condition in enzyme catalysis reactions. Extracting the necessary information from the enzyme science to be applied to the development of NBSs such as the enzyme electrode is an extremely difficult task. References will be used to outline some of the enzyme properties necessary to describe enzymatic NBSs. Consider a simple reaction, with a single substrate S, that combines with enzyme E to form the enzyme–substrate intermediate complex, ES.

This unstable complex undergoes a new reaction resulting in product P. The formation and consumption rates of the complex are equal. As soon as E and S enter the reaction, the system becomes unbalanced, the concentration of the complex will be zero, and the formation speed of the complex is much higher than the rate of its consumption. As the reaction unfolds, ES increases and implicitly increases the rate of disappearance of the complex relative to its rate of formation. Initially, the excess of the substrate determines the consumption of the enzyme, and during the course of the reaction, the enzyme's constant regeneration begins to reach its steady state. The analysis of these reactions results in two important conclusions:

- At a low concentration of the substrate, the rate of the reaction is proportional to the substrate concentration and inversely proportional to the rate of the formation and extinction rate of the complex or the dissociation reaction rate in the initial reactants plus the decomposition reaction rate in products.
- At a high concentration of the substrate, maximum speed is limited by enzyme concentration. Thus, the two sequences correspond to the two processes that can control the overall reaction rate (Stein et al. 2011).

When the reaction takes place in homogeneous solutions at a uniform rate, the same in the entire environment, it is necessary to consider the change in the concentration of the components over time. Three mechanisms of mass transport occur in solution: diffusion, convection, and migration.

12.5 Recent Advances in Electrochemical NBSs

An electrochemical NBS is an autonomous, self-contained device capable of providing specific quantitative or semiquantitative analytical information using as a molecular recognition element, a biochemical receptor (biological identification element) that is in direct spatial contact with an electrochemical transducer. Electrochemical NBSs are distinguished only by the nature of the transducer regardless of the nature of the biological component according to the classification in Table 12.3.

Due to their ability to be calibrated in a repetitive manner, an electrochemical NBS is distinguished by a bioanalytical system requiring additional processing steps, such as the addition of reagent. NBSs for a single type of measurement, or unable to continuously monitor concentration analysis or not to be rapidly and reproducibly regenerated, are defined as "disposable."

NBSs are classified according to their biological specificity—with reference to the mechanism or to the interpretation of the physical–chemical signal (the transducer) (Barroso et al. 2015).

The biological recognition element is based on a catalyzed chemical reaction or an equilibrium reaction with macromolecules that have been previously isolated or synthesized in their original biological environment. In the case of reversible reactions, the steady state can be reached if there is no net consumption by the agent of

Table 12.3 Types of receptors used in NBSs coupled with electrochemical measurement techniques for specific species recognition

S. no.	Analyte type	Receptor/chemical/biochemical recognition system	Measurement technique/the nature of the transducer
1.	Ions	Multivalent metal oxides, ion-conductive inorganic crystals, permselective ion, biological ionophores, enzymes, ion exchange glasses	Potentiometric, voltametric
2.	Dissolved gasses, vapors, and odors	Double lipid layer or hydrophobic membranes, inert metal electrode, enzymes, antibodies	Amperometric, voltametric, impedance, piezoelectric, optical
3.	Substrates	Enzymes, cell membranes, receptor membranes, animal, or plant tissue	Carbon electrodes, conductometric, piezoelectric, optical, thermometric
4.	Antibodies/antigen	Duplex oligonucleotides, aptamers, labelled enzymes, chemiluminescent or fluorescent labelled enzymes	Amperometric, potentiometric, impedometric, piezoelectric, surface plasmon resonance (SPR), optical
5.	Various proteins, low molecular weight substances	Protein receptors, specific ligands, specific fluorescent labelled enzymes	

In addition to quantitative determination of analytes, NBSs are also used to detect and quantify microorganisms: the receptors are bacteria, yeasts, or oligonucleotides coupled with electrochemical, piezoelectric, optical, or calorimetric transducers the immobilized biocomplex and incorporated into the NBSs. Electrochemical NBSs can be classified according to the analyses and reactions they monitor: direct monitoring of the concentration of the analytes or their production or consumption reactions and, alternatively, an indirect monitoring of the inhibitor or activator of the biological recognition element (the biochemical receptor).

Criteria include calibration characteristics (sensitivity, linearity, operational range of concentration, quantitative determination limits, and specific detection), selectivity, equilibrium state and response time, reproducibility, lifetime, and stability (Fang et al. 2015).

The notion of recognition is used in NBSs or in nanobiosensory systems by association with the sensory systems of the plants.

Sensations such as smell or taste are made up of systems that contain an identification receiver cell coupled with neurotransmitter signal-processing pathways. Such phenomena also occur in biochemosensors but at a much-simplified level compared to the complexity of molecular recognition in living systems (Barroso et al. 2015).

Examples of single or multiple transfer signals, limited to the main biochemosensors, are shown in Table 12.3. For the receptor types shown in Table 12.3, different electrodes and measurement methods can be selected from Table 12.4 to form an electrochemical NBS. NBSs are classified by the recognition element (Table 12.3) or by the transduction mode (Table 12.4). NBSs irrespective of the type of classification should be treated unitarily as a microsystem, the biological recognition element being in direct contact with the transducer element.

An electrochemical NBS is an NBS with electrochemical transducer (Table 12.4). It is considered to be a chemically modified electrode (CME), the electric conductor

Table 12.4 Types of electrochemical transducers, type of measurement, and corresponding analyte

Type of measurement	Transducer	Analyte
Potentiometric	Ion-selective electrode (ISE);	K^+, Cl, Ca^{2+}, F
	Glass electrode	H^+, Na^+
	Gas electrode	CO_2, NH_3
	Metal electrode	Redox reactions
Amperometric	Metal electrode, carbon electrode, chemically modified electrode (CME)	O_2, sugars, alcohols, phenols, oligonucleotides
Conductometric, impedometric	Metal electrode, interdigitated electrode	Urea, oligonucleotides
Field effect transistors (FET)	Ion-sensitive field effect transistor (ISFET) FET enzyme (ENFET)	H^+, Na^+

NBSs may use several other types of non-electrochemical transducer: (a) piezoelectric NBSs; (b) NBS-SAW, measures surface acoustic waves in a resonance circuit (*shear and surface acoustic wave*); (c) thermometric NBSs (the active element is coupled with a thermistor); (d) optical NBSs, uses optical phenomena: planar wave guide, optical fiber, surface plasmon resonance) SPR NBSs use the immobilized analyte–receptor interaction on a metal film deposited on an optical prism measuring the variance of the refractive index due to changes induced in the metal's electrical charge that transmits the electrons from the interaction process to the outside in the electronic measuring system. The electrode may be a metal, a semiconductor, or an ionic conductive material coated with a biochemical or bioactive film. Electrochemical NBS is an integrated transducer microsystem capable of providing selective, quantitative, or semiquantitative analytical information using a biological identification element. It can be used to monitor biological and nonbiological elements. Chemical NBSs that incorporate nonbiological components as receptors, although used to monitor biological processes (pH or NBSs of oxygen), are not NBSs.

The Clark electrode is of importance in the NBSs' measuring range. Similar physical NBSs used in biological environments such as those measuring pressure, etc. are not considered NBSs (Jacoby et al. 2015).

12.5.1 Classification

Electrochemical NBSs according to the terminology set out in Tables 12.3 and 12.4 can be classified according to their biological specificity, by mechanism or mode of signal transmission, or alternatively, the combination of two.

They can be amperometric, potentiometric, field effect (FET), or NMSs' conductometric (electrical conduction measurement) respectively impedance metrics. Alternatively, they may be called enzymatic amperometric NBSs to specify the nature of the receptor and the transducer. The first NBSs that were studied are the enzymes and immunosensors (Fang et al. 2015).

12.5.2 The Biocatalytic Recognition Element Receptor

NBSs are based on a catalyzed reaction of biomacromolecules present in the original biological medium that is preisolated or synthetically produced. The reaction is monitored by an integrated detector (transducer) that measures the stationary or transition states or the final reaction product via the immobilized biocidal product in NBSs. Types of commonly used biocatalysts are enzymes (simple or enzymatic complexes)—most commonly used as recognition systems, cells, microorganisms (bacteria, fungi, eukaryotic cells, or yeasts), cellular organs, or component (cell walls, mitochondria) sections of plant or animal tissues.

NBSs with biocatalyst recognition elements are the best known and studied since the beginning of their approach by Clark and Lyons. One or more analytes, commonly called S and S′ substrates, react in the presence of one or more enzymes, cells, etc., to produce the P and P′ products (Fang et al. 2015). There are four strategies whereby the associated transducer can monitor the consumption of S-analyte through the biocatalytic reaction:

- Detection of S′ cosubstrate consumption, oxygen depletion through the oxidase-induced reaction chain, bacteria, or yeast. The measured signal is the decrease in cosubstrate consumption compared to the initial value.
- Recycling of the reaction product P such as peroxyhydrogen, H^+, CO_2, and NH_3, in oxidoreductase reduction schemes, hydrolysis, lysis, etc. The signal from the transducer will be amplified.
- Detection of active centers in the biocatalyst: redox, cofactors, prosthetic groups evolving in the presence of substrate S by using an immobilized mediator. It reacts quickly with the biocatalyst and is easily detected in the transduction chain. Various ferrocene derivatives, such as tetrathiafulvalene, tetracyanochinodimetane (TTF + TCNQ), organic salts, quinones, quinone dyes, Ru, or Os complexes in polymeric matrices, can be used as mediators.
- Direct electron transfer is made between the enzymatic redox reactive site and the electrochemical transducer. The third strategy eliminates, partially or totally, the dependence of the NBSs' response on the cosubstrate concentration, S′, which decreases the influence of interference between species.

The use of mediators leads to the decrease of the substrate concentration together with the reaction chains by using a suitable membrane, whose permeability favors the transport of the cosubstrate. When enzymes are immobilized within the same reaction chains, it can improve the performance and abilities of NBSs. Three possibilities are commonly used:

- Some enzymes facilitate biological identification by sequentially converting the products of the enzyme reaction series into an electroactive final form: this way allows for a wide range of NBS analysis.
- The enzymatic complex, applied in series, can regenerate the cosubstrate of the first enzyme and amplify the NBS output signal by regenerating another cosubstrate of the first enzyme.
- The parallel enzyme complex improves selectivity of NBSs by lowering the local concentration of electrochemical interfering substrate: this sequence is an alternative to the use of a permselective membrane or a sequential method (e.g., interpretation of an output signal generated by an NBS and a reference NBS without biorecognition element).

The operation of NBSs is based on the interaction between the analyte and the macromolecules or organized molecular assemblies. Upon reaching the balance, there is no consumption of analyte by the biocomplex agent immobilized in the substrate. The response to the biocomplex analyte–reagent reaction is monitored by an integrator detector. In some cases, the biocomplex reaction is self-monitored by a complementary biocatalytic reaction. The integrator detector monitors stationary or transient states. Antibody–antigen interactions, the most relevant examples of NBSs using biocomplex receptors, are based on immunochemical reactions, e.g., binding an antigen (Ag) to the characteristic antibody (Ab).

Complexes formed by Ab–Ag can be detected provided that other nonspecific reactions are minimized, for each determination of Ag corresponds to a certain Ab that must be isolated, purified, etc. Some recent studies have analyzed direct monitoring of Ag–Ab formation using ion-selective field effect transistors (ISFETs). Increasing the sensitivity of immunological NBSs is achieved by adding specific enzymes to Ag–Ab couples, but this requires additional synthesis steps. As the binding strength or affinity constant varies widely, these systems operate irreversibly (disposable NBSs) or are coupled to flow injection analysis (FIA) systems; then Ab can be regenerated from dissociation of the complex with agents such as glycine–HCl to pH 2.5 (Kurien et al. 2010).

12.5.3 Receptor: Antagonist/Agonist

Recently, they have been used as molecular recognition systems in conductometric analysis, ISFET, or optical NBSs with receptors with ion channels, membranes, or protein structures. A transporting protein, lactose–permease (LP), can be incorporated into a liposomal bilayer that permits protonic carbohydrate transport with a stoichiometric ratio of 1:1. This mechanism was identified through the pH-dependent fluorescence of a fluorophore immobilized in liposomes. Liposomes with LP were incorporated into a lipid bilayer deposited on a pH-sensitive ISFET. Preliminary results show that this modified ISFET is capable of irreversibly detecting lactose from an FIA system.

Protein receptor NBSs have been recently discovered. Binding of analytes, here called agonists, to immobilized receptor proteins is monitored by changing the flow of ions through these channels. Glutamate, as an agonist, can be determined in the presence of other agonists that can interfere with the determination of Na^+ or Ca^{2+} streams using conductometric method or ion-selective electrodes. Due to the dependence of the ionic channel on the nature of the linkages, it produces an independence toward the enzyme nature in order to achieve the desired sensitivity. Two methods have been approached. The first refers to oligonucleotide duplex interleaving during the formation of the double helix structure of the DNA of a molecule that is electrically active. The second method is the direct detection of guanine which is electroactive. Some of these NBSs cannot operate through analytical-sensing membrane separation membranes. The sensitive layer often has to be in contact with the biological environment where the analytes are located (Fang et al. 2015).

12.5.4 Indirect Inhibitor or Activator Monitoring of Biochemical Receptors

NBSs have been developed for indirect monitoring of organic pesticides or inorganic compounds (heavy metals, fluorides, cyanides) that inhibit the biocatalytic properties of enzymes used in the construction of NBSs (devices are irreversible).

In immunosensors, the initial biological activity can only be regenerated by chemical treatment and therefore is not part of the reconditioned or reusable NBS class. Their application potential is to warn and not to accurately monitor a specific analyte (considered as disposable). NBSs with cyanide (i.g. inhibition of cytochrome c oxidase) that are used as inhibitor to cytochromoxidase are regenerated by washing with a phosphate buffer at pH 6.3 (Armstrong and Beckett 2011).

12.5.5 Immobilization of Biological Receptors

With the development of enzymatic glucose NBSs, an experiment in which glucose oxidase is immobilized between two membranes, literature has emerged about techniques for immobilizing biological receptors. Enzymes, antibodies, cells, or tissues with high biological activity can be immobilized in a thin film on the surface of a transducer through a variety of methods. The following immobilization procedures of biological receptors are used:

- Immobilization on the membrane on the surface unexposed to the analyte: an enzymatic solution, a cell or tissue suspension, rests between the permeable membrane to the analyte and the measuring electrode (electrochemical detector).
- Retaining of biological receptors in a polymeric matrix, polyacrylonitrile, agar gel, polyurethane (PU) or polyvinyl alcohol (APV), redox hydrogels with redox centers such as $[\mathrm{Os\ (bpy)\ 2Cl}]^{+/2+}$.
- Retaining of biological receptors between self-assembled layers (SAM) or in membranes from the double lipid layer (BLM).
- The covalent binding of membrane surface receptors through bifunctional groups: glutaraldehydes, carbodiimides, SAMs, avidin–biotin silanized.
- Modification of the entire electrode structure (modified carbon paste with enzymes or graphite in epoxy resins).

Receptors are modified either alone or mixed with other proteins, such as bovine serum albumin (BSA), either directly on the surface of the transducer or in the polymer membrane. Reactivated membranes can be used directly to immobilize enzymes or antibodies without chemical modification. The covalent binding and cross-linking are more difficult than immobilization or the retaining of receptors on the membrane. In the case of microsensor structures where the membrane is directly deposited on the transducer, the covalent bonding is safer and more stable (Muñoz et al. 2008).

12.6 Internal Membranes and External Membranes

Besides reactive layers or membranes with immobilized receptors, many NBSs, those for clinical or biological applications, incorporate one or more internal or external separation auxiliary membranes with three important functions: the barrier, the outer diffusion barrier for the substrate, and the biocompatible surfaces. For any NBS built on the principle of molecular recognition, it is important to characterize it by its response, which is related to operating parameters and limiting reaction speeds. Accuracy, precision, sensitivity, and reproducibility are basic criteria for estimating NBS performance. These parameters are in direct relation to the reaction mechanisms, the transport phenomena, and the kinetics of the processes in the volume at the interface. Most criteria have been developed for enzymatic NBSs, being the most studied in the literature. In the case of immunosensors, the key element is the ability to capture the surface, i.e., the number of surface molecules that is active. One method of checking this parameter is to measure the specific activity, meaning the ratio of the number of active molecules to the number of immobilized molecules. This estimation is dependent on the immobilization mode (molecular orientation, number of attachment points or active sites), and the ratio ranges between 0.15 and 0.3, rarely reaching the unit. Capture capability becomes important when the surface decreases as in microfluidic applications. A problem encountered in immunosensors is that of regenerating the surface without significant loss of activity. There was a lack of rigor in the performance criteria (Affi et al. 2016).

The response signal is corrected for background noise, the reference concentration is usually estimated in mol/L although this high value is never used when measuring ranges refer to 10^{-10} mol/L, and currently sensitivities of the order nmol/L and pmol/L have been reached.

Transient response is important for dynamic assay analysis and sampling techniques but is less significant in continuous monitoring. The transient response is estimated by the slope (dR/dt) max after the addition of the analyte in the measuring cell. One evaluation method is to introduce NBSs into an FIA system for sequential sample analysis in a specified hydrodynamic regime. The sensitivity and linear range of measurement of stationary concentration are determined through graphical representation. This method is more concise than the current calibration curves used to plot the response corrected to the baseline based on its concentration or logarithm. Parameters are estimated in the linear response range of NBSs.

Any electrochemical NBS has a superior linearity of the response. This limit is directly related to the biocatalytic or biocomplex properties of the biochemical or biological receptor. More in the case of NBSs with enzymes, this limit is significantly influenced by membranes and immobilized substrates where the diffusion barriers and secondary kinetics play a role. The local concentration of the analyte in the reaction layer may be two orders of magnitude smaller than the volume of the solution (Michelini and Roda 2012).

Enzymatic kinetics are described by Michaelis–Menten mechanisms and expressed by KM and VM parameters. For the kinetics of the enzyme in the solution phase, KM is usually determined from the Lineweaver–Burk graphical representation. For any electrochemical NBSs, the number of standards used and how the standard sample matrix can be simulated or duplicated should be set, being required to specify the procedures for each type of NBSs related to its application. These are important for the disposable NBSs' case using immunoaffinity or inhibition reactions. Sensitivity is the slope of the curve and should not be confused with the quantified detection limit (LOD) relative to the baseline or noise signals. The range of work concentrations is determined by lower or higher detection limits (Fang et al. 2015).

Selectivity and safety are determined as any kind of amperometric or potentiometric NBSs. They depend on the choice of receiver and transducer. Most enzymes are specific, but there are also nonselective enzyme classes, such as alcohol oxidases, the group of oxidases sugars, peroxidases, lactases, tyrosinases, ceruloplasmin, alcohol dehydrogenases, glucose dehydrogenases, NADH dehydrogenases, etc.

They have been used to develop NBSs to determine environmental phenols or to monitor food quality. On the other hand, oxygen electrodes, pH electrodes, and ISFETs have a pronounced selectivity, the same as metal electrodes that are sensitive to many substances. Their selectivity may be changed when these transducers are associated with receptors. ENFET is pH sensitive to the buffer and protonation but its selectivity is not altered. When the transducer interferes with other substances, known as ascorbate or urease, to glucose NBSs based on hydrogen peroxide detection, these side effects may be restricted by the use of outer or inner permselective membranes.

Alternatively, NBSs with and without biological receptors that work by differential NBSs are designed. Safety in operation of NBSs depends on the selectivity and reproducibility and accuracy of the measurements (Heyl et al. 2012).

12.6.1 Clark Electrode: Applications in Plant Nanobionics

The Clark construction principle studied electrochemically oxygen as a reducing gas and platinum as a metal electrode. Platinum used for detecting electrochemical oxygen is known as the Clark electrode. The electrode has an organic membrane covering the electrolyte layer and two metal electrodes. Oxygen diffuses through the membrane and is electrochemically reduced to the cathode. Between the cathode and the anode, a fixed voltage is applied, for which the oxygen reduction reaction takes place.

Temperature greatly influences reaction speed and solubility. This is a polarographic electrode used to measure the concentration of oxygen in body fluids or gases. The sample is in contact with a membrane (polypropylene or Teflon) through which the oxygen diffuses into a measuring chamber containing 50% saturated potassium chloride solution. Inside the room are two electrodes, one is reference, Ag/AgCl, and the other is platinum, coated in the glass.

The electrical current at the polarization potential of –600 mV is proportional to the oxygen concentration in the solution. For reverse polarization at +600 mV, hydrogen measurements can be made. Reactions are very sensitive to temperature and should be maintained at ±0.1 °C. The electrode is calibrated using a mixture of the two gas–oxygen and hydrogen-known concentrations. Oxygen electrode or Clark electrode has proven to be an analyzer of raw gas or developed gas when performing chemistry analyses in the clinical laboratory and in the field of medical care, ambulatory, or intensive care (on the surface of the platinum electrode an enzyme reacts with oxygen).

The enzymes are placed in a closed membrane to the surface, which can be recognized as the simplest model of NBSs. The oxygen concentration curve was proportional to the glucose concentration. It was the first NBS built, which helped the progress of laboratory analyses a lot. Oxygen diffuses through the membrane and is electrolytically reduced to the cathode. The higher the partial oxygen pressure, the more oxygen diffuses at a time.

The temperature NBSs attached to the sample allow the membrane to compensate for the diffusion and solubility rate. The measuring instruments record cathode current, sample temperature, membrane temperature, barometric pressure, and salinity. With this information one can calculate the oxygen contained in the sample, either in parts per million (ppm) or in percent of oxygen saturation. The geometric configuration of the Clark electrode is of great importance.

In particular, the thickness of the electrolytic layer between the cathode and the membrane must have a certain limit, to ensure linearity and decrease of the drift current. Calibrating a polarographic system is a must. Proportionality between current and oxygen concentration must be ensured, with errors below 1% (biological samples role and air parameters are essential).

Air, as a gas mixture that has a constant oxygen content of about 20.9%, when in contact with water, the dissolved amount depends on several factors: the optimal time for oxygen dissolution, homogeneity of the water solution, water temperature, air pressure, salts contained in water, and other water-soluble substances that are oxygen-consuming. Oxygen contained in water is determinant for biological and chemical processes, so measurement of dissolved oxygen in water is important to find the partial pressure of dissolved oxygen; it must be saturated in pure water at a certain temperature (Wolfbeis 2015).

12.6.2 The Enzymatic Electrode

The enzymatic electrode (in some references known as the enzyme electrode) is a combination of an electrochemical probe of any type (amperometric, potentiometric, or conductometric) with a thin layer (10–200 microns) of immobilized enzyme. In these devices the function of the enzyme is to provide selectivity in virtue of its biological affinity for a substrate of molecules. An enzyme can catalyze a reaction of a given substrate for a specific isomer from a plurality of substrates with different isomers.

Typically, the degree of advancement of an enzymatic reaction (directly related to the concentration of the analyte) is monitored by the rate of product formation or the disappearance of a reagent. If the product or reagent is electrically active, then the response can be directly monitored by amperometry, i.e., the variation of the current for a given applied potential.

The main considerations are: Does the enzyme contain active redox groups? Are the biochemical reaction products electroactive? Is one of the substrates or cofactors electrically active? What is the speed and response time? What is the final application of NBSs? If the enzyme does not contain redox groups, then NBSs are limited to measuring the product or substrate consumption by their reaction to the transduction electrode. The electrical current is directly related to the analyte concentration. NBSs are based on electrochemical response due to H_2O_2. Most common enzymes used in the design of enzyme electrodes are those that contain redox groups that change their redox state during the biochemical reaction. Redox enzymes are oxidases and dehydrogenases, pyrroloquinoline quinone (PQQ). They act by oxidizing the substrate, accepting electrons during the process, and further transforming in a reduced state.

These enzymes return to the oxidized active state by transferring electrons to the oxygen molecule resulting in hydrogen peroxide (H_2O_2). Both oxygen and peroxide being electrochemically active, they continue by reducing to cosubstrate (oxygen) or oxidation of peroxide (reaction product).

The method based on the reduction of oxygen to the O_2 electrode is one of the simplest methods but suffers from several disadvantages, namely, slow response, miniaturization difficulties, low accuracy, and reproducibility. Measurements on peroxide oxidation overcome the above difficulties and are currently the most popular method. Mediator systems—a major limitation of the above—described hydrogen permeation system is the high operating potential (about 0.8 V against the Ag/AgCl reference electrode) required for oxidation of peroxide which leads to increased interference. The use of mediators (molecules that can carry electrons between the enzyme redox center and the electrode) can minimize this inconvenience.

Depending on the nature of the mediators, the potential applied may be reduced below the limit of interferences of species such as ascorbate, urate, and paracetamol. A large number of compounds are able to act as mediators in the enzyme electrode. Of these, the most popular are the metallic complexes. Representatives for organometallic complexes are ferrocenes and their derivatives because they have redox potentials and are independent of pH. Bienzymatic systems' recent works have focused on the direct communication of electron transfer between enzymes and electrodes. Successes in the field are the peroxidase enzyme HRP (horseradish peroxidase) that catalyzes the reduction of hydrogen peroxide for a number of organic compounds. When the enzyme is immobilized on the electrode, the need for the organic reducer is prevented by the electrode itself providing the reducing equivalences. The coupling of peroxidase with an enzyme oxidase allows for the construction of bienzymatic systems through which the peroxide produced by the oxidase is detected by the electrode–peroxidase system which operates at lower potentials relative to a simple platinum electrode. This is where the minimization of active species interferences results from (Frederickson Matika and Loake 2014).

12.7 Fiber-Optic Biosensors (FOBS) in Plant Nanobionics

Optical fiber as a nanobiosensor can be placed in the surface or inside the plant to directly measure parameters. NBSs with optical fiber are proposed to be used in many and rapid medical determinations, and its applications are continuously expanding. It can be attached inside a hollow-like tubular instrument, serving to dilate a hole or channel, and inserted into the tissue, performing a minimal monitoring where it is needed. NBSs with optical fiber are nontoxic, chemically inert, and can be successfully used inside the plant. It can be associated with plant monitoring equipment. It's easy to handle with negligible weight.

The evolution of fiber-optic NBSs is based on multiple performance and biocompatibility. Biocompatibility is the first step in the plant's comfort; NBSs should not affect the physiological parameters of the plant, but its functionality must not be compromised by plant disassimilation products. Fiber-optic NBSs can be classified as extrinsic, fiber acts as a way for signal and intrinsic, interactions occur in the fiber itself. There are two types of FOBS: minimally invasive NBSs that are introduced into the cavities of the plants and invasive NBSs that are introduced into the organs or in wood conductive tissue (Liu et al. 2015).

12.8 Applications in Plant Nanobionics

In the last decade, optical fiber is a product that is widely used in all the cutting-edge fields of advanced science and technology. Given the ease with which it can be manipulated, unlimited sterilization possibilities, and reduced costs, it can be estimated that this product will increasingly gain market. The following applications are known to have used fiber-optic NBSs: in epidermis and vascular tissues, for analysis of raw sebaceous elements, saturation in oxygen, raw sewage gas analysis, sap pH; in plant breeding monitoring; easy pH determination with a microabsorbent indicator and pH–modulator, acid–alkaline; in vegetal tissues, when it is intended to monitor the temperature, or to diagnose small and very small injuries that are difficult to reach; in epidermis for can test the quality and integrity of the layers, so, small lesions can be detected, can be used to stimulate tissues, a FOBS based on oxygen demand (BOD) can be used; in the stem can identify very small injuries that are inappropriate. Another possible application is to appreciate the color or integrity of the vascular tissues. Optic-fiber NBSs can now monitor electrolytes from raw or elaborated sap as well potassium, sodium, and calcium. It takes the form of a tubular instrument, able to expand an optic-fiber channel (0.5 mm diameter) that can be inserted into vascular tissues. It can measure the gas concentration and the pH of the raw or elaborated sap and oxygen saturation also.

The materials that make up the chemical transducers are ionophores that can be reversibly attached to the electrolyte by a molecular separator (spacer) and fluorophore, respectively. The degree of fluorescence, through excitation with electroluminescent diodes in purple, is modulated by ionophores proportional to the analyte concentration. NBSs are used either extracorporeally in the external raw or elaborated sap gas analysis circuit or intracorporeally for continuous blood gas monitoring in critical situations. The chemical parameter capable of monitoring cell state is pH because lactic acid, formed when cell tissue dies, produces a decrease in pH. Any drop in the pH of the raw or elaborated sap from 7.4 indicates cell death (McLamore et al. 2010).

Achievements in the domain are invasive pH NBSs that determine the state of the cell. NBSs are composed of a fluorescent dye encapsulated in a gel matrix (polyacrylamide) attached at the end of the optical fiber. The dye is characterized by the emission of the acidic form centered on 580 nm and the alkaline form centered on 680 nm. The two forms are pH sensitive.

Excitation occurs at 533 nm for both forms. Separation of emission is done directly through optical filters, and sensitivity is 0.05 pH units far below acceptable clinical standards (0.1 pH). A bacterial disorder is a multifactorial condition that is characterized by demineralization of the inorganic portion and an organic destruction of the substance. Each bacterial perturbation has as an etiological agent as pathogenic species. The content of the raw or elaborated sap in terms of bacterial load is about 109/mL raw or elaborated sap. Therefore, raw or elaborated sap can be considered as a selective medium for bacterial growth. A significant correlation has been demonstrated between the number of pathogens in the raw or elaborated sap and their prevalence in the problems. A simple method has been adapted for detecting and counting the pathogen; it is a device consisting of a special support made with an agar culture medium containing 20% sucrose. It is inoculated with raw or elaborated sap, and the density of growth of the pathogen is assessed after incubation for 48 hours at 37 °C. Next comes the morphological identification of distinct colonies on selective and nonselective agar, on distinct cell form, visible in the light of the microscope.

The technique also has some disadvantages that it takes time for bacterial growth and also requires additional laboratories. To monitor pathogen activity in the sap, a FOBS was developed that monitors the pathogen-mediated sucrose reactions through a photosensitive indicator immobilized in a porous glass coating. The surface of the optical fiber core is treated or coated in a porous glass film using the sol–gel technique (Kozan et al. 2007).

Spectroscopic analysis showed that there are two phases in light absorption at 597 nm over a duration of 120 min: between 0–60 min and 60–120 min. The investigation shows the potential of NBSs in monitoring plant activity. The sol–gel technique is used to immobilize the photosensitive indicator, and it is simpler than compared with the principle of selective medium which takes time and is laborious. Criteria at the base of the experiment: pathogens are partially anaerobic with optimal growth at 37 °C; glucosyltransferases and fructosyltransferases from pathogens catalyze the synthesis of water-insoluble glucan and fructanic polymers in sucrose to form lactic acid found in acidic sap; pathogenic agents in the sap synthesize both extracellular and intracellular polysaccharides from sucrose; extracellular polysaccharides help the adhesion of bacteria to the surface, while intracellular polysaccharides are stored for bacterial energy; polysaccharides, intracellularly, help the bacterium to continue fermentation even when there is no exogenous form of food. Acid tolerance of pathogens causes their activity to continue even at a low pH; a pH indicator, photosensitive, produces a characteristic color, according to a color gradient, depending on the pH of the raw or elaborate sap and is used in the FOBS construction (Miranda et al. 2011).

On the basis of these considerations, an experimental assembly was designed and performed with a double beam UV spectrometer in which optical fiber was introduced instead of a cuvette. In the reference well, the blue bromophenol buffer solution was used for different pH values, from 4 to 7. The initial experiment helped determine the wavelength and peak characteristic to the buffer indicator and for different pH values in the sap, induced by bacterial activity. UV spectroscopic analysis at a pH of 4 and 7 of the blue bromophenol solution showed slightly prominent at 590 nm wavelength; peak intensity decreases from pH 7 to 4. Comparison with literature data showed a good concordance, observing that in the medium with sap, sucrose and bromophenol blue, the absorption was stable at 590 nm wavelength for a time interval of 15 min, 30 min, 1 h, and 24 h. For each set of corroded and processed fibers set, it requires independent calibration due to the in homogeneities resulting from the optic-fiber preparation steps. FOBS proves to be a rapid quantity measurement test of pathogen activity in raw or elaborated sap. This test can also be adapted to other plant nanobionics where bacterial activity is involved in cellular or tissue destruction.

The method of forming a biosensor from an optical fiber for the observation and detection of the pathogen, the experiments of this study followed the phase of biochemical recognition of the signal and the phase of the spectroscopic analysis. The idea of nanobionic plants has evolved to create solar cells that heal themselves from plant cells. The next step was the desire to try to amplify photosynthesis in isolated chloroplasts in plants to be used in solar cells.

Chloroplasts host everything they need for two-step photosynthesis. In the first step, pigments such as chlorophyll absorb light, which generates the stimulation of electrons that circulate through the chloroplast tilacloids. The plant captures this electrical energy and uses it to fuel the second stage of photosynthesis, creating glucose. Chloroplasts also have these reactions after they have been removed from the plants, but after a few hours, they break down because light and oxygen destroy their photosynthetic proteins. Normally, unlike extracted chloroplasts, plants can repair this damaging process. To prolong chloroplast productivity, researchers have attached ceric oxide nanoparticles. These particles are, in fact, powerful antioxidants that remove oxygen radicals and other high reactivity molecules produced by light and oxygen, protecting the decomposition chloroplasts.

The researchers introduced nanoparticles into chloroplasts using a new technique called LEEP (*lipid exchange envelope penetration*). By wrapping the particles into polyacrylic acid, a heavily charged molecule allowed the particles to penetrate the lipid hydrophobic membranes surrounding the chloroplasts. In these chloroplasts, the level of decomposition of molecules has decreased tremendously. Using the same technique, the researchers introduced semiconductor carbon nanotubes embedded in negatively charged DNA into chloroplasts. Plants use only one tenth of the available sunlight, but carbon nanotubes have functioned as artificial antennas that have allowed chloroplasts to capture unusual light waves such as green, ultraviolet, and near infrared. When carbon nanotubes functioned as prosthetic photoabsorbents, photosynthesis, measured by the activity of electrons in tilacloids, was 49% more intense than in chloroplasts isolated without attached nanotubes. When cerium oxide was joined with carbon nanotubes, the chloroplasts remained active for the next few hours (Nikolelis et al. 2008). Researchers went to live plants and used a technique called vascular infusion to attach nanoparticles to *Arabidopsis thaliana*, a small flower plant. Using the above method, the researchers applied a nanoparticle solution on the lower side of the leaf, penetrating the stomata that usually allow the carbon dioxide to get in and the oxygen out. In these plants, the nanotubes have penetrated into chloroplasts and have increased the photonic electron circuit by about 30%. It is also to be discovered how these percentages influence the sugar production of plants. Scientists have been able to transform the *Arabidopsis thaliana* plant into a chemical NBS by implanting nanotubes that detect nitric oxide, a pollutant produced by combustion (Hines et al. 2015).

NBSs have been created on the basis of carbon nanotubes for several chemicals, including hydrogen peroxide, trinitrotoluene, and sarin gas. When molecules attach to polymers encased in nanotubes, the fluorescence of these nanotubes is altered. Carbon nanotubes can be used to create NBSs that detect real-time particle free radicals or signal the presence of molecules with a very low level of concentration and too difficult to detect. This is a tremendous demonstration of how nanotechnology can be combined with synthetic biology to modify and enhance the functions of living organisms of plants. The way that nanoparticles arrange themselves can be used to enhance plant photosynthetic capacity, being used as NBSs and stress reducers.

By adapting NBSs to targets, researchers hope to develop plants that could be used to monitor environmental pollution, pesticides, fungal infections, or exposure to bacterial toxins. Attempts to incorporate electron nanomaterials into plants, such as graphene, are currently being made. Researchers have long tried to find the best way to transmit information in a timely manner, focusing on electronics and mechanics of NBSs for their tasks. NBSs used for agricultural purposes are not new. Recombinant DNA technology now offers the possibility of obtaining new biological insecticides that preserve the benefits of “classic” biological control agents, plus some new features. These technologies are not accessible to all possible users, especially if they are poor, and furthermore, they have also generated a series of public debates about their usefulness and effects on organisms other than the target or the environment.

Obtaining pest-resistant plants is perhaps the most spectacular field of genetic engineering applied to plants, since it allowed the regeneration of plants containing genes of bacterial origin that provide protection against harmful insects. This ensures, on the one hand, the obtaining of richer harvests and, on the other hand, the reduction of farmers' costs for pesticides (Lukács et al. 2006; Prasad et al. 2014, 2017).

A series of new genes for resistance to insect attack, transferable to plants (genes encoding δ-endotoxin production from *B. thuringiensis*) has been discovered; genes for the synthesis of enzymes or enzyme inhibitors; plant genes encoding the synthesis of specific lectins; genes that cause induction of synthesis of plant compounds such as phytoalexins.

The development of cloning methodology was based on the observation that there is a group of Gram-positive bacteria belonging to *B. thuringiensis* species that produce a toxin called δ-endotoxin or crystalline protein capable of killing a wide range of insects (Coleoptera, Lepidoptera, Diptera), depending on the bacterial strain. Of great interest is strain *B. thuringiensis* var. *tenebrionis* that synthesizes an effective δ-endotoxin against the Colorado beetle. The genes involved in the synthesis of this protein are localized, on most bacterial strains, to large plasmids (75 kb), the production of the toxin occurring during sporulation. It has been shown that crystalline protein (δ-endotoxin) is normally expressed as a large inactive protoxin, which undergoes proteolytic processing in the intestine of the sensitive insect, becoming an active toxin. It recognizes the specific receptors in the intestinal cells and blocks the functions of these cells, leading to the death of the insects.

Studies on genes that encode inhibitory proteins produced by *B. thuringiensis* led to their grouping into four types based on target species specificity and nucleotide sequence: type I cry genes, encode specific 130 kDa proteins for lepidopteran larvae; type II cry genes, encode active 70 kDa proteins on dipterous and lepidopteran larvae; type III cry genes, encode 70 kDa specific activity on coleopteran larvae; and type IV cry genes, encode inhibitory proteins for Diptera larvae.

The number of genes identified that are coding for δ-endotoxin-like proteins is high: 140 genes specific for lepidopteran, coleopteran, and diphtheria (Genfa et al. 2005).

It has been achieved to obtain crystalline protein genes from several strains of *B. thuringiensis* by genetic amplification (PCR). Because the whole gene for the crystal protein was found to be very poor in the transformed plant cells, a modified gene was created, containing only the N-terminal portion of the protein (amino acids 1–645). To increase gene expression in plants, the natural sequence for amino acids 1–415 rich in AT was replaced by a synthetic sequence, rich in GC, containing the preferred codons for plant cells.

These recombinant genes were introduced into Ti plasmid-derived vectors (binary vectors containing the duplicate CaMV promoter, which increases the transcriptional and fivefold transcription and selection marker genes for antibiotic resistance or phosphinothricin herbicide) transferred to cells by *A. tumefaciens* containing Ti disarmed plasmids. The size of recombinant plasmids obtained ranges between 5000 and 10,000 pb, depending on the size of the bacterial gene and the promoter sequence integrated into the vector. Recombinant bacterial strains were then used to infect test plants (potato, tobacco, cotton). Selection was first performed according to vector-borne selection markers (antibiotic resistance, GUS test, herbicide resistance, etc.), and finally regenerated plants were subjected to insect attack (Takakusagi et al. 2013).

Regenerated plants have shown resistance to attack by insect pests, the specific character being maintained and expressed in experiments in the field. The first transgenic plant that manages the insect attack resistance belongs to the *Nicotiana tabacum* species, expressing the whole or truncated cry 1A gene, cloned under the control of a constitutive promoter, so that the inhibitory protein represents 0.02% of the total plant protein (leaf). There were obtained cotton plants into which the modified cry 1A (c) gene, cloned under the control of the CaMV 35S promoter or under the control of a promoter and a sequence for a chloroplast transit peptide isolated from *Arabidopsis* so that the expression level of the gene of interest led to a high level of toxin: 0.1% of total protein, 1%, respectively.

Another variant of cloning the bacterial toxin gene was that of using genetic elements that ensure expression of the gene of interest exclusively in the green portions of the plant (the promoter derived from the gene for PEPC) or pollen (by using a gene derived promoter for a calcium dependent protein kinase (CDPK). A similar methodology has been used to transform rice plants, and by cloning a synthetic cry III gene, they have obtained tobacco and potato plants resistant to the attack of Colorado beetle (Vigneux et al. 2007).

A modified 1A (b) modified gene was used for cloning under the control of the CaMV promoter and obtained sugarcane plants with resistance to *Diatraea saccharalis* larvae. Given the practical significance of plant resistance to harmful insects, research has been extended to other plant species, producing eggplant plants resistant to the attack of Coleoptera, broccoli with resistance to certain lepidopteran species, maize with resistance to *B. fusca*, etc., as well as a number of advances in leguminous plants.

Toxicity studies conducted on plants expressing the gene for δ-endotoxin have shown that the existence of the transgene does not alter the normal features of the plants, except resistance to insect attack. In addition to δ-endotoxin produced by *B. thuringiensis* strains, other bacterial species have also been identified that produce insecticidal proteins (Liu et al. 2011). This is the case for *B. cereus* strains producing two VIP1 and VIP2 proteins with effect on insects, their mode of action being similar to δ-endotoxin.

12.9 Genes for the Synthesis of Enzymes or Enzyme Inhibitors with Insecticidal Effect

Expression by plants of enzymes such as chitinase, cholesterol oxidase, lipoxygenase, phenol oxidase, peroxidase, or isopentenyl transferase (ipt) could be an alternative to using the δ-endotoxin gene. Of the enzymes that can provide plant protection against insect attack, a particular place is occupied by chitinases, enzymes that act on chitin, a basic component of insect coatings. Tobacco plants expressing genes for chitinase isolated from insects or beans exhibit increased resistance to lepidopterans. It has been observed that by cloning the isolated chitinase gene from the *S. marcescens* bacterium, a synergistic effect of endocytinase produced by plants containing the endotoxin gene in addition to *S. littoralis* larvae has been revealed. Another enzyme of bacterial origin that exhibits insecticidal action is cholesterol oxidase.

The introduction and expression of cho A gene for cholesterol oxidase from *Streptomyces* sp. in tobacco plants have led to increased plant resistance to *A. grandis* larvae. The use for cloning the gene for the enzyme bacterial isopentenyl transferase (ipt) (involved in cytokine biosynthesis) by fusion with the protease inhibitor II (PI–IIK) gene promoter determined the production of *N. plumbaginifolia* lepidopteran-resistant plants (*M. sexta* or *M. persicae*).

Another embodiment was that of introducing into the plant cells the cpt2 gene that encodes a trypsin inhibitory protein isolated from *Vicia faba*. This protein has antimetabolic effect, protecting plants from the attack of pests. Similarly, other genes encoding protease inhibitors (Kunitz trypsin inhibitor, *Bowman–Birk* proteinase inhibitor) or lectins have been cloned into different hosts, and encoded proteins may be true “defense guns” for the plants that contain them. It is known that insects, such as lepidopterans, depend on serine proteases (trypsin, chymotrypsin, or elastase), these being the first enzymes to digest (Alvarez-Fernandez 2010).

A series of genes encoding different inhibitors for serine proteases have been isolated from various sources (plants, microorganisms) and cloned into various plant species, such as *M. sativa*, tobacco, corn, etc.; the plants obtained showed increased resistance to various insect pests compared to normal non-GM plants. In some cases, it has been noted that the insertion of additional genes to plants for protease inhibitors to join endogenous genes causes an increased level of pathogen resistance of transformed plants. However, the use of protease inhibitors for controlling insect pests requires thorough studies of plant and insect interactions because it has been observed that for some inhibitors such as serine proteases, the insecticide effect also manifests on useful insects (e.g., on bees). Insect carbohydrate metabolism is another target for inhibitory agents tested in numerous studies. Genes for different α-amylase inhibitors (wheat and beans) were isolated and characterized; after cloning the isolated gene from wheat in tobacco plants, an increase in lepidopteran larval mortality of up to 40% was observed. In the case of cloning the α-amylase inhibitor gene from beans in pea plants under the control of the pha 1 gene promoter, an increased expression of the foreign gene in the seeds was obtained, which resulted in a higher resistance to *Callosobruchus* sp. (Ramirez and Spears 2014).

Vegetable lectins are a special group of glycoproteins that have protective functions against a number of harmful organisms. Studies on these glycoproteins have shown that they produce strong effects on the development of various types of insects. The first example of plants containing genes for nonspecific lectins that show toxicity to pests is tobacco plants in which the lectin genes from the pea have been cloned. However, many of the vegetable lectins also have a toxic effect on mammals, which limits their use as agents to increase pest resistance. Special attention has been given by many specialists to lectin specific for mangosteen from guinea pigs and concanavalin A: the genes for these lectins have been cloned into different plant species (tobacco, tomato, potato, sugarcane, rice, wheat), and the heterologous proteins synthesized by them have determined a reduced sensitivity to the attack of harmful insects (lepidopteran, aphids, coleopteran larvae).

The results suggest that the use of plants containing insecticide genes (such as for lecithin) together with integrated management represents promising possibilities for controlling pests from many plant species, including wheat or rice (Richard et al. 2014). Contrary to the remarkable results achieved so far, the genes used to transform crop plants are either too specific or only partially effective on the targets of insect pests. To use plants as true "weapons" for pest control, it would be necessary to have genes at their level to determine the synthesis of compounds with different actions on the same target.

The researchers are relatively recent and aim mainly to combine genes for a *B. thuringiensis* δ-endotoxin with another inhibitory gene in the same host gene: for example, the gene for the *V. faba* trypsin inhibitor (CpTI) or for serine proteases and the protein gene in the potato virus Y coating. Another interesting approach is that which introduced the cry1A (c) gene into a *P. fluorescens* strain able to colonize the sugarcane by means of two plasmids, pDER405 and pKT240, in which the gene is found in 13 and 28 children, respectively. Testing of recombinant bacterial strains on sugarcane-specific insect pests revealed greater resistance of plants treated with the respective bacteria than untreated. Also, although pest-resistant plants have been obtained for several plant species, fewer results have been reported for cereals, vegetables, and oleaginous plants (Ibrahim et al. 2008).

Plant resistance to various diseases (microbial, viral, and nematode phytopathogens) has been a subject for long-term studies, identifying a relatively large number of resistance genes. Although it was thought that endogenous resistance genes would provide a sustainable effect for the appropriate plants, this was true in very few cases. In the case of potato, the control program for certain diseases, such as the rot caused by *Phytophthora infestans*, had to be abandoned because the resistance to this disease of potato plants obtained by transferring the 11 resistance genes on the basis of crossbreeds with the *Solanum demissum* species proved to be of short duration. Identifying genes of resistance in the genome of different plant species and transferring them to other crop plants are extremely difficult and time-consuming if traditional methods (intra- and interspecific hybridizations) are used. The process is considerably accelerated by the use of molecular markers generated by restriction fragment length polymorphism (RFLP) techniques, randomized amplified polymorphic DNA (RAPD), single sequence repeat (SSR), or single nucleotide polymorphism (SNP).

The application of molecular markers allowed the isolation of nearly 20 resistance genes (R-genes) from genetically well-characterized plant species, proving that many of them are grouped into specific chromosomal regions (they form clusters). Of these resistance genes, some have been transferred to other plant species than to their origin through molecular cloning techniques, with the help of specific vectors that ensure the transfer of large fragments, revealing that in this way, the R-genes act synergistically and provide lasting resistance to some diseases. As it has already been mentioned, few R-genes have been shown to provide a lasting control of plant diseases. This is the case for pepper Bs2 genes and rice Xa21 which provide resistance to different phytopathogenic strains of *X. campestris* or *X. oryzae* in the case of species in which the genes have been cloned (e.g., tomatoes). Resistance to these genes is due to the recognition of proteins produced by bacteria or phytopathogenic fungi, resulting in the occurrence of a plant hypersensitivity phenomenon and necrosis of affected tissues. Another example of the long-acting R-gene is the barley recessive mlo gene which provides the resistance of the plants containing it to all *E. graminis* strains, through the accumulation in plant cells of a phenolic antifungal compound named p-coumaroylhydroxyagmatine.

It is expected that this gene will be used for suppressing the antisense technique of the dominant mlo gene from wheat or other plant species susceptible to *Erysiphe* sp. In vitro processing of the R-genes and then introducing them into new hosts provide new possibilities for resistance. This is the case for the tomato avrPto gene which, after cloning under the control of a strong promoter such as 35S to CaMV, determines the resistance of transformed tomato plants to *P. syringae* pv. strains, *tomato*, and to unrelated pathogens such as *X. campestris* and *C. fulvum*. Researchers' efforts to obtain resistance systems applicable to a larger number of plant species are not limited to R-genes but also include systemic acquired resistance mechanisms (SAR). Several genes involved in SAR have been isolated and characterized, of which the Npr1 gene encoding a transcriptional regulator is a key gene in this system. Overexpression of this gene increases the resistance of *Arabidopsis thaliana* or rice plants to a wide variety of pathogens (Knecht et al. 2010).

An interesting behavior has been observed in the Myb1 gene which is induced by VMT infection of resistant tobacco plants and which causes the synthesis of a transcription factor that binds to the promoter of a gene involved in pathogenesis (the PR1a gene). Modifying the expression level of the Myb1 gene in tobacco plants leads to increased resistance to viral infection (with VMT) as well as to *R. solani* pathogenic fungus (Raymond et al. 2007).

Along with this, another recently cloned gene, Pad4, isolated from *Arabidopsis thaliana*, proves to be extremely interesting for the development of broad-spectrum resistance: overexpression of the gene in plants increases resistance to phytopathogens. Numerous biotech companies and universities have begun to assess the performance of plants that express antifungal proteins through both "in vitro" and field experiments. Both plants containing R-genes or genes involved in SARs, as well as genes such as those which encode the glucosidase (AGO) from *Aspergillus* sp., defensins, H_2O_2-generating enzymes, glucanases or chitinases, have been examined. Although at the laboratory level potato plants containing the fungal gene for glucose oxidase showed an increased resistance to phytopathogens, the results were inconclusive when they were put into the field. For other genes such as chitinase and intracellular α-1,3-glucanase, overexpression of these in tomato plants resulted in significant resistance to *Fusarium oxysporum* (Werner et al. 2016).

Companies have created NBSs that farmers can use to detect information such as air pollution, soil humidity, and so on. However, given that plants are really good NBSs and that they can naturally react to external stimuli and changes, they can be used instead. This is the idea behind the latest NBSs initiative called *Advanced Plant Technologies*. The idea is that, through genetic manipulation, researchers will be able to create self-sustaining plants, which in turn enable them to act as a kind of NBS when it comes to detecting chemical substances, pathogens, etc. This is not the first time this idea with plants as NBSs appears, but before that, resources that plants needed to survive were used, which in turn reduced their resistance. This new idea indicates that NBSs can be sustained by themselves, which means they can work longer in isolated parts. In the future, plants could be used to detect when a *biological attack* will take place. In addition, because they are plants, it also means that they can be placed anywhere and nobody will think twice about their presence and that they might be some NBSs.

12.10 Conclusions and Remarks

Through such examples, nature teaches us to optimize by exploring diversity. In this context, integrated nanoscale systems (NBSs), energy sources (biocombustible cells) that use plants metabolism, manipulators for nanoscale surgery, and drug reservoirs embedded in intelligent polymers are explored. All of these are virus-sized. The proliferation of these types of NBSs leads to a large number of applications, and combinations of these in the future will lead to microminiaturization, versatility, and functionality. Plant species present a great diversity of genetics, and wild ones constitute a large genetic reservoir, from which genes that are important from a practical point of view can be obtained. Plant genetic engineering research has a great theoretical significance, facilitating the knowledge of how genes of these organisms act, the effects of phytohormones on plant development, genes inactivation mechanisms, etc. By applying molecular biology techniques, useful information can be obtained on the genome of plants used for amelioration, the localization of genes of interest, the degree of relationship between different species, etc. As far as practical applications are concerned, a number of significant results have been obtained so far, some of which have already been applied, such as virus-resistant plants, plants resistant to the attack of pests, herbicide-resistant plants, plants of horticultural interest (ornamental plants with new phenotypes, plants producing softening resistant fruits), plants capable of synthesizing secondary metabolites in increased amounts, and plants producing “edible” antibodies, and enumeration could continue.

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Chapter 13
Toxicity of Nanomaterials in Plants and Environment

Majid Peyravi, Mohsen Jahanshahi, and Ali Bali Eslami

Contents

13.1 Introduction

Nanomaterials are chemical materials or substances that are produced and used at a very small scale. The most important feature of nanomaterials is their small size which ranges between 1 and 100 nm. These intrinsic unique features are the reason for the widespread potential applications of NMs (Ball 2002). Smaller size of NMs helps them to penetrate particular cellular sites and their additional surface area simplifies more adsorption and targeted distribution of substances (Kashyap et al. 2015). The NMs exist in anthropogenic waste materials like coal combustion,

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M. Peyravi (✉)
Department of Chemical Engineering, Babol Noshirvani University of Technology, Babol, Iran

Nanotechnology Research Institute, Babol Noshirvani University of Technology, Babol, Iran
e-mail: majidpeyravi@nit.ac.ir

M. Jahanshahi · A. B. Eslami
Department of Chemical Engineering, Babol Noshirvani University of Technology, Babol, Iran

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welding fumes, diesel exhaust (incidental NMs), as well as in volcanic dust, mineral composites, etc. (natural NMs) (Monica and Cremonini 2009). Moreover, engineered nanomaterials (ENMs) produced with nanoscale dimensions are commonly grouped into four kinds, viz., metal based NMs, carbon based NMs, metal oxides, composites, and dendrimers (Ju-Nam and Lead 2008). Due to their wide range in uses, NMs might easily be intentionally or incidentally released into the environment (Hashimoto et al. 2017).

Nanomaterials have been shown to affect plants at every step of their life cycle (Liu et al. 2016a). NPs play important role in the conservation of plants against diverse abiotic stresses such as cold, drought, and salinity. Tiny size and large active surface area of NPs provide access for toxic metals for binding and thus alleviate accessibility and toxicity of metals (Worms et al. 2012). Apart from their positive effects several NMs illustrate toxicity symptoms. The presence of NMs in the soil and water induces oxidative stress and causes loss of photosynthesis, chlorophyll (Chl), biomass and nutritive value of crop plants (Peralta-Videa et al. 2014), and decrease in germination rate, root, and shoot length (Da Costa and Sharma 2016; Wang et al. 2016c). Also, when released into the environment, ENMs can interact with a wide array of environmental pollutants (e.g., organic pollutants and heavy metals), which may effect on environmental behavior (Deng et al. 2017; Canesi et al. 2015). At the same time, an interaction between ENMs and pollutants may also effect on physicochemical property and bioavailability of ENMs (Cui et al. 2016). Therefore, it is necessary that we understand the destiny and toxicity of NMs, specifically in plants and environment.

In this chapter, toxicity of nanomaterials in plants and environment is investigated. First the toxicity effect of NPs on plant growth and then the effect of ENMs on the toxicity of environmental pollutants are discussed.

13.2 Toxicity Effects of NMs on Plant Growth

13.2.1 Plant Uptake of ENMs

It is not completely clear as to how NMs may penetrate into the plant. However, NMs penetrate into the plant through adsorption on the root surface, incorporation into the cell wall, and uptake into the cell (Nowack and Bucheli 2007). The NMs, larger than the cell wall pore size, stick to the epithelial root cells causing physical injuries to the cells (Miralles et al. 2012), pores fouling, and decrease root hydraulic conductivity leading to changed color of the roots surface(Martínez-Fernández et al. 2016), alleviated water absorption, and nutrient uptake capacity. However, NMs smaller than the pore size of cell could diffuse through lateral root junctions and have been found in the roots, stems (xylem and phloem), and leaves of the plant (Tripathi et al. 2017). It is also noted that NMs can enter the nucleus, mitochondria, and chloroplast of the plant cell as well as directly interact with DNA, RNA, or proteins (Serag et al. 2010). Direct interaction of NMs to DNA, RNA, or proteins causes mechanical infraction and affects integrity of cell membrane and cell walls (Jang et al. 2003).

13.2.2 Carbon Based Engineered Nanomaterials

A wide use of carbon-based NMs (CNMs) has led to its potential transport to living systems, either intentionally in discharges, or incidentally in spillages, and greater probability of the unfavorable environmental effects (Baughman et al. 2002). Among CNMs, the most studied materials are carbon nanotubes (CNTs) and graphene oxide (GO). As CNMs are considered extremely hydrophobic with the great tendency to aggregate, these could be expected to reside in the living system (De La Torre-Roche et al. 2013). This feature would increase the CNMs capability to interact with various organic substances. So, the low surface friction of CNTs is needed to help the transfer of organic substances into the cytoplasm (Santos et al. 2013).

13.2.2.1 Carbon Nanotubes

Carbon nanotubes (CNTs) may have possibly single or multiple layers of carbons established in a cylinder. CNTs are in the form of fibers, with the properties very diverse from massive graphite or carbon. Thus, CNTs have great tensile strength and are possibly the powerful, smallest fiber recognized. There is proof that CNTs could dislocate to systemic sites, such as roots, leaves, and fruits, which could involve a potent interaction with the cells of the tomato seedling. This resulted in considerable alteration in roots gene expression, leaves, and total fruits. CNTs have phytotoxic effects on plant cells because of accumulation and reason cell death in a dose dependent manner. Cell death is illustrated by electrolyte leakage and the swelling of the cell plant. Also, alterations in the content of plant metabolites after exposure to CNTs have been identified. For example, the tomato treated with CNTs showed an increase in fruit metabolites, such as alkaloid senecionine and terpenoids (McGehee et al. 2017).

13.2.2.2 Graphene and Graphene Oxide

Graphene is a two-dimensional allotropic form of carbon. It can be considered as a one atom layer of graphite. At higher concentrations of graphene (1000 mg L^{-1}), the root growth of red cabbage and spinach alleviated compared to the control plant (Begum et al. 2011; Al-Ghamdi et al. 2014; Ye et al. 2012) (Fig. 13.1). This is because of the accumulation of graphene using H_2O_2 visualization, together with observable

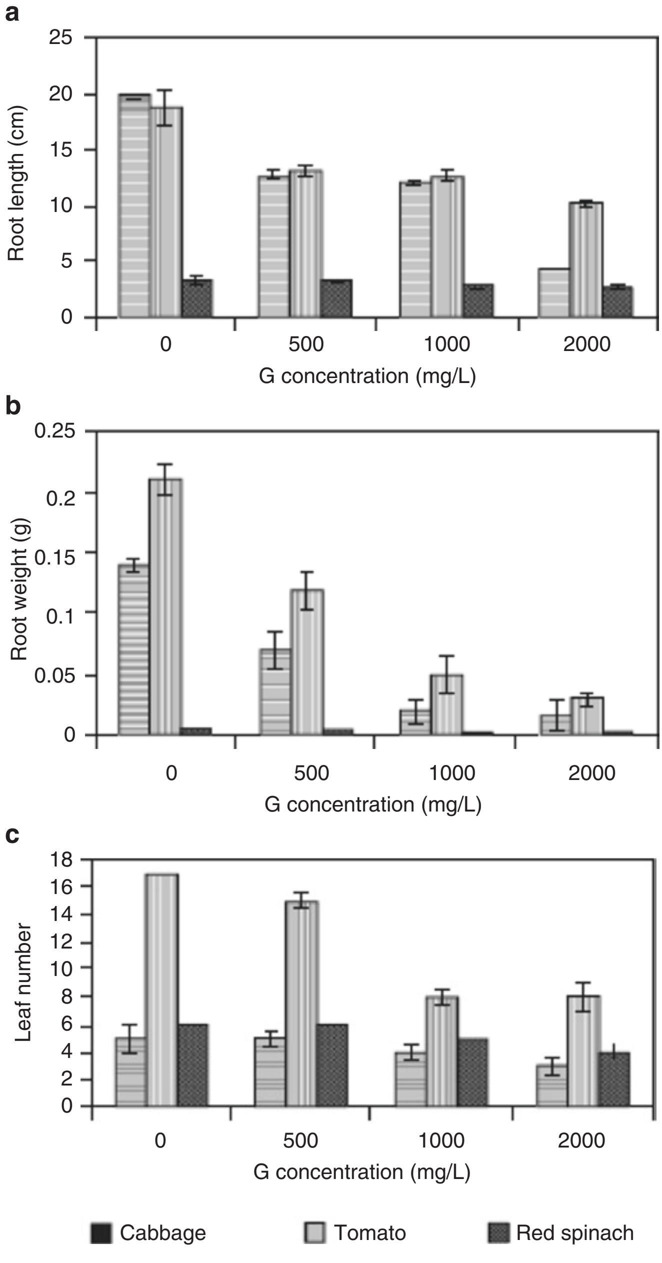

Fig. 13.1 Effect of graphene (G) on red spinach, cabbage, and tomato seedlings. At 21 days seedling growth on Hoagland media with graphene (0, 500, 1000, and 2000 mg L^{-1}) was utilized for all measurements. (**a**) Root length, (**b**) shoot length, (**c**) root weight, (**d**) shoot weight, (**e**) leaf number, and (**f**) leaf area (Begum et al. 2011)

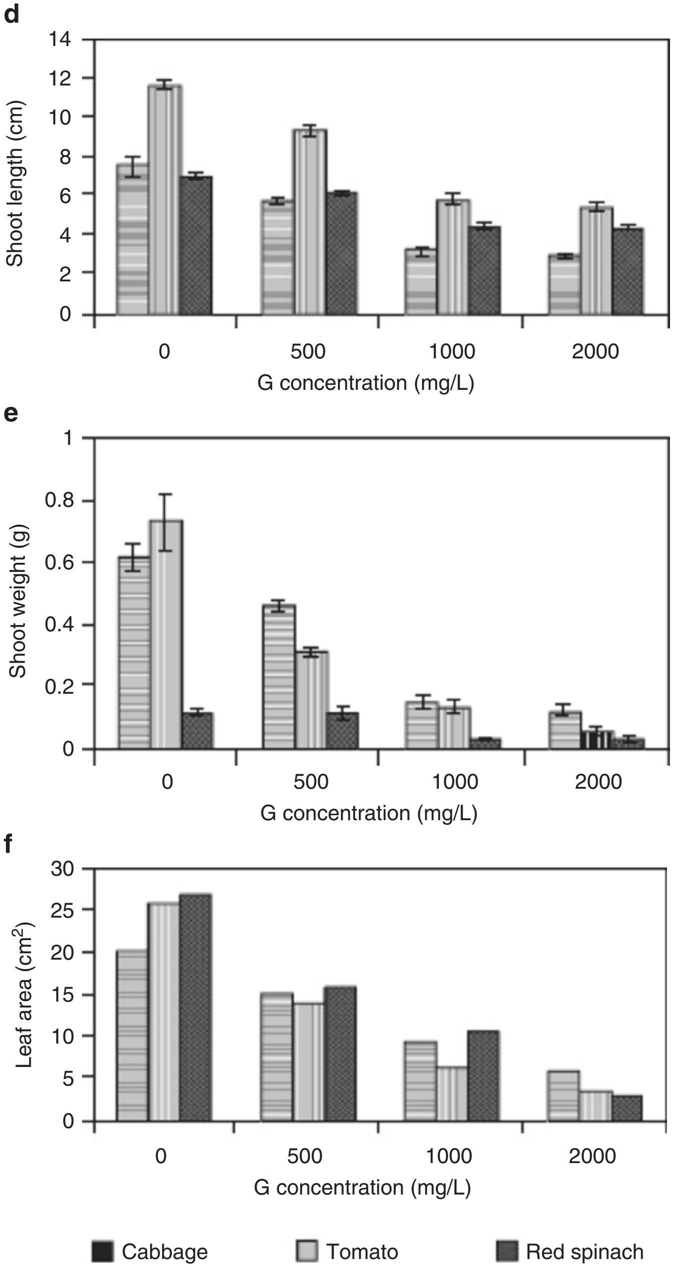

Fig. 13.1 (continued)

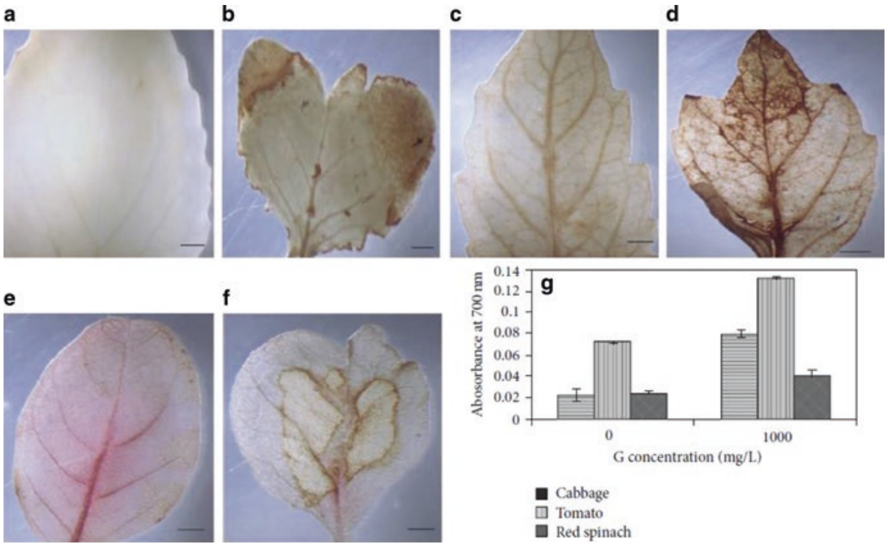

Fig. 13.2 Influence of graphene (G) on accumulation of H_2O_2 in leaves tested by means of the ROS-sensitive dye DAB of tomato, red spinach, and cabbage seedlings. At 21 days leaves treated with or without 1000 mg L^{-1} graphene were employed for all measurements. (**a**), (**c**), and (**e**) are cabbage, tomato, and red spinach leaves untreated, respectively. (**b**), (**d**), and (**f**) are cabbage, tomato, and red spinach leaves treated, respectively. The brown staining shows the formation of a brown polymerization product when H_2O_2 reacts with DAB. (**g**) Influence of graphene (1000 mg L^{-1}) on the aggregation of H_2O_2 in treated leaves as measured utilizing DAB (Begum et al. 2011)

signs of necrotic damage lesions and proof of a bulky electrolyte leakage, showing an oxidation stress mechanism (Begum et al. 2011; Mogharabi et al. 2014).

For example, intracellular decrease in oxidation system possibly has a crucial function in the induction of loss of cell life induced by graphene (Fig. 13.2). It explained the aggregation graphene as leading to cell death, demonstrated by electrolyte leakage from cells. The use of extra graphene may cause swelling in *Origanum vulgare* and *Origanum* (Begum et al. 2011). Graphene is known as inducing phytotoxic effects in cells of plants because of the aggregation mechanism. This causes loss of cell life and the aggregation in a dose-dependent manner (Akhavan and Ghaderi 2010; Sasidharan et al. 2011). There is inevitably proof that graphene could translocate to systemic sites, such as roots, leaves, and fruits, which engage in a strong interaction with the tomato seedlings cells, leading to essential modifications in total gene expression in leaves, roots fruits, and applying toxic effects (Anjum et al. 2014; Kim 2013). With that, it is unexpected to detect the graphene toxicity effects on earthy plant species, in cabbage, red spinach, and tomato (Lee and Kim, 2014; Kim, 2013). Past studies observed the similar growth pattern in cabbage, red spinach, and tomato utilizing graphene NMs (Anjum et al. 2013; Lee and Kim 2014). At high concentrations of graphene (1000 mg L^{-1}), the root hair growth of red spinach and cabbage compared to control plants was alleviated (Begum et al. 2011) (Fig. 13.3).

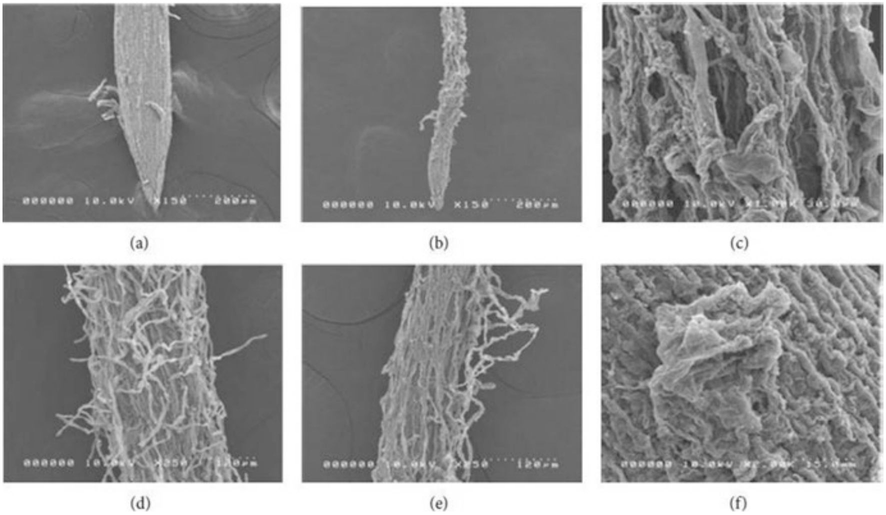

Fig. 13.3 Effect of graphene (1000 mg L^{-1}) on the root surface of tomato seedlings grown in Hoagland medium. (**a**, **d**) SEM image of the untreated control of tomato root elongation and root hair zone, respectively. (**b**) Root elongation zone of tomato root and (**c**, **e**, and **f**) demonstrate surface detachment and aggregates of graphene on the tomato roots surface treated with graphene

Graphene oxide can affect phytohormones of plant. Phytohormones were also affected following exposure of rapeseed to graphene oxide. In a recent research, abscisic acid (ABA) and indole-3-acetic (IAA) levels were changed after exposure to 0–100 mg L^{-1} graphene oxide. ABA increased at high concentrations of graphene oxide, showing that the plant may be under stress. IAA reduced with an increase in graphene oxide concentration. The roots of rapeseed were shorter in plants exposed to high concentrations of graphene oxide. IAA is in the auxin class (growth promoters) of phytohormones; therefore, a reduction in IAA can destructively effect on root growth in plants (Cheng et al. 2016).

13.2.3 Metal and Metal Oxide Engineered Nanomaterials

Metal oxide NPs represent a field of materials chemistry which attracts significant interest owing to the potential technological applications of these compounds. Research has shown that the metal/metal oxide NPs production has increased more than three times in the last decade (Niederberger 2007; Stoimenov et al. 2002). Metal/metal oxide NPs exhibit size dependent properties, such as photocatalytic degradation, magnetism, or fluorescence, which has biotechnological applications in sensor development, agrochemicals, and soil remediation (Franke et al. 2006; Kolmakov and Moskovits 2004). In environment, the effect of metal/

metal oxide via plants is expected to depend mostly on the colloidal properties such as organic content, sediments, and soil or sludge, as well as chemical properties. The most studied metal-based NMs are CeO_2, Fe_3O_4, TiO_2, and ZnO NPs (Niederberger et al. 2006; Moisala et al. 2003). Indeed, Fe_3O_4 NPs induce some durability effect on aquatic suspensions of carbon nanotubes and fullerene. It has been proved that the effect of varying pH and humic acids can combine the effects on the destiny of Fe_3O_4 NPs by enhancing pH, resulting in a higher content of accumulation. A same effect was lately shown for CeO_2. Metal NPs, under low concentration conditions, play a vital role at the restriction of plant endurance in the growth of plants (Stoimenov et al. 2002). The absorption of excess amounts of metals by plants causes toxic effects such as reduction of growth and disarrangement in cell division (Niederberger 2007; Kolmakov and Moskovits 2004). In this case, extra metal NPs, acting as cofactor for enzymes, are involved in the development of intermediate metabolites. However, the reaction of plants to metal NPs is affected by the stage of growth, type of plant species, and the nature of the metal.

13.2.3.1 Gold (Au)

Gold (Au) is classified as a noxious substance, and the toxicity of Au in many studies has been reported in ionic or dissolved form (Karamushka and Gadd 1999; Murphy et al. 2008; Goodman et al. 2004; Boisselier and Astruc 2009). Au NPs have been utilized in many applications as antibacterial. In this case, the toxicity of Au has been limited in the form of Au NPs (Goodman et al. 2004; Murphy et al. 2008). The production and the utilization of Au NPs in the environment and its potential transport to the environment might cause intense toxicity problems in the long term (Hauck et al. 2008; Khlebtsov and Dykman 2011; Johnston et al. 2010). For instance, *Medicago sativa* and *Brassica juncea* displayed an enhancement in Au uptake, with a conforming betterment in the layer of Au exposure time and concentration (Saison et al. 2010; Perreault et al. 2012; Zhai et al. 2014).

The Au NPs to be found in the nucleus and the usage of defamation suggested at both types are considered as hyperaccumulators of Au NPs (Arora et al. 2012; Gardea-Torresdey et al. 2000; Green and Renault 2008). Additionally, it is proved that Au NPs are transported inside the cells via plasmodesmata. TEM[1] images of rice roots revealed that various Au particle sizes are stored inside the cells of root in the form of vacuoles. The cell damage happened because of penetrations of large Au NPs entering through small pores (Perreault et al. 2012).

Au NPs are noted to disrupt the onion root tip cells (*Allium cepa*), thus negative effect on the cell division process by causing the formation of cell disintegration, stickiness, and chromatin bridge (Feretti et al. 2007).

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[1] Transmission electron microscope.

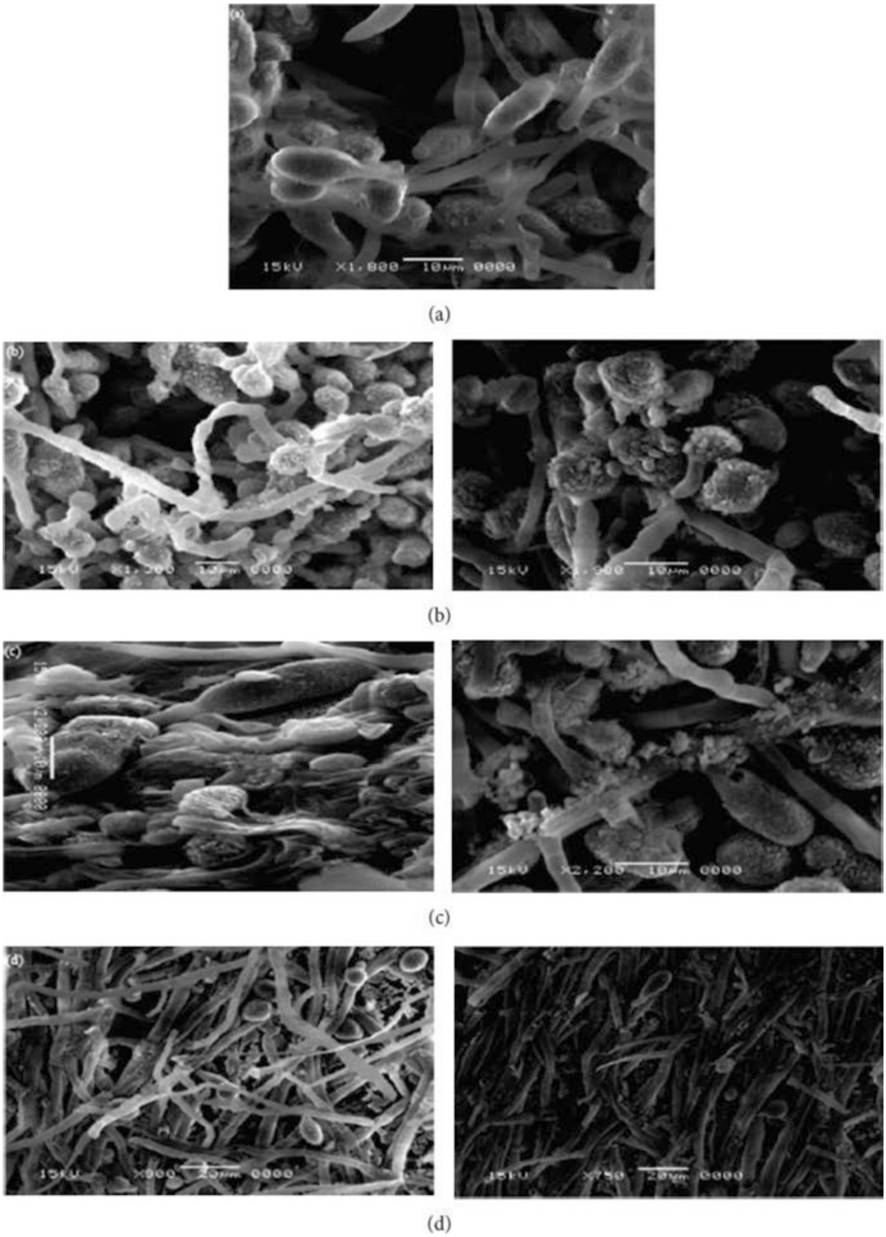
13.2.3.2 Silver (Ag)

Silver (Ag) NPs have played an essential role in the field of biomedicine chemical sensing including imaging utilization. Ag NPs are produced using different methods, electrochemical, chemical, laser ablations photochemical, and others (Rizzello and Pompa 2014). Although bulk Ag is regarded "safe," Ag NPs need to be tested for biocompatibility and environmental impact if they are to be manufactured for in vivo utilization on a large scale (Wagner et al. 1975; Jasim et al. 2017; Belava et al. 2017). Moreover, exposure data had shown Ag NPs to be widespread in the environment, at low but enhancing concentrations, with estimation of up to 0.1 and 2.9 mg L^{-1} at the surface water and sludge (Ferguson and Hogstrand 1998; Lee et al. 2005; Wood et al. 1996). Thus, some research demonstrated that the biological effect of dissolved Ag+ ions might be seen at concentrations of up to 1000 times higher than that for the Ag NPs (Lee et al. 2005). Also, some results from the research documented that the toxic effect of Ag NPs is minor at exposures as low as 5 mg L^{-1}, with higher inhibitions of growth (Vishwakarma et al. 2017).

It is obvious that Ag NPs within the environment pose a potential hazard to greater plants, and thus, the function of ecosystems (Bianchini and Wood 2003; Lee et al. 2005). Ag NPs illustrate different effects on root, shoot growth, and seed germinations at concentrations of 6000 μg mL^{-1}, 3000 μg mL^{-1}, and 4500 µg mL^{-1} on species of Mung bean (*Vigna radiata*), Chinese cabbage (*Brassica campestris*), and rice (*Oryza sativa*), respectively (Justin and Armstrong 1991; Nguyen et al. 2003; Mao et al. 2004). Furthermore, Ag NPs with sizes of about 40 nm have the potential to cause toxic effects in *Cucurbita pepo* and *Chlamydomonas reinhardtii* algae. In the case of Cucurbita pepo, Ag NPs induced 4.4–10 times more alleviation in transpiration rates and biomass, rather than bulk sizes (Ouda 2014; Cheng et al. 2011). Meanwhile, the limits of uptake and the distribution of Ag NPs have been studied for *Medicago sativa* and *Brassica juncea* species (Ouda 2014; Kumari et al. 2009; Saxena et al. 2010) (Fig. 13.4). Meanwhile, research has been done on the limits of distribution and the uptake of Ag NPs for *Brassica juncea* and *Medicago sativa* species.

Diverse groups have tested the cellular uptake and cytotoxicity of Ag NPs in systems of plant. Research on the root development and the seed germination of zucchini plants in hydroponic solution modified with Ag NPs presented no negative effects, whereas alleviations in plant transpiration and biomass were detected on prolonging the plants' growth in the existence of Ag NPs. The cytotoxic and genotoxic effects of Ag NPs have been reported on the onion root tips. In this case, the results showed that the use of Ag NPs caused cell disintegration and impaired the stages of cell division (Yin et al. 2012; Cheng et al. 2011). There are some notes on greater toxic impacts in the *Chlamydomonas reinhardtii* algae exposed to Ag NPs as $AgNO_3$, at the particle size of about 40 nm (Cheng et al. 2011).

There are some researches concentrated on impact of Ag NPs on aquatic plant (Inokuchi et al. 1997). The studies noted on utilization of *Lemna minor L. clone St* to study the phytotoxicity of Ag NPs. The results illustrated that the inhibition of plant growth was apparent after exposure to a wide speared range of Ag NPs (20–



(a)

(b)

(c)

(d)

Fig. 13.4 Antifungal impact of Ag NPs on culture filtrate and cell. SEM images of hyphae of *Alternaria alternata* treated with silver, copper, or copper/silver NPs. Fungal hyphae grown on potato dextrose agar plates as (**a**) control or supplemented with 15 mg L^{-1}, (**b**) Ag, (**c**) Cu, or (**d**) Ag/Cu nanoparticle solution, respectively, images were taken at 7 days after the incubation period (Ouda 2014)

100 nm), even at low concentrations (5 mg L^{-1}) (Unrine et al. 2012). The impacts of Ag NPs have also been assessed in many different studies involving plant mediums (Lee et al. 2012). This research focused on soil nematodes, soil microbial community, and other associated concerns. It has been proved that Ag NPs with sizes of up to 29 nm employed visible alleviation effects on the germination of lettuce seeds and cucumber, but no toxic impact has been detected and noted on the alleviation germination of ryegrass and barley exposed to Ag NPs.

Ag NPs with sizes less than 100 nm have also displayed to alleviate the biomass and transpiration of pumpkin (*Cucurbita pepo*) (Ratte 1999). It noted enhanced Ag NPs content in the common grass *Lolium multiflorum*, with enhancing concentration of Ag NPs. Additionally, the cytological impacts of onion (*Allium cepa*) have been noted to include chromatin bridge, stickiness, disturbed metaphase, and other impacts. The majority of nano-toxicological studies illustrated on plants thus far have used alternative methods rather than soil media. Most of these studies have been conducted in an aqueous media, such as basal medium, distillation water, or Hoagland medium (Slade and Pegg 1993). Few studies proved the toxicity impact of Ag NPs on seed germination, translocation, and plant uptake of NPs in soil (Roh et al. 2009). Furthermore, the toxicity and bioavailability of Ag NPs to species *Polyboroides radiatus* and *Sorghum bicolor* were calculated in both agar and soil medium (Kumari et al. 2009)

Polyboroides radiatus and *Sorghum bicolor* in agar media presented Ag NPs' concentration dependent-growth inhibition and the EC50s values of *Polyboroides radiatus* and *Sorghum bicolor* measured to be 13 and 26 mg L^{-1}, respectively (Dimkpa et al. 2013). *Polyboroides radiatus* were not influenced via the hindrance within the examined concentration in the soil media. *S. bicolor* demonstrated a slightly alleviated growth rate (Lee et al. 2012). Bioavailability and impact of Ag-ions dissolved from Ag NPs are reported to be less in soil than in agar. The results of these studies confirmed that bioaccumulation, phytotoxicity, and dissolution of Ag NPs are obviously affected by the exposure medium (Dimkpa et al. 2013).

All such researches throw light on the need for a more genotoxic and cytotoxic assessment by considering the features of Ag NPs, uptake, distribution, and translocation in diverse plant tissues.

13.2.3.3 Cadmium (Cd)

The short-term impacts of cadmium (Cd) NPs for the root growth of cucumber, tomato, lettuce, and carrot species were tested, using standard toxicity examining (Jiang et al. 2003). The results demonstrated that the growths of seedling were inversely associated to the exposure concentration of Cd, and among the analyzed plants, the sensitive endpoint be visible in order of tomato, carrot, lettuce, and cucumbers (Kashem and Kawai 2007). The growth of root has not been meaningfully inhibited by the existence of Cd NMs, except for tomatoes, but unusually promoted by specific Cd NMs (Clarke and Brennan 1989). Microscopic images demonstrated the roots of analyzed plants exposed to Cd displaying an alleviation in the root diameter and wilt and the decomposition of the root epidermis; the clutter root surface displayed obvious stress in Cd solution (Groppa et al. 2008). After the adding of Cd NPs, many root hair and a lack of decomposition on the surface soft of the root system were detected, and Cd NPs crystals were also observed on the plants' root surface (Cho and Seo 2005).

13.2.3.4 Titanium Oxide (TiO_2)

Although titanium oxide NPs (TiO_2) are extensively used in daily life products, the study of their uptake and translocation in the plant is limited, especially on food crops (Seeger et al. 2009; Kurepa et al. 2010). Because of small size of TiO_2 NPs (<5 nm), these tend to form a covalent bond with most of the nonconjugate natural organic matter, translocate, and follow the tissue and specific distribution of cell (Song et al. 2013). The general toxic impacts of TiO_2 NPs are found in the algal species, for instance, *Desmodesmus subspicatus* (Hund-Rinke and Simon 2006). Moreover, TiO_2 NPs generate reactive oxygen species on interaction with ultraviolet radiation or organisms (Wang et al. 2011). For instance, with the existence of TiO_2, the root of *A. thaliana* releases *mucilage* and procedures a pectin hydrogel capsule neighboring the root (Elghniji et al. 2012). TiO_2 NPs display that an enhancement in nitrate reeducates in soybean (*Glycine max*), increases the capability to absorb/use water, and stimulates the antioxidant system.

For instance, TiO_2 NPs treated seeds produced plants that had 73% more dry weight, and 45% increase in chlorophyll, a formation compared to the control over the germination period of 30 days (Qi et al. 2013). The development rate of spinach seeds, on the contrary, is proportional to the size of the materials, showing that the smaller the NMs, the better the germination. Some researches show that the TiO_2 NPs might have raised the absorption of inorganic nutrients, enhanced the decomposition of organic substances, and caused quenching by oxygen free radicals formed during the photosynthetic process, consequently improving the photosynthetic rate (Zheng et al. 2005). To enhance seed germination rate, the penetration of NMs into the seed is crucial (Han et al. 2010; Gao et al. 2008) (Fig. 13.5).

Meanwhile, TiO_2, in the anatase phase, rises plant growth in spinach by modifying nitrogen metabolism that promotes the adsorption of nitrate (Wu et al. 2012). The same research illustrated the negative impacts of TiO_2 NPs upon the seed germination percentage and the number of roots for the species *Oryza sativa L.* This, in turn, increases the conversion of inorganic nitrogen into organic nitrogen, so enhancing the fresh and dry weight (Foltête et al. 2011).

Utilizing TiO_2 NPs at 60 mg L^{-1} increased sage and seed germination percentages (Feizi et al. 2013). Exposure of sage seeds to 60 mg L^{-1} TiO_2 NPs achieved the lowest mean germination time, but higher concentrations did not enhance the mean germination time (Feizi et al. 2013).

For spinach seeds, TiO_2 NPs helped to water absorption, and thus enhanced seed germination (Zheng et al. 2005). Thus, some studies declared that altered TiO_2 NPs

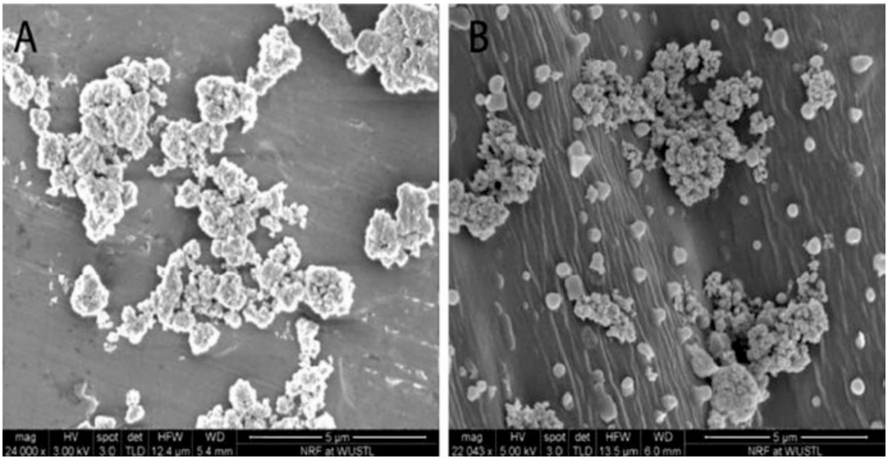


Fig. 13.5 SEM images for NPs/lettuce seeds. In the aqueous phase, the SEM image shows that metal oxide NPs (**a**) (TiO_2 NPs 1000 mg L^{-1}) and (CuO NPs 1000 mg L^{-1}) were adsorbed on (**b**) the seed surface (Wu et al. 2012)

were tested in the liquid phase on the plant model *Vicia faba*, which was exposed to three nominal concentrations: 5, 25, and 50 mg commercial sunscreen TiO_2 NPs per liter for 48 h. Plant growth, photosystem II maximum quantum yield, genotoxicity by micronucleus examination, and phytochelatins levels illustrated a lack of change compared to the control samples. TiO_2 NPs seem not to exert deleterious effects on our plant model in 48 h, but detected important clogging onto the roots (Xie et al. 2011).

It is shown that a blend of nanosized TiO_2 could improve the nitrate reductase enzyme in soybean (*Glycine max*), enhance its abilities of absorbing and using fertilizer and water, encourage its antioxidant system, and actually hasten its germination and growth (Molina-Barahona et al. 2005). In addition, it is stated that the positive effects of TiO_2 could be due to antimicrobial properties of ENMs, which can improve the stability and strength of plants to stress. Therefore, the acute toxic effects of TiO_2 NPs are considered low, with the effects not following a clear dose impact relationship. This is perhaps due to particle agglomeration and subsequent sedimentation. Genomic DNA quantification was observed in the root tips of cucumber after 7 days and displayed that plants treated with 2000–4000 mg L^{-1} of TiO_2 NPs alleviated the genomic DNA compared to the control sample (Elghniji et al. 2012). The toxic effect of TiO_2 NPs is possibly not attributed by the released Ti^{2+} ions from particles that are tentatively proved by the limited dissolution of Ti from a TiO_2 sample (Qiu et al. 2013).

13.2.3.5 Aluminum (Al)

Al is not necessary for crop growth and expansion; but, Al toxicity is primarily caused via Al^{3+} which is a high limiting factor for crop growth in acidic soils (Von Uexküll and Mutert 1995). Al ions are very toxic to plants at elevated level concentrations (Kochian et al. 2004).

Toxic levels of Al prevent the growth and decrease the efficiency of Al-sensitive crops with disrupting different cellular processes and components through binding with phosphate, sulfate, and carbonyl functional groups (Valle et al. 2009).

Physiological studies imply that plants utilize two principal techniques to resist Al toxicity: obstruction of Al^{3+} uptake and detoxifying cellular Al by the formation of inoffensive complexes with organic ligands, which are then separated to particular organelles (Ma and Furukawa 2003). Comparative proteomic analyze and bioinformatic strategies are impressive tools for manifesting the molecular mechanisms underlying replies to abiotic stress (Xu et al. 2010). Soybean is susceptible to Al toxicity (Xu et al. 2006). Comparative proteomic analyze has manifested that Al induces tolerance-related proteins in the tolerant cultivar; while, proteins relevant to stress responses are raised in the susceptible cultivar (Duressa et al. 2011).

In the Al-tolerant soybean cultivar, the raise in ROS scavenging depends on the enhanced plenty of proteins preoccupied in sulfur metabolism. Furthermore, the levels of ABC transporter ATP-binding proteins facilitate in transmitting Al far from the roots. In response to Al toxicity, the cysteine synthase and glutathione reductase played main role in the soybean conformity to heavy metal stress (Duressa et al. 2010). Glutathione-S-transferase was enhanced under the Al stress in soybean (Duressa et al. 2011). The antioxidation and detoxification enzymes played a main role in Al tolerance in rice, soybean, and tomato (Zhen et al. 2007). Rice is the most Al-tolerant species (Foy 1988); but, exposure of rice to Al causes intense efficiency decrements (Fageria and Carvalho 1982). Comparative proteomic studies considering mechanisms of Al tolerance in rice manifested that the relative plenty of vacuolar H+-ATPase was enhanced in Al-tolerant rice cultivars compared to Al-sensitive cultivars, while structural proteins were diminished in both cultivars (Wang et al. 2013).

Furthermore, Al toxicity in rice caused enhancement in antioxidative, carbohydrate, and nucleotide anabolism-related proteins in the resistant cultivar, whereas a number of pathogenesis and carbohydrate catabolism-related proteins were enhanced in redundancy in the sensitive cultivar. Another study indicated that activation of the glycolysis/gluconeogenesis shunt becomes clear to be a quick and impressive way to equilibrium the levels of accessible energy to barricade an intracellular energy deficiency resulting from the increased cellular levels of Al. In wheat, exposure to Al enhanced proteins containing S-adenosylmethionine synthase, oxalate oxidase, malate dehydrogenase, and cysteine synthase (Oh et al. 2014). In barley, a comparative proteomic study manifested that proteins preoccupied in energy, cell growth, protein synthesis, protein destination/storage, transmit, signal transduction, and disease/defense were enhanced in the tolerant cultivar in reply to Al toxicity (Dai et al. 2013). The recognized proteins were related with Al tolerance and indicated that Tibetan wild barley is a new genetic resource. In Arabidopsis thaliana, the proteins depend on the tricarboxylic acid cycle, glycolysis, reactive oxygen quenching, detoxification, and signal transduction pathways that played role in mediating plant response toward Al stress (Karuppanapandian et al. 2012). Comprehending the mechanism of action of Al at the molecular level is significant for the expansion of stress-tolerant crop.

Also, phytotoxicity of uncoated and phenanthrene-coated alumina (Al_2O_3) NPs displayed that uncoated Al_2O_3 NPs at 2 mg L^{-1} concentrations inhibited the root elongation of corn, cabbage, carrot, soybean, and cucumber [224–226] (Kollmeier et al. 2000). It is noted that the toxic effect is possibly not nanospecified but is because of the dissolution of Al_2O_3 NPs. The effects of submicron Al_2O_3 particles were examined to evaluate the chemical material that might be toxic against the growth of seedling roots. Therefore, particle surface features play an acute role in the phytotoxicity of Al_2O_3 NPs (Tian et al. 2007). Research has supported the fact that the existence of Al_2O_3 can stunt root growth in cucumber, corn, carrot, cabbage, and soybean, although preliminary findings suggest that very high concentrations of such particles are essential to induce harm (Kinraide et al. 1992). The existence of Al_2O_3 NPs did not have a harmful effect on the expansion of *Lolium perenne* and *Phaseolus vulgaris* in the tested concentration range (Rangel et al. 2007).

13.2.3.6 Fe_3O_4

The extra amount of iron oxide (Fe_3O_4) as a magnetic NMs resulted in some negative effect against plant growth. For instance, "Chlorophyll a" levels were amplified at low Fe_3O_4 NPs fluid concentrations, while at higher concentrations it inhibited it (Zhu et al. 2008). A small repressing effect was found on the growth of the plantlets that led to brown spots on leaves at higher volume fractions of Fe_3O_4 NPs fluids (Kraemer 2004).

The extra Fe_3O_4 NPs treatment produced some oxidative stress, which in turn affected photosynthesis and resulted in alleviated rates of metabolic process. The oxidative impact was induced by the Fe_3O_4 fluid concentration in the tissues of living plants (Raven 1988).

In order to overcome such limitations, the coating provides Fe_3O_4 NPs with a large adsorption surface and biocompatible characteristics (Chen et al. 1980).

For instance, in the case of pumpkin (*Cucurbita pepo*), the extent of carbon coated-Fe_3O_4 at certain concentrations within some cells and in extracellular space reduces the problems for plant tissues and the amount of chemicals released into the environment (Katsoyiannis and Zouboulis 2002). Moreover, the effect of tetramethylammonium hydroxide coated Fe_3O_4 NPs on the development of corn (maize) found that the chlorophyll level enhanced at low Fe_3O_4 NPs fluid, while at higher concentrations it was inhibited. A slight inhibitory effect was detected in the growth of the plantlets, which in turn resulted in brown spots on leaves at greater volume fractions of the magnetic fluid (Liu et al. 2006). The oxidative effect was induced by the Fe_3O_4 NPs fluid toward the living plant tissue (Ma et al. 2010). The extra Fe_3O_4

NPs generated some oxidative effect, affected photosynthesis, and resulted in the decrease of metabolic process rates.

13.2.3.7 Zinc (Zn)

Zn NPs are a vital micronutrient for various cellular processes and are required for both animal and plant growth (D'Alessandro et al. 2013). In particular, Zn NPs serve as a cofactor for enzyme reactions involved in carbohydrate and energy metabolism, energy transfer, protein synthesis, protein folding, and gene expression regulation (Maret 2013). The significance of Zn NPs in cellular functions is highlighted by the finding that 10% of protein binding sites contain Zn (Andreini et al. 2006). However, at high level concentrations, Zn is toxic for plants. The main response to Zn toxicity is expansion inhibition and is determined by alleviated root growth, impaired cell division/elongation enhanced, and enhanced root thickening (Barceló and Poschenrieder 1990). Comparative researches on Zn-sensitive A. thaliana and tolerant *A. halleri* revealed that toxicity leads to the changed expression of genes involved in metal binding and homeostasis. The proteomic analysis of the leaves and roots of *A. thaliana* indicated that protein profiles were significantly changed in response to Zn NPs toxicity. In the leaves, the declined proteins were predominantly associated to one-carbon metabolism, such as glycine decarboxylase P protein, serine hydroxymethyltransferase, and methionine synthase (Weber et al. 2004).

In the roots, Zn toxicity reduced V-ATPase activity results in growth defects (Fukao et al. 2011). In the shoots of *A. thaliana*, Zn mostly affected the levels of proteins associated to ribosomes, photosynthesis, and transporter (Zargar et al. 2015). Enhanced Zn NPs concentrations induce metabolic reprogramming in *Beta vulgaris* (Van Assche and Clijsters 1990). In response to Zn treatment, a shutdown of metabolism because of alleviation aerobic respiration, lipid peroxidation, and cell death was detected in *B. vulgaris* (Gutierrez-Carbonell et al. 2013). In the *Populus* × *euramericana* roots (clone 10214), Zn NPs modulate the abundance of proteins associated to the antioxidant system, carbohydrate/energy, and amino acid metabolism. In addition, coordination between cell death and proliferation was identified and was speculated to be an attempt by the plant to alleviate the harm caused by Zn stress (Romeo et al. 2014). *Noccaea caerulescens* is a part of the Brassica family and a great model system for checking the effects of Zn NPs hyperaggregation (Milner and Kochian 2008). In *N. caerulescens*, several glutathione S-transferases are enhanced in the epidermal cells and function to alleviate oxidative stress caused by extra Zn NPs (Schneider et al. 2013). Furthermore, the concentrations of citrate and malate were also enhanced, demonstrating the important role of these metabolic intermediates in the complexation of epidermal Zn NPs.

13.2.3.8 Copper (Cu)

Cu is a vital micronutrient for plant development and growth, as it is mostly connected with proteins involved in electron transfer and redox reactions, and is also as a cofactor in oxidative stress responses, mitochondrial respiration, ethylene transduction signals, and photosynthesis. Despite its significance for enzymatic function, Cu is toxic to plants at high concentrations because it is able of catalyzing Fenton and Haber–Weiss reactions, leading to the production of ROS that have the potential to harm cellular constituents (Bona et al. 2007).

Recently, Adrees et al. (2015) studied the effects of extra Cu on the growth and physiology of crops. Exposure to high concentrations of Cu caused growth inhibition, oxidative damage, and antioxidant responses in cucumber, sunflower, maize, rice, and wheat. Cu treatment also changes enzyme activities, chlorophyll content, mineral nutrition enzyme activities, and leaf photosynthetic; leading to alleviation growth and yield. In the *Elsholtzia splendens*, a tolerant species, cellular metabolism redox homeostasis, and cellular metabolism pathways are redirected in cells of root as a significant survival response under Cu stress. It has also been illustrated that Cu NPs effect on antioxidant defense/signaling pathways, protein, and energy synthesis in *E. splendens* (Liu et al. 2014). In roots of rice, Cu stress effects on the proteins involved in antioxidant defense, carbohydrate metabolism, nucleic acid metabolism, protein folding/stabilization, protein transport, and cell wall synthesis (Chen et al. 2015a).

A comparative proteomic study between Cu-tolerant and Cu-sensitive rice cultivars was conducted to better understand the molecular mechanisms involved in plants responses to Cu stress (Chen et al. 2015a). The identified Cu-responsive proteins were involved in antioxidant defense, detoxification, pathogenesis, and regulation of gene transcription. Karmous et al. (2014) examined the role of the ubiquitin-proteasome pathway and peptidases in plant responses to Cu stress in bean cotyledons. Cu induced the inactivation of the ubiquitin-proteasome pathway and leucine/proline aminopeptidases, and/or limitation of the role in modulating the removal of regulatory and oxidative damaged proteins. However, the activities of trypsin and chymotrypsin were increased due to Cu stress and the activities of their inhibitor were decreased, indicating that these endoproteases play a role in protecting cells against Cu toxicity.

In *Agrostis capillaris*, exposure to Cu increases the abundance of Cu/Zn superoxide dismutase, leading to the increased detoxification of superoxides, and also associated with changes in the cytoskeleton and ethylene metabolism (Hego et al. 2014). The resulting increase in the levels of L-methionine and S-adenosylmethionine facilitates the production of nicotianamine, which binds to Cu and is required for the synthesis of metallothioneins and glutathione. In rice, Cu exposure regulates the activities of metallothionein-like, membrane-associated, and pathogenesis-related proteins.

13.2.3.9 Other Metal

In addition to the above-described heavy metals, the effects of several other trace metals on plants have been tested in diverse species. In a recent proteomic research of rice seedlings, the effects of Cr toxicity were examined (Zeng et al. 2014). The duration of Cr exposure affects the antioxidant enzymes, such as ferredoxin-NADP reductase, glyoxalase I, NADP-isocitrate dehydrogenase, and glutamine synthetase. Furthermore, the Cr NPs were found to be immobilized into cell walls and have alleviated translocation, and also activated the antioxidant defense system. In maize, Fe exposure adjusts the proteins involved in oxidative stress, development regulation, and cell wall stability and synthesis (Hopff et al. 2013). Hg is also of excellent concern because of its deleterious impacts on the human health and environment. In Suaeda salsa, Hg exposure controls proteins associated to immunosuppression, signaling pathways, stress responses, photosynthesis, energy metabolism, metabolic processes, and protein fate (Liu et al. 2013). In roots of rice, Hg controlled numerous proteins are involved in stress responses, metabolism, signal transduction, redox homeostasis, and regulation (Wang et al. 2012). Between the enhanced proteins, translationally adjusted tumor protein was assessed for its important role in Hg tolerance of rice, providing evidence for its role in decreasing Hg harm. The findings from these researches suggest that many processes in plants are affected by metal toxicity; studying that the effects of metal toxicity in combination may be helpful for understanding the molecular mechanisms underlying plant responses to metal toxicity.

13.3 Effect of ENMs on the Toxicity of Environmental Pollutants

Joint toxicities of pollutants and ENMs can be classified as synergistic, antagonistic, multiple effects. Inferior plant, aquatic life, and mammalian cells are mostly used as model organisms for studies on the joint toxicity. Generic research on the influence of ENMs on the toxicity of pollutants is summarized briefly and organized by NMs classification (Tables 13.1 and 13.2).

13.3.1 Carbon Nanomaterials

CNTs have an extremely high affinity for environmental pollutants (Yang and Xing 2010). Four different kinds of CNTs have been shown to considerably increase the critical toxicity of Cd to *Daphnia magna* (*D. magna*), this enrichment of Cd toxicity was observed to enhance in the following order: single-walled CNTs (SWCNTs) > multiwalled CNTs (MWCNTs) > hydroxylated MWCNTs

Table 13.1 Carbon nanomaterials affecting the toxicity of environmental pollutants

Carbon nanomaterials/ concentrations	Pollutants/ concentrations	Organisms/cells	Exposure time	Joint toxicity	Reference
Synergistic effects HNO_3-MWCNT1, 2 μg mL^{-1}	Pb 0.1, 0.5, 2 μg mL^{-1}	Nile tilapia (*Oreochromis niloticus*)	96 h	HNO_3-MWCNTs increased the histopathological alterations elicited by Pb	Barbieri et al. (2016)
HNO_3-MWCNTs0.1–3 μg mL^{-1}	Pb 0–2.12 μg mL^{-1}	Nile tilapia (*Oreochromis niloticus*)	24, 48, 72, 96 h	HNO_3-MWCNTs increased the lethality of Pb	Martinez et al. (2013)
OH-MWCNTs 0.1–5 μg mL^{-1}	As 0–2.12 μg mL^{-1}0.6–16.7 μg mL^{-1}	*D. magna*	48 h	OH-MWCNTs increased the lethality of As	Wang et al. (2016a)
GO 5 μg mL^{-1}	As (2.5 μM) and paraquat (100 μM)	Human hepatoma cell line HepG	24 h	GO inhibited the function of efflux transporter	Liu et al. (2016b)
Antagonistic effects SWNTs 0.3, 3 mg g^{-1}	Pyrene37.5 μg g^{-1}	Earthworms (*Eisenia foetida*)	0–28 d	SWCNTs alleviated the bioaccumulation of pyrene	Petersen et al. (2009)
GO 2–20 μg mL^{-1}	PCB 5275 μM	Human–hamster hybrid (AL) cells	24 h	GO alleviated the cytotoxicity and mutagenicity of PCB	Liu et al. (2016c)
Multiple effects SWNTs 0.5–6.1 μg mL^{-1}	Phe3.1–800 μg L^{-1}	Algae *Pseudokirchneriella subcapitata*	0–72	SWCNTs had different effects on the lethality of Phe	Glomstad et al. (2016)

Table 13.2 Metal and metal oxide NPs affecting the toxicity of environmental pollutants

Metal nanomaterials/ concentrations	Pollutants/ concentrations	Organisms/cells	Exposure time	Joint toxicity	Reference
Synergistic effects *n*TiO 2 μg mL^{-1}	Cd 66–200 μg L^{-1}	*D. magna*	24 h, 48 h	*n*TiO_2 increased the lethality of Cd	Li et al. (2017)
nTiO_2 0.1 μg mL^{-1}	PCP 0–30 μg L^{-1}	Zebrafish (Danio rerio) embryos or larvae	6 d postfertilization	*n*TiO_2 increased the oxidative stress of PCP	Fang et al. (2015)
nTiO_2 10 μg mL^{-1}	As (III) 0.5, 1, 2 μg mL^{-1}	Human-hamster hybrid (AL) cells	24 h	*n*TiO_2 elevated the genotoxicity of As (III)	Wang et al. (2017)
Antagonistic effects *n*TiO 5 μg mL^{-1}	Cu 0.06, 0.07 μg mL^{-1}	*Microcystis aeruginosa*	0–72 h	*n*TiO_2 reduced Cu-induced oxidative stress to cellular membrane	Chen et al. (2015b)
*n*TiO 1–1000 μg mL^{-1}	As(V) 0–120 μg mL^{-1}	Nauplii *(Artemia salina)*	48 h	*n*TiO_2 decreased the lethality of As(V)	Yan et al. (2017)
Multiple effects *n*TiO_2 0–30 μg mL^{-1}	Atrazine 0–0.4 μg mL^{-1}	Algae (*Chlorella pyrenoidosa)*	96 h	*n*TiO_2 exhibit distinct effects on the toxicity of organic pollutants	Zhang et al. (2017)
	PCB 77 0–0.01 μg mL^{-1}				
	PeCB 0–0.66 μg mL^{-1})				

(OH-MWCNTs) > carboxylated MWCNTs (COOH-MWCNTs) (Wang et al. 2016b).

For instance, OH-MWCNTs were noted to enhance the toxicity of *D. magna*, with LC50[2] values alleviating by 14.1% for As (III) and 14.9% for As(V) in the existence of OH-MWCNTs after 48 h of exposure (Wang et al. 2016a). Also, nitric acid treated MWCNTs (HNO_3-MWCNTs) increased the toxicity of Pb to Nile tilapia: after 24, 48, 72, and 96 h of incubation, the respective LC50 values alleviated from 1.65, 1.32, 1.10, and 0.99 mg L^{-1} for Pb only to 0.32, 0.25, 0.20, and 0.18 mg L^{-1} for Pb–CNTs mixtures (Martinez et al. 2013). The excess of HNO_3-MWCNTs also enhanced the pathological changes regarding epithelial structure, displacement of epithelial cells, hyperplasia, and the structure in the secondary lamella in the Nile tilapia (Barbieri et al. 2016). Apart from synergistic effects, carbon NMs may also alleviate the toxicity of environmental pollutants. SWCNTs have been displayed to increase the removal rate of pyrene, and thereby, alleviate its bioaggregation in earthworms (Petersen et al. 2009). Pretreatment of 20 μg mL^{-1} GO has been noted to enhance the livability of cells exposed to PCB[3] 52 from 67.7% to 86.3% (Liu et al. 2016c). Multiple effects of joint toxicity occur when ENMs interact with various pollutants, when diverse ENMs with different physicochemical properties interact with similar pollutant, or when exposure conditions change (e.g., time and concentration).

The existence of SWCNTs reduced the toxicity of Phe with values of 50% development inhibition extremely enhanced from 438.3 for Phe only to 528.4 for a mix of Phe and SWCNTs; however, negligible diversity exists between MWCNTs and Phe (Glomstad et al. 2016). BC[4] alleviated the toxicity of TBT[5] to *D. magna* at pH 6 and 8, while the toxicity of DBT was only negligibly affected via the addition of BC (Fang et al. 2011).

13.3.2 Metal and Metal Oxide Nanoparticles

Examples of metal and metal oxide NPs, such as ZnO, AgNPs, and TiO_2, have been thoroughly studied and intensively utilized mainly in personal care and medical products, which naturally enhanced the possibility for them to release into environment and further interact with pollutants.

TiO_2 enhanced the toxicity of Cd to *D. magna*, with the EC50 of Cd reducing by 48% after a 48 h exposure with $n\mathrm{TiO}_2$ (Li et al. 2017).

TiO_2 increased the concentration of ROS[6] induced by As(III) and alleviated the disturbed metabolism and total antioxidant capacity of As (III) in the estuarine polychaete *Laeonereis acuta* (Nunes et al. 2017).

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[2] Median lethal concentration.

[3] Polychlorinated biphenyls 52.

[4] Black carbon.

[5] Tributyltin.

[6] Reactive oxygen species.

Moreover, TiO_2 enhanced the negative effects of PCP[7] by increasing the oxidative stress such as DNA damage and lipid peroxidation in zebrafish larvae (Fang et al. 2015). Also, TiO_2 was illustrated to enhance the genotoxicity of As(III) in human–hamster hybrid (AL) cells (Wang et al. 2017).

AuNPs[8] were noted to enhance the bioaggregation and toxicity of As_2O_3 by facilitating its uptake as well as inhibiting its removal (Guo et al. 2009). In addition to synergistic effects, TiO_2 was illustrated to relieve the lethality of Cu in *D. magna* (Rosenfeldt et al. 2015) and *Microcystis aeruginosa* (Chen et al. 2015b), decrease Cd-induced toxicity in green algae (Yang et al. 2012) and *D. magna* (Tan et al. 2016). Multiple effects exist between metal/metal oxide NPs and pollutants. TiO_2 performed absolutely distinct joint toxicity with four kinds of organochlorine contaminants toward algae (*chlorella pyrenoidosa*). A synergistic toxicity was found for $n\mathrm{TiO}_2$ and atrazine, antagonistic interactions happened between TiO_2 in combination with HCB,[9] or PCB 77,[10] whereas additive responses were reported for the combination of $n\mathrm{TiO}_2$ and PeCB[11] (Zhang et al. 2017). As a generally utilized sort of metal NPs, AgNPs were proved to facilitate the bioaccumulation of As(V), Cu, and Cd but only increase the acute toxicity of Cd to *D. magna* (Kim et al. 2016).

In general, due to the diverse properties of ENMs, receptor species, pollutants, and environmental conditions in the exposure scenarios, intricate interactions happen between ENMs and environmental pollutants, thus leading to opposite results when studying the joint toxicity of ENMs and environmental pollutant. Thus, in depth exploration on the biological and physicochemical mechanisms involved in the joint toxicity is necessary.

13.4 Conclusions

In summary, the presence of nanomaterial in environment such as (soil and water) can have significant toxicity effects on plants and the environment. Since the utilization of NMs is predicted to enhance, it is important that we continue to study the fate and toxicity of these NMs to plants and environments.

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[7] Pentachlorophenol.

[8] Gold nanoparticles.

[9] Hexachlorobenzene.

[10] 3,3′,4,4′-tetrachlorobiphenyl.

[11] Pentachlorobenzene.

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Chapter 14
Nanocellulose as Polymer Composite Reinforcement Material

Benu George, Nidhi Lal, and T. V. Suchithra

Contents

14.1 Introduction

There is an increasing demand for bio-based materials which are degradable and free from causing environment crisis caused by non-renewable and nondegradable materials. Thus researchers are inclined to develop materials that can be durable and cost-effective to reduce.

the destruction caused by industrial and technological development (Abdul Khalil et al. 2016). Cellulose is a perfect candidate for a biomaterial which is even abundantly available (De Moura et al. 2011). Through plant photosynthesis, cellulosic fibers are plant derived embedded in hemicellulose and lignin (Karimi

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B. George · N. Lal · T. V. Suchithra (✉)
School of Biotechnology, National Institute of Technology, Calicut, Kerala, India
e-mail: drsuchithratv@nitc.ac.in

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et al. 2014). The top-down approach is used to extract cellulose and used to reinforce polymers for multifunctional architectures (Karimi et al. 2014). They comprise of cellulosic material within one nanometer range whereas the elementary fibrils are made up of cellulose molecule is about 5 nm (Minelli et al. 2010). Upon the method of preparation nanocellulose is bifurcated into nanofibrillated cellulose (NFC) and cellulose nanocrystals (CNC) (Thiripura Sundari and Ramesh 2012). After complete dissolution of the noncrystalline fractions by chemical hydrolysis, nanocellulose crystal can be extracted from cellulose fibers whereas nano-fibrillated cellulose produced by high pressure and shearing forces of mechanical fibrillation after pre-treatment (Besbes et al. 2011). Polymeric reinforcement property of NFC and CNC as polymeric reinforcement have been extensively introduced, but when compared between both CNF proved to be more desirable due to its load-bearing constituents, greater ability to improve toughness, strength, and stiffness between matrix (Srithep et al. 2013). CNS's have about 65–95% crystalline nature and higher modulus of 138–150 GPa than NFC 70 GPa, theoretical such value of modulus represents a perfect crystal (Lu and Hsieh 2010). NFC provides highly flexible fibrils with better reinforcement property as they easily interconnect and form rigid web-like fibrils networks (Silvério et al. 2013). Irrespective of its advantages, NFCs have some disadvantages in polymer matrix during extrusion compounding, mostly because of its network structure and high aspect ratio. It tends to get coaggregated or actively entangles the long nanofibrils via strong hydrogen bonding (Lee et al. 2011). Furthermore, NFC consist of disordered amorphous segments which pose a threat to the mechanical properties as a filler and even composites by lowering the density (Zimmermann et al. 2010).

Hence, the chemically derived CNC from various cellulosic sources (Fig. 14.1) is of particular interest as it is a superior reinforcement agent in a polymer (Abdul Khalil et al. 2016; Rebouillat and Pla 2013; Jonoobi et al. 2009). Mainly, the wide availability of cellulose sources, potential mitigation of other inorganic reinforcing agent and the biodegradability of cellulose materials feature make it advantageous over other available reinforcement material.

As CNC have been gaining widespread attention as a versatile material with applications like structural reinforcement and as a biomedical material for tissue engineering, drug delivery, tissue repair, as carrier material for immobilization of enzymes or other proteins and as tissue substitutes. The material exhibits an extraordinary physical and chemical properties that make it biocompatible and relatively less toxic. Being of non- petroleum origin, it is also very sustainable as well as renewable. Naturally, occurring cellulose has the primary function of conferring structural integrity, and therefore mechanical strength to plants. It is therefore unsurprising that this property of nanocellulose is harnessed in reinforcing other materials. The underlying reason for this strength is the presence of surface hydroxyl groups, which cause them to self- associate, which in turn also affects their ability to be uniformly dispersed in a polymer matrix (Dufresne 2013).

Most naturally occurring polysaccharides contain both crystalline and amorphous material, from which it is possible to degrade the amorphous regions alone under controlled conditions, leaving the crystalline part undamaged. Nanocellulose obtained through different forms is product of cellulose sourced through plant, ani-

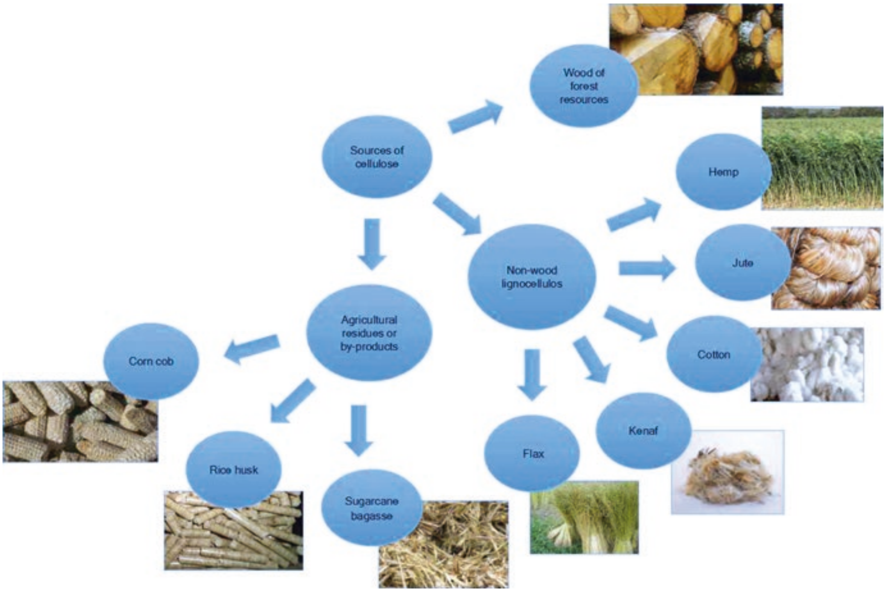

Fig. 14.1 Various potential natural sources of cellulose

mal and bacteria. Thus they are simplified by classifying them in three class (a) cellulose nanocrystals (CNC), also referred as nanocrystalline cellulose, cellulose (nano) whiskers, rod-like cellulose microcrystals; (b) cellulose nanofibrils (CNF), also known as nanofibrillated cellulose (NFC), microfibrillated cellulose (MFC), cellulose nanofibers; and (c) bacterial cellulose (BC), re-framed as microbial cellulose. CNCs and CNFs are obtained from most plant materials, with some common sources being wood, sugarcane, hemp, sugar beet, potato tuber, algae, and cotton. CNCs are primarily produced by acid hydrolysis and heat controlled techniques, while CNFs are produced from cellulosic fibers by three methods: mechanical treatments which include homogenization, grinding, and milling, chemical treatments which include TEMPO oxidation, and combinations of chemical and mechanical treatment methods (Abitbol et al. 2016).

The third type of nanocellulose is bacterial (BC) or microbial cellulose in origin. While the first two classes use a chemically or physically induced deconstructing strategy, bacterial cellulose is synthesized and assembled into its characteristic structure by the organism. Cellulose of microbial origin contains less or no impurities like hemicelluloses, lignin, and pectin and hence does not require intensive purification (Lin and Dufresne 2014). Nevertheless, its production is somewhat limited on a commercial scale compared to CNC and CNF, due to high costs and low yield (Lin and Dufresne 2014). Several novel techniques of nanocellulose extraction have also come into existence during recent times, such as enzyme mediated production, mechanical separation processes like ceramic membrane filtration, sonochemical-assisted hydrolysis and combined mechanical shearing, enzymatic and acid hydrolysis extraction (Lin et al. 2012). The recent focus has been on optimizing the extraction process to become more energy efficient, and as a result, the fibers are first treated physically, chemically, or enzymatically before homogenization (Klemm et al. 2011). Having exceptional physical and chemical properties, nanocellulose could potentially revolutionalize many spheres of science, most importantly biomedical engineering.

This entry focuses on physical properties of nanocellulose which places these materials as a perfect candidate for reinforcement in polymers and its production stages. The present literature also highlights the possible modification which will enhance the properties of nanocrystals for strengthening.

14.1.1 Cellulose Nanocrystals Plant Derived

A plant cell consists of an extra cytoplasmic boundary, a non-homogenous membrane of a complex, layered structure with thin peripheral primary wall and secondary wall. The secondary wall is made up of three distinct layers, out of which the middle layer consists of cellulose fibers which maintain the shape and rigidness of the plant cell (Abdul Khalil et al. 2014). Lignocellulosic natural fibers encompass the middle layer which comprises lignin and hemicelluloses (Kalia et al. 2011). Besides it consist of some other non-structural components like waxes, pectin, inorganic salts and nitrogenous salts also existed in cellulose fibers (Majeed et al. 2013). The cellulose fibers, is surrounded by polysaccharides and glycoproteins like lignin, hemicellulose and pectin (Abdul Khalil et al. 2014). It is an assembly long-chain cellulose microfibrils that form bricks to the middle layer (Kalia et al. 2011). An estimate of 30-100 individual cellulose molecules chain together and form the elementary fibrils at nano-scale of cellulose fibers (Lavoine et al. 2012). The primary units are a repetitive linear syndiotactic polysaccharide, consist of D-glucose and β-D hydroglucopyranose units linked by β-(1 → 4)-glycosidic bonds (Brinchi et al. 2013; Jiang and Hsieh 2013). The structural units are held together by inter and intra hydrogen bonding thus the assembly is known as microfibrils or nano-sized fibrils (Abdul Khalil et al. 2016).

The interchain bonds at equatorial region due to the presence of three hydroxyl (OH) group in each glucopyranose unit of cellulose chains (Kalia et al. 2011). These bonds can be stabilized by specific chemical process that results to highly ordered crystalline rods (Panaitescu et al. 2013; Alemdar and Sain 2008). But due to the absence of hydroxyl group in particular region, cellulose fibre form amorphous cellulose segments which are further apart with lower density in the crystalline structure (Dalmas et al. 2006). Nevertheless, through active acidic treatment, the amorphous region can be hydrolyzed and restructure it to a highly crystalline residue (Floros et al. 2012). Depending on the nature of the plant source, purification, pre-treatment and acid hydrolysis the rod-like crystalline cellulose obtained after acid treatment are known as cellulose nanocrystal of diameter range between 2 and 20 nm its lengths vary by 100 nm (Floros et al. 2012; Siqueira et al. 2010).

14.2 Distinguishable Properties of CNCs for Reinforcement Material

Factors like origin, soil characteristics, climate and age of the plant affect the structural and chemical composition of raw fibers. Thus a knowledge about properties to exploit CNCs to the best would provide a robust reinforcing filler for composite materials (Majeed et al. 2013). CNC has abundant hydroxyl groups, large specific surface area, high aspect ratio, high crystallinity, excellent mechanical properties and high thermal stability, making it a good choice as a reinforcing agent, as explained in Table 14.1.

Table 14.1 Properties of CNCs for reinforcing the purpose (Ng et al. 2015)

Specific characteristic	Features
Surface hydroxyl group abundance	Hydroxyl groups on surface render active site for hydrogen bonding with matrices
	High-stress resistance can be achieved since there is effective stress transfer between filler-matrix
	The interface is rigid filler – matrix which reduce diffusion of the water molecule and thermal properties
	The abundance of hydroxyl groups enable high reactive nature and versatility in chemical modification
	The density of hydroxyl group on surface progressed as untreated fiber < alkali treated fiber < bleached fiber < microfibrils < nanocrystal
Large specific surface area	It is estimated that a particular surface area of CNC is more than 100 $m^2 g^{-1}$
	Bondability, as well as interfacial interaction with a compatible polymer, is amplified by high specific area
	The specific surface area is directly proportional to aspect ratio and a decrease in diameter of CNC
	Contact surface with compatible polymer increased due to the presence of abundant surface
	A more excellent molecular distribution could be archived with an increase in interfital interaction
High aspect ratio	It is a parameter that determines the reinforcing capacity of the nanofiller into a polymeric matrix
	Depending upon CNCs source and preparation conditions, nano element of aspect ratio 30-100 prove to be better reinforcement when compared to nanofillers of having lower aspect ratios.
	Its nano-enabled functional properties, tangling effects and percolation effects CNC of high aspect ratio are considered
	High aspect ratio facilitate an excellent interfacial interaction, even stress distribution, fillers display good flexible properties
	In comparison to nanofiberils which are rod-like particles, nanocrystals provide better material properties

(continued)

Table 14.1 (continued)

Specific characteristic	Features
High crystallinity	A high compact crystalline packing of cellulose chain is attained due to the presence of OH group of the monomer
	The crystalline structure is due to hydrogen bond thus makes it inaccessible to most traditional organic solvent and water
	High impermeable crystalline creates a convoluted path for the diffusion of the penetrable molecule in the polymer (e.g., water, gas, etc.)
	Inducing nucleating effect results in a much prominent hardening effect and could be observed in a crystalline polymer matrix
	Crystal packing enhances the degree of crystallization of polymer, increment of stiff and rigid crystalline structure of the polymer
Excellent mechanical properties	Crystalline region hydrogen bonds play a prominent role in fiber strength, stiffness, and functional strength
	A high elastic modulus a Youngs modulus is observed by reinforced material
	hydrogen bond stabilizes arrangement of cellulose chain in the material
	The mechanical properties of CNCs also depend on their cellulose type as they vary depending upon cellulose source
	Biodegradable and thermoplastic with noncompetitive mechanical properties limitations causing high strength CNCs could eliminate post-processing variation in properties
	Plant oil-based materials have relatively weak mechanical properties, however, by the introduction of CNC these proprieties can be modified easily
High thermal resistance	CNCs are cellulose chains arranged in a highly ordered manner attached by hydrogen bond stabilization thus the compact system impart thermal stability
	Hydrogen bonds in crystalline region interchain favor high-temperature resistance, preventing cellulose from melting
	Incorporation of CNCs in biopolymer (PLA, PHAs, etc.) would prove to a thermal stable reinforced composite
	Inherited by the property to hider heat flow thermal degradation of composite could be delayed

14.3 CNC Production Steps

The nanocrystals production involves various stages, the preparation method is detailed in Table 14.2, and the general procedure has been briefly mapped in Fig. 14.2. These stages are: (a) Separating the crystalline residue. (b) Dissolve the unordered part to washout; the process involves the mechanical size reduction, purification, and acid hydrolysis (Williamson 2015).

Thus, by mechanical treatment CNC is resolved into a stable suspension (Floros et al. 2012). Emphasising on conditions in each stage and its influence on reinforcing the ability of final product Table 14.2 will provide an insight.

Table 14.2 Production of CNC steps (Ng et al. 2015)

Stages	Process	Description	
First stage	Mechanical treatment	Through milled, grinding, cutting, etc. Clean fibers (crude) broken down	
		Powdered to order to obtain uniform size	
		Uniformity in size will offer more convenience in chemical treatment and improve swelling capacity in water	
		Commonly used Wiley mill/ Fritsch Pulverisette mill or grinding machine for chopping, milling and grinding Pulverisette mill or grinding machine	
		Milled fibers are then passed through 55-mesh to 60- mesh sieve	
		More excellent fibers improve contact surface area between chemicals and the active group as well as the rate of reaction	
	Wash treatment	Grounded fibers washed in distilled or deionized water	
		Thus fibers become soft and comfortable to split	
		Washing improves the efficiency of alkali treatment by removal of dirt and increasing the interaction of alkali solution and cellulose fiber	
		The external surface, i.e. fiber cell wall consist of impurities and wax substance which are removed by filtering	
		For ground fibers, before wash treatment, a pretreatment using soxhlet apparatus is favorable	
Second stage	Purification	Alkali treatment	Subjected to a robust base solution which enables to remove alkali soluble substance and expose short length crystallites
			Removes hemicellulose and other impurities covering fiber cell wall
			OH bonds disrupt by ionizing to become alkoxide
			The alkali treatment tends to form a vacancy in a structure which lead to swelling, changes in physical, dimension, morphology, structural and mechanical properties of the fiber
			Voids enable us to wash out wax, natural fats, pectin material along with hydroxyl groups Alkali treatment also ensures removal of hydrophobic obstruction for fiber to bond as well as the wetting issue with the polymer matrix
			Done by two methods alkali solution heating and alkali cooking by autoclave or digester
			Alkali solution heating process composed of mechanical stirring and exposure of high temperature ranged between 70 -90 °C
			Treatment by cooking process or alkaline retting involves a combination of high temperature and pressure
			For active degradation and removal of lignin and hemicellulose fibers treated with alkaline sulfate and acid sulfite chemicals. To boot the delignification process anthraquinone solution is used

(continued)

Table 14.2 (continued)

Stages	Process	Description	
		Bleach treatment	Following to alkali treatment, the residual lignin on fiber is removed by bleach treatment
			The operation involves boiling of fibers with the salt solution under the acidic condition (acetate buffer solution)
			Until white fibers are not archived the process is repeated many times
			White color indicates the relative amount of lignin is removed for further process
			CNC which are subjected to a higher number of bleach treatment is more thermally stable
Third stage	Libration of cellulose nanocrystal	Due to disordered amorphous with imperfect axial orientation, the thermal and mechanical properties are altered for CNC	
		Through acid hydrolysis, CNC can be enhanced for various reinforcements	
		Sulfuric acid treatment enables surface reaction and easy extraction of CNCs in a more stable colloid suspensions which are failed by HCl treatment	
		Further CNCs are subjected to centrifuge after acid treatment, as to extract the desired nano crystals	
		The pellet is subjected to wash bout 3-4 times to ensure complete removal of acid and its impurities	
		The precipitate is also filtered using Whatman 541 filter paper or glass microfiber filter	
		Final stage leads to drying to remove excess of water content in CNC since this water content can interfere during reinforcement process	
		Oven drying, freeze drying, supercritical drying, and spray-drying are the conventional drying methods adopted	

14.4 Characterization of Nanocellulose

The following methods have been widely used for the characterization of nanocellulose obtained by various chemical and physical treatments.

14.4.1 Measurement of Zeta Potential (ξ)

The potential at the electrochemical border between the diffuse layer on the surface of the particle and the stationary counter ions, also called the slip plane, is known as the zeta potential. In other words, zeta potential is the potential between the bulk fluid and the immobilized fluid layer absorbed on the particles present in the

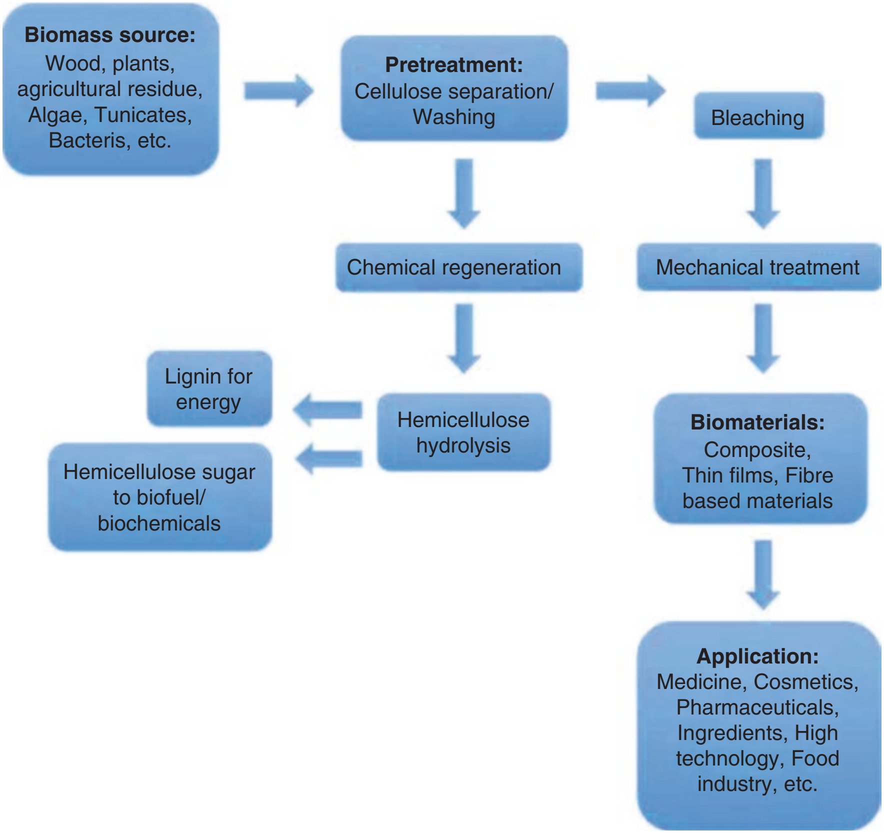

Fig. 14.2 Brief outline of CNC production steps

colloidal dispersion. It is calculated using the following formula (Uetani and Yano 2012):

$$\xi = (U_E \eta) / (\varepsilon \mathrm{f}(\kappa a))$$

Where U_E is the electrophoretic mobility, η is the viscosity, ε is the dielectric constant, and f(κa) is Henry's function, with the value being 1 when $\kappa a >> 1$ and 2/3 when $\kappa a << 1$. Here, κ is the inverse of Debye length and a is the major particle radius.

The electrophoretic mobility U_E is given by the equation:

$$U_E = (\lambda \Delta v) / (2nE \sin(\theta / 2))$$

Where, λ is the wavelength of incident light, $\Delta\nu$ is the shift in frequency, occurring due to the Doppler effect, E is the applied voltage and θ is the angle of scattering.

Cellulose nanocrystals isolated from rice straw by sulfuric acid hydrolysis, treated for 15,45 and 60 minutes have zeta potential values of −66.7 ± 0.3, −57.3 ± 2.7 and −63.8 ± 2.2 mV, respectively and cellulose nanofibrils prepared by TEMPO-mediated oxidation has a zeta potential value of −113.3 ± 1.5 mV, the negative value in the former case consistent with the presence of surface sulfate groups and in the latter case consistent with the presence of highly polar surface carboxyl groups (Jiang and Hsieh 2013).

14.4.2 X-Ray Diffraction (XRD)

X-ray diffraction can be used to study the crystallinity of the sample. With the removal of non cellulosic polysaccharides, fibers begin to align along a specific axis and show increased crystallinity. The crystallinity index is calculated using the following equation (Mwaikambo and Ansell 2002):

$$\mathrm{Ic} = \left(\mathrm{I}_{(002)} - \mathrm{I}_{(\mathrm{am})}\right) / \mathrm{I}_{(002)} \times 100$$

where Ic denotes the crystallinity index, $\mathrm{I}_{(002)}$ is the counter reading at maximum intensity at a 2θ angle of around 26°, corresponding to crystalline material and $\mathrm{I}_{(\mathrm{am})}$ is the reading at maximum intensity with a 2θ angle of around 18°, corresponding to amorphous substances. For nitrocellulose obtained from sisal fibers, the crystallinity index was found to be around 75 ± 1(Morán et al. 2008).

14.4.3 Thermal Analyses

14.4.3.1 Thermogravimetric Analysis (TGA)

TGA is used for the analysis of physical and chemical changes occurring in a substance with a change in temperature, by measuring the mass over time. TGA analysis of cellulose shows decomposition starting from 315 °C and continuing up to 400 °C (Yang et al. 2007). Cassava bagasse nanofibrils show initial decomposition at 220° due to depolymerization of starch and cellulose (Teixeira et al. 2009).

14.4.3.2 Differential Scanning Calorimetry (DSC)

DSC is an analytical technique that can reveal useful data such as glass transition temperatures, fusion temperatures, etc. The heat required to increase the temperature of a material is compared with that of reference material, and the heat difference is measured as a function of temperature. Thermograms for nanocellulose obtained from sisal fibers show a characteristic endothermic peak from 30 °C to 140 °C due to evaporation of water and a similar mass loss of about 71% ± 3% for all the samples (Morán et al. 2008).

14.4.3.3 Fourier Transform Infrared (FTIR) Spectroscopy

FTIR is used to find the chemical structure of a compound by identification of the functional groups present in it, depending on the absorption or emission spectra obtained. The following peaks can be obtained on analysis of various samples of plant fibers: untreated plant fibers show a C=O stretch in the acetyl or uronic ester functional groups present in hemicellulose, or the ester linkage present in lignin corresponding to the peak at 1732 cm^{-1}, as well as the C=C stretch of lignin's aromatic rings corresponding to the peak at 1507 cm^{-1}, which get diminished on bleaching and acid hydrolysis, indicating the loss of hemicelluloses and lignin; C-H and C-O stretches show peaks at 2916 and 1629 cm^{-1}; O-H bending of water molecules absorbed onto cellulose show characteristic peaks at around 1647–1638 cm^{-1}, C-C ring stretch at 1151 $cm^{-1}$and C–O–C glycosidic ether linkages at 1105 cm^{-1}; all samples show C–O–C stretch of pyranose ring corresponding to bands at 1027 cm^{-1}, the glycosidic linkages between glucose units in cellulose, corresponding to bands at and 898 cm^{-1}, and the free O–H stretch from the hydroxyl groups in cellulose corresponding to the broad absorption band at around 3500–3300 cm^{-1} (Deepa et al. 2015).

14.4.4 Microscopy

The morphological and structural analysis is performed using the microscopic techniques described below:

14.4.4.1 Scanning Electron Microscopy (SEM)

This method is used specifically for the study of the morphology of nanocellulose. SEM images of raw pineapple leaf fibers show smoothly surfaced fibrils neatly stacked in bundles, which undergoes defibrillation on subjecting to a steam explosion in the presence of alkali at high temperatures due to the removal of the cementing materials, and undergoes further defibrillation on bleaching (Cherian et al. 2010).

14.4.4.2 Transmission Electron Microscopy (TEM)

Transmission electron microscopy is used for measuring dimensions of the nanocellulose particles. Although it gives good estimates of the dimensions, there is the chance that the data obtained is misleading since the conclusions are based only on a tiny sample, used in the imaging, and therefore light scattering methods may give a better overall picture. In the case of nanocellulose obtained from raw cotton linter, TEM images show agglomerated bundles of crystals with the average whisker length being 177 nm, width being 12 nm and the aspect ratio (L/D) being 19 (Morais et al. 2013).

14.4.4.3 Atomic Force Microscopy (AFM)

For cellulose fibers originating from sugarcane bagasse, treated by acid hydrolysis, both the height image (topographical image) and amplitude image (contrast image of sections of soft and hard polymer) show particles that lie in size range 70–90 nm (Mandal and Chakrabarty 2011).

14.4.5 Dynamic Light Scattering (DLS) for Measurement of Particle Size

This technique is used for statistical analysis of the size distribution of particles in a sample, by measuring the Brownian motion of suspended particles. The hydrodynamic radius (r_h), which is the radius of a spherical particle with the same viscosity or diffusion coefficient of the particle under observation, can be obtained from the Stokes-Einstein equation as follows (Fraschini et al. 2014):

For spherical particles,

$$r_{\mathrm{h}} = \left(\mathrm{k_b} T\right) / \left(6\pi\eta D_{\mathrm{t}}\right)$$

Where, k_b is the Boltzmann constant (in $\mathrm{J.K^{-1}}$), T is the absolute temperature (in K), η is the medium viscosity (in $\mathrm{kg.m^{-1}.s^{-1}}$), D_t is the translational diffusion coefficient (in $\mathrm{m^2.s^{-1}}$), which is obtained experimentally.

For a rod-shaped particle, D_t is calculated with the following equation:

$$D_{\mathrm{t}} = \left(\mathrm{k_b} T / \left(3\pi L\right)\right)\left(\delta - 0.5\left(\gamma^{\perp} + \gamma \parallel\right)\right)$$

Where, $\delta = \ln(2\ L/d)$,

$\gamma^{\perp} = -0.193 + 0.15/\delta + 8.1/\delta^2 - 18/\delta^3 + 9/\delta^4$ and

$\gamma\parallel = 0.807 + 0.15/\delta + 13.5/\delta^2 - 37/\delta^3 + 22/\delta^4$

Most of the particle sizes fall in the nanometric range, as can be observed in a Maxwell distribution obtained on making a plot of particle count v/s size, with the upper and lower size limits being 18.17 nm and 220 nm respectively, and the peak corresponding to 32.84 nm for nanocellulose obtained from sugarcane bagasse (Mandal and Chakrabarty 2011).

14.4.6 Birefringence Analysis

Birefringence refers to the property, where the refractive index of a substance depends on the polarization and the direction of distribution of light. This method provides an excellent way to analyze the dispersibility of nanocellulose in water, with the birefringence resulting from structural or flow anisotropy (Silvério et al. 2013). Aqueous nanocellulose suspensions have shear-induced birefringence, indicating the ability of the form of a chiral nematic liquid crystalline phase that can exist in equilibrium with isotropic phase (Fortunati et al. 2012). Casting nanocellulose suspensions can produce transparent films with a smooth surface (Deepa et al. 2015).

14.4.7 Inverse Gas Chromatography (IGC) Analysis

IGC is used for the study of surface properties of the sample, such as surface energy, surface area, free energy of adsorption, adsorption isotherm, acid-base characteristics, surface heterogeneity, monolayer capacity and permeability. The material under analysis would serve as the stationary phase, and the mobile phase contains a probe molecule. The surface properties of nanaocellulose would highly influence its ability to be used in nanocomposites, as it is a result of its chemical composition. Banana rachis nanocellulose shows dispersive surface energy ($\gamma^{D}{}_{S}$), Kb/Ka ratio (denotes Lewis basic character) and surface area (S_{BET}) of 43.77 mJ/m^2, 1.07 and 0.86 m^2/g respectively, while the corresponding values for sisal nanocellulose are 40.69 mJ/m^2, 1.17 and 0.82 m^2/g, those of kapok nanocellulose are 49.49 mJ/m^2, 1.00 and 0.88 m^2/g, those of pineapple leaf nanocellulose are 40.71 mJ/m^2, 1.60 and 0.82 m^2/g and those of coir nanocellulose are 48.37 mJ/m^2, 1.83 and 0.99 m^2/g (Deepa et al. 2015).

14.4.8 Rheological Characterization

Nanocellulose prepared by high-pressure homogenization of sugarcane bagasse shows a higher storage modulus (G´) than loss modulus (G”), indicating gel like properties (Li et al. 2012).

14.5 Modifications Achievable in Nanocellulose Crystals

Due to dissimilar in polarity and chemical functionality, the conjunction between hydrophobic polymers such as PLA, PE, etc. and CNCs is hindered. This cause some adverse effects as shown in Fig. 14.3 (Prateek et al. 2012; Sehaqui et al. 2011).

Thus physical/ chemical assisted surface modification of CNC is opted to improve dispersibility and compatibility of CNCs (Zhang et al. 2011). Generally, four surface modifications are preferred. Briefly, they are outlined in Table 14.3. With an aim to reduce the specific surface energy to avoid agglomeration as well as poor interfacial adhesion to the polymer matrix, these modifications are carried out (Kuo et al. 2013). Thermodynamically, due to the highly developed specific surface, nano-scale cellulose structures have enhanced thermodynamic potential. Thus attribute the reason for the instability of CNCs and form aggregation (Islam et al. 2013).

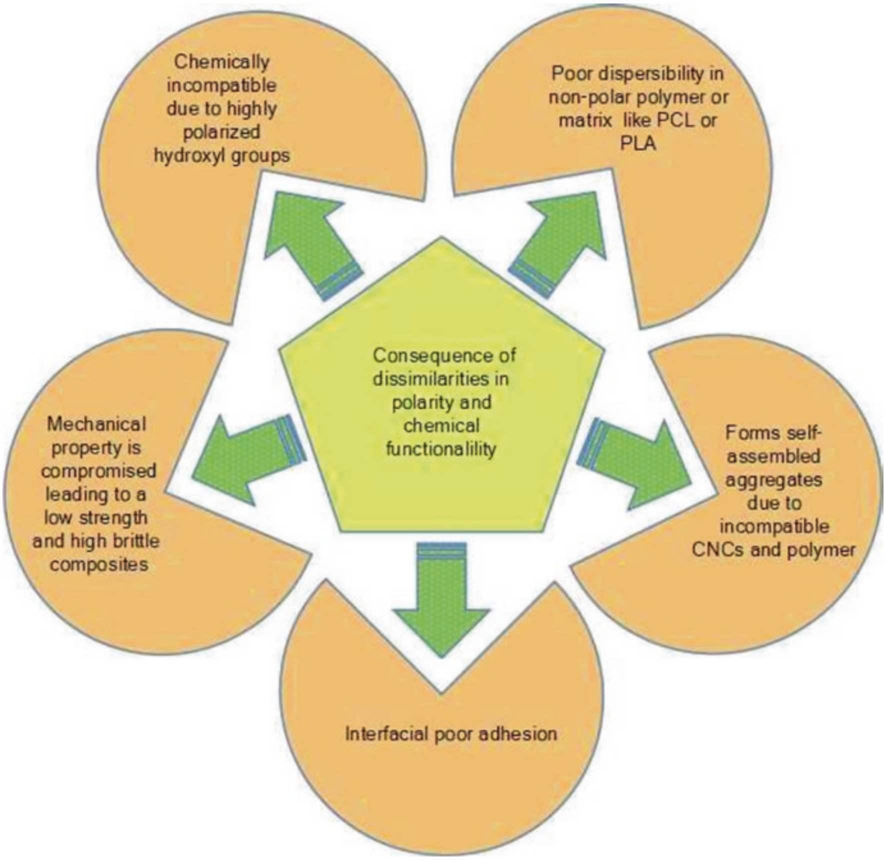

Fig. 14.3 Negative effect of dissimilarities in polarity and chemical functionality between CNC and hydrophobic polymer

Table 14.3 Modifications achievable in nanocellulose crystals (Ng et al. 2015)

Type of surface modification	Silent features
Electrostatic group introduction	The aim is to insert electrostatic group
	Such electrostatic introduction hinders the hydrogen attachment among the cellulose chain
	Most preferred treatment is carried by sulfuric acid, whereas TEMPO-mediated oxidation enhance negative charge
	Epoxypropyltrimethylammonium chloride leads to cationization of surface
	Cationization results in, (a) Aqueous suspension stability with CNC (b) Avoid thixotropic unexpected gelling (c) Retain the inherent crystal morphology
Chemical modification	Compatibilizing agent, coupling agent, acetylating agent, polymer grafting agent modification is easily possible due to surface hydroxy groups availableness
	Most favored method relays on the usage of compatibilizing agent as it induces interface bonding between contradictory phases
	The compatibilizer consist of co-polymers of the polymeric matrix and an anhydride (e.g., Maleic anhydride)
	Peroxide assisted initiator for chemical modification improve the interfacial bonding between hydrophilic CNCs and hydrophobic polymer matrix
	Alternatively another compatibilizing agent like permanganate, lignosulfonate, etc. Enhance the adhesive property
	Coupling agents (e.g., Organo functional silanes and titanate coupling agent) improve the interfacial adhesion property
	Through esterification, hydrophobic ester groups on the surface of CNC helps in covalent chemical modification
	Polymer grafting onto CNC surface could be done by, grafting-onto and grafting-from
Physical Modification	It is carried out to enhance the mechanical bonding (matrix) and properties (composite)
	The methods involved are electric discharge (corona, cold plasma), dielectric-barrier discharge, ultrasonic, irradiation, mechanochemical treatment
	To attain surface oxidation, Corona treatment is preferred
	Removal of protons and creation of unstable radicals on the surface of cellulosic material could be done by cold plasma treatment
	A better interaction between matrix-reinforcement and level of filler distribution small particle size and large specific surface area lignocelluloses are chosen

(continued)

Table 14.3 (continued)

Type of surface modification	Silent features
Bacterial Modification	Bacterial nanocellulose coat the lignocellulose surface when a cellulose-producing bacteria is grown in the presence of lignocellulose
	On the surface of natural fibers, Crystalline nanocellulose of bacteria can be seen in the form of hairy fibers
	There is an active hydrogen bonding between bacterial cellulose and the lignocellulose hydroxyl groups
	Mechanical properties in both dry and wet states, porosity, water absorbency, moldability, biodegradability, and excellent biological affinity can be easily modified

14.6 Conclusion

Nanocellulose is available abundant quantities, an inexhaustible and cheaply sourced. The production cost of CNCs is comparatively low. It can hold the account for the unused agricultural residues that are produced every year. Due to these reasons, CNC could be a better alternative than synthetic reinforcing fibers like carbon or glass. As compared to man-made engineered fillers that are harmful to environment nanocellulose are biodegradable and cause less impact to harm the environment. Such prominent characteristics of nanocellulose could be a perfect candidate as reinforcement material in bio-polymers resulting it to a superior material with apical applications for a clean future.

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Chapter 15
Nanomaterials and Their Applications in Bioimaging

Ruma Rani, Khushboo Sethi, and Geeta Singh

Contents

R. Rani · K. Sethi
ICAR-National Research Centre on Equines, Hisar, India

G. Singh (✉)
Department of Biomedical Engineering, Deenbandhu Chhotu Ram
University of Science and Technology, Sonipat, India
e-mail: geetasingh.bme@dcrustm.org

R. Prasad (ed.), *Plant Nanobionics*, Nanotechnology in the Life Sciences,
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15.1 Introduction

Nanomaterials have been widely studied by the researchers for their application in the area of nanomedicine for the diagnosis, monitoring, treatment, and prevention of disease. Change in the properties of nanomaterials compared to bulk materials occurs mainly because of large surface-area-to-volume ratio and dominance of quantum effects at nanoscale. These two effects enhance the properties such as reactivity, strength, electrical characteristics, optical characteristics, and magnetic characteristics and also in vivo behavior of nanomaterials. Moreover, in the field of chemistry, biotechnology, and biomedicine, nanomaterials have been used actively. Furthermore, biosensing, gene/drug delivery, bioimaging, multiplexed detection, and cancer chemotherapy have also been influenced from nanomaterial (Biju 2014). Recently, inorganic nanoparticles have attracted attention in the fields of imaging owing to their electronic, optical, magnetic properties and their inertness. The various abilities of nanomaterials allow one to use these for the detection of the structures and functioning of subcellular organelles and biomolecules. Moreover, they provide an emerging alternative for image-guided therapies in disease diagnosis and treatment of various diseases.

According to the perception of most people, ‘imaging’ is a kind of photography. But in scientific domain, it is far beyond this. Bioimaging is the visualization of biological processes in real time with less interference in life process and also gave output in the form of 3D (three-dimensional) images of any part of the body from outside. Various bioimaging techniques are available by which one can observe cells in tissues up to whole organism by using different sources of light, such as ultrasound, fluorescence, X-ray, electrons, magnetic resonance, and positrons. On the basis of the above source used, there are different bioimaging techniques such as magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET), ultrasound, and fluorescence imaging that have been obliged to for disease diagnosis in clinical studies (Fig. 15.1). Out of the above said imaging techniques, MRI with the use of nanomaterials as contrast agents for in vivo imaging is the largest field of application (Li et al. 2015). Contrast agents are generally used in these bioimaging techniques in order to diagnose the organ or tissue of interest as well as identify healthy tissue from diseased tissue. The accurate diagnosis at the early stage of diseases is the need of hour that require a sensitive, specific, and high-quality imaging probes which can be possible with the following prerequisite qualities of the contrast agent:

- Stability of the agent in physiological environment with varying ionic strengths, pH, or temperature)
- Maintenance of colloidal solution with proper dispersion
- High retention time in bloodstream
- Proper imaging time and image contrast
- Longtime circulation in bloodstream after intravenous administration
- More biocompatibility of the agent
- Less cytotoxicity with systemic clearance

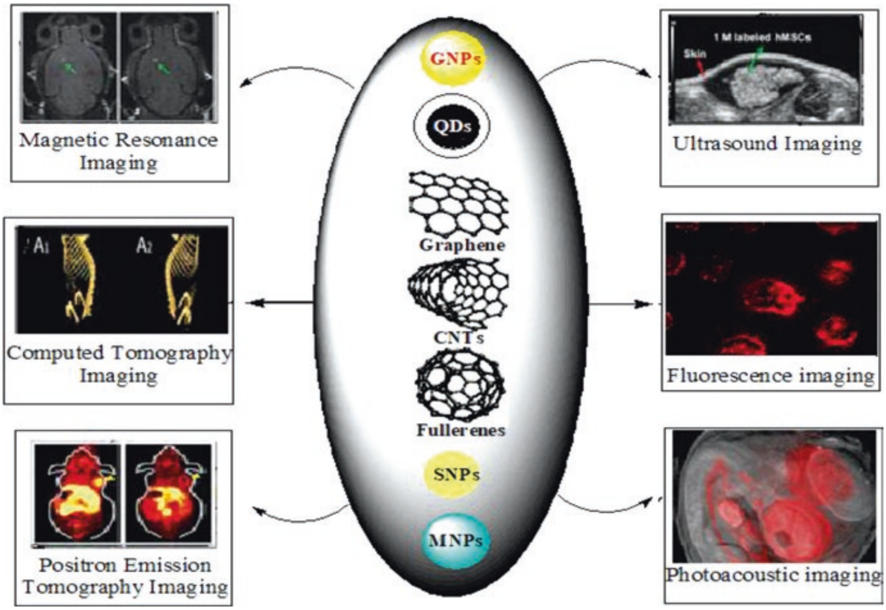

Fig. 15.1 Schematic representation of various imaging applications including magnetic resonance imaging (MRI), computed tomography (CT), positron emission tomography (PET), ultrasound imaging (USI), fluorescence imaging (FI), and photoacoustic imaging (PAI) with reference to different nanomaterials

Nanomaterial can be categorized into organic and inorganic nanomaterials that can be employed for imaging application. Due to ease in the synthesis and modification of inorganic nanomaterials, these novel designs and formulations are impacting conventional ones and show perspective employment in bioimaging (Cherukula et al. 2016). Among nanomaterials, gold nanoparticles, silica nanoparticles, magnetic nanoparticles, quantum dots, carbon nanotubes, fullerenes, and graphene have been used for imaging applications.

15.2 Nanomaterials for Bioimaging

15.2.1 Gold Nanoparticles

Gold nanoparticles (GNPs) are the most commonly used nanocarriers owing to their brilliant coloring, size, shape, and tunable surface plasmon properties which make them attractive for various applications such as sensing, diagnosis, catalysis, drug delivery, and bioimaging (Saha et al. 2012; Shi et al. 2012; Liang et al. 2015). The importance of colloidal gold was realized when monodispersed GNPs were prepared by the citrate reduction of gold ions. Schiffrin–Brust, in 1994, gave the most popular synthetic method for GNPs with a biphasic approach by using a simple method and common reagents. In this method, gold ions were reduced by $NaBH_4$ in an aqueous phase; then, these were transferred to an organic phase with alkane thiol supplemented for the synthesis of thiol-protected gold nanoparticles (Brust et al. 1994). Afterward, Murphy et al. (2008) and Dreaden et al. (2012) gave GNP preparation method using seed-mediated growth having different kinds of size and shapes such as nanocubes, nanocages, and nanorods with satisfactory reproducibility. Templeton et al. (2000) synthesized GNPs with water dispersion characteristic by performing various ligand exchange reactions for the functionalization of terminal moiety on alkane thiol-protected GNPs. Their simple formulation and reactive surface allow for a variety of molecules to be attached which include drugs, targeting peptides or proteins, contrast agents, or other moieties. Different types of shapes like spheres, hollow shells, star shapes, rods, clusters, and cubes and size of particles ranging from 1 nm to over 100 nm have important effect on the optical properties of GNPs and their application (Mahan and Doiron 2018). For the first time, GNPs were investigated as an X-ray contrast agent by Hainfeld, who imaged the organs and vasculature of mice by injecting bare GNPs intravenously (Hainfeld et al. 2004, 2006). Nanomaterials shape also plays an important role in the application part like nanospheres, and nanorods of gold provide excellent contrasts in the dark-field optical and photothermal imaging of cells and tissues, whereas the nanoshells, nanospheres, nanorods, and nanocages are ideal for optical coherence tomography and photoacoustic imaging of deep tissues, circulatory systems, and lymph nodes (Biju 2014).

15.2.2 Silica Nanoparticles

Silica nanoparticles (SNPs) are another important group of inorganic delivery system. They are ideal candidates for bioapplications such as bioimaging/delivery applications owing to the straightforward, size-controllable morphologies, hydrophilic surface with biocompatibility, and ease of functionalization. Silica is accepted by FDA (US Food and Drug Administration) and has been widely used in cosmetics (Contado et al. 2013). Furthermore, Ow et al. (2005) reported that Cornell dots (commercial name) of SNPs encapsulating fluorescent dyes have also been evaluated as cancer-targeted imaging probes for stage I human clinical trial. The basis of silica nanoparticle preparation is based on the controlled hydrolysis of silyl ethers into silanols in the presence of ammonia in a mixture of water and alcohol followed by the condensation of silanols which results in the formation of 50–2000 nm silica particles. By varying the concentrations of silyl ether and alcohol, or the normal or reverse, one can control the size of SNPs (Trewyn et al. 2007). Mesoporous SNPs are prepared by the sol–gel process, involved in situ polymerization of silyl ethers and further more stabilized by surfactants in amphiphilic templates. Aggregation of SNPs can be avoided by optimizing the concentration of silyl ether or by the addition of various nonionic surfactants, polymers, triethanolamine, or propanetriol. Size can also be controlled by varying parameters like changing the pH of the solution, solvent composition, and introduction of certain swelling agents. Thereafter, the amphiphilic templates can be removed by using different processes like solvent extraction, thermal decomposition, dialysis, or oxidation. Reactive functional groups can be added onto the SNP surface either at the time of preparation or after preparation (Wu et al. 2013). Modification of SNPs with surface functional groups such as primary or secondary amino, carboxyl, hydroxyl, alkyl halogen, or azide group is necessary for the conjugation of various biomolecules, contrast agents, and drug molecules to the surface as well as inside the pores of NPs. Moreover, hydrophilic nature of SNPs makes them one of the friendliest nanomaterials for biomedical applications such as drug and gene delivery, bioimaging, and therapy.

15.2.3 Magnetic Nanoparticles

Magnetic nanoparticles (MNPs) are made up of maghemite (Fe_2O_3) or magnetite (Fe_3O_4). Iron oxide materials are biodegradable, biocompatible, less toxic, and approved by FDA. MNPs possess superparamagnetism, as they are present in nanometric scale and smaller than the single domain limit. Moreover, in the absence of an external magnetic field, they have H_c (coercive field-minimum energy reverse the material net magnetization zero) and M_R (residual magnetization with no applied field) equal to zero, which make it a superparamagnetic and ideal candidate for bioapplications. MNPs have been widely used in various applications like multimodal imaging, targeted drug and gene delivery, hyperthermia for cancer treatment, biomedical separation, and tissue repair particularly owing to their unique superparamagnetic properties, tunable size as well as their conjugation with many biological and drug molecules (Liang et al. 2015). In general, there are several chemical methods for the synthesis of MNPs such as sol–gel, microemulsion, thermal decomposition, solvothermal hydrothermal protocols, electrochemical approaches, etc. (Laurent et al. 2008; Reddy et al. 2012). For targeted/therapeutic application of MNPs, one has to modify the organic shell surrounding the magnetic core, further giving rise to a water-soluble biocompatible product which can be further functionalized with chemically reactive groups. After modification of the organic shell for MNP attachment, NP surface can also be modified with the targeting moiety for targeted delivery. MRI, based on computer-assisted imaging within the human internal organs excited by radiofrequency waves under a gradient magnetic field, has become a useful diagnostic tool in medical science. MRI suffers from less sensitivity as well as inadequate spatial or temporal resolution. Therefore, MRI is combined with imaging techniques (MRI/PET, MRI/CT) for reducing their disadvantages. Lee et al. (2012) synthesized biocompatible Fe_3O_4–TaO_x core–shell NPs to achieve the benefits of two imaging techniques CT and MRI for imaging newly formed blood vessels in the tumors and tumor microenvironment, respectively.

15.2.4 Quantum Dots

Semiconductor quantum dots (QDs) are one of the most important QDs, whose size and shape can be accurately controlled by optimizing the time duration, temperature, and ligand molecules used in the synthesis. QDs are mainly composed of groups II–VI or III–V elements, such as CdTe, CdS, ZnSe, InP, or InAs, with a size range between 1 and 10 nm, which give rise to quantum confinement effect with narrow emission bands and broad absorbance bands. QDs are also reported to have extended photostability over molecular fluorophores for long-time imaging and prevent photobleaching, high quantum efficacy, the capacity of simultaneous multicolor imaging through single-light source excitation, and ease of modification (Li et al. 2015). Therefore, due to various appealing features of these nanomaterials, the use of QDs in imaging applications has been quickly evolved with comparison to conventional fluorescence dyes (Hildebrandt 2011). For the first time, Murray et al. (1993) reported the synthesis of CdX quantum dots at a high temperature from dimethyl cadmium and trioctylphosphine chalcogenides or hexamethyl disilathiane as base. The synthesized CdX quantum dots were found to be highly hydrophobic and incompatible in the aqueous phase. Thereafter, biocompatible QDs were synthesized from cadmium perchlorate in aqueous phase (Vossmeyer et al. 1994). The problem related to quantum efficiency and size distribution of QDs was further overcome by Peng and Peng (2001) by introducing greener methods for the synthesis of QDs from $Cd(CO_3)_2$, CdO, and $Cd(acetate)_2$. The best-quality quantum dots are synthesized in the organic phase and are capped with highly hydrophobic aliphatic ligands. The ligand exchange reactions and surface modifications are found to be necessary for biological applications of QDs. The most important things that have to be kept in mind during the surface modification of QDs are that the vital properties of QDs should be remained unaffected and uniformly dispersed and the conjugated molecules should also be biocompatible for biological applications. QDs capped with small organic molecules such as thioglycolic acid, dihydrolipoic acid, or mercaptopropionic acid may help in the direct interaction with cells and translocation into the cytosol. QDs conjugated with peptides such as nucleus localization signal or mitochondrial localization signal help in targeted intracellular labeling and imaging of nucleus or mitochondria, respectively. However, nontargeted QDs modified with surface molecules such as polymers, gelatin, carboxylic acids, and polyarginine are also explored for imaging various targeting sites such as blood vessels, lymph nodes, tumors, etc. Moreover, quantum dot–D-lactose conjugates have also been used for targeted labeling and imaging of leukocytes in in vivo applications (Vlasceanu et al. 2017; Martynenko et al. 2017).

15.2.5 Carbon Nanotubes

Carbon nanotubes (CNTs) are one of the most commonly used nanomaterials in the field of healthcare (Kumar et al. 2017). CNTs are constructed as hollow cylindrical tubes consisting of carbon (graphite) with a high aspect ratio and sp^2 hybridization. Depending on the number of graphite layers, CNTs can be classified as single-walled nanotubes (SWNTs), double-walled nanotubes (DWNTs), and multiwalled nanotubes (MWNTs). Carbon nanotubes can be synthesized by various methods including arc discharge, laser ablation, and chemical vapor deposition (CVD). Arc discharge and laser ablation techniques developed earlier generally require high temperature (>1700° C) during synthesis, and CVD and their modified CVD methods have replaced these methods as they can be conducted at lower temperatures (<800 °C). Synthesized CNTs were found to be in the form of aggregate or bundle due to hydrophobic nature, while its uniform suspensions in aqueous buffers have to be used for bioimaging, drug delivery, photothermal therapy, and also in other applications. Dispersion of CNTs in the aqueous phase can be done by controlled sonication of an aqueous suspension of CNTs with amphiphilic molecules or surfactants. Moreover, functionalizations (covalent and noncovalent) are the most effective method for the stable dispersion of CNTs in the organic as well as in the aqueous phase. Fundamental properties responsible for bioimaging are the broad absorption band, outstanding photoacoustic response, NIR photoluminescence, and unique Raman/surface-enhanced Raman scattering effect (Kostarelos et al. 2009). Graphite mode (G-band) of CNT provides the most prevailing fingerprint Raman band for bioimaging. Moreover, its NIR excitation for Raman imaging is helpful in the minimization of autofluorescence of biological specimen and photobleaching of CNTs (Kostarelos et al. 2009). Additionally, photoacoustic imaging property of CNT provides another auspicious technique for bioimaging. CNTs offered excellent photo-to-acoustic conversion efficiency and photothermal–acoustic response, which make these materials one of the most auspicious contrast agents in photoacoustic imaging of tumors (discussed later). Also, conjugated CNTs with radionuclides, fluorescent dyes, other nanoparticles, or inorganic complexes act as contrast agent for various bioimaging techniques such as MRI, CT, PET, SPECT (single-photon emission computed tomography), etc.

15.2.6 Fullerenes

Fullerenes are the zero-dimensional form of graphitic carbon in the form of a hollow sphere, ellipsoid or tube. Spherical fullerenes are also referred to as buckyballs. An important property of C_{60} molecule is its high symmetry, containing 20 hexagons and 12 pentagons. For the first time, it was prepared by the laser vaporization of graphite on a preparative scale; thereafter, Kratschmer–Huffman (1990) introduced its macroscopic-scale synthesis, where a vacuum arc discharge was used for the synthesis of C_{60} from graphite rods. For enhancement of C_{60} applications, functionalization is very important, and one has to start from its suspension in an organic solvent. Various free-radical reactions like cyclopropanation or cycloaddition reactions can be used for covalent conjugation of C_{60} with molecules.

Partha and Conyers (2009) reported multiple iodine-functionalized C_{60} as a promising X-ray contrast agent, with prolonged retention in the blood and exceptional in vivo biocompatibility when compared with other commercially available X-ray contrast agents such as iopamidol and iohexol. The most interesting properties of C_{60} include absorption light in the UV–vis region, photothermal effect, the ability to accommodate multiple electrons and endohedral metal atoms, long-living triplet state, and singlet oxygen production which added the application of fullerenes in radioimaging, gene/drug delivery, oxidative stress reduction, and cancer therapy.

15.2.7 Graphene

Graphene is an allotrope of carbon in the sp_2-hybridized state with 2D honeycomb lattice, which is the raw material for the synthesis of other types of carbons like fullerene and CNTs. Naturally, graphene is an aromatic structure having many unsaturated carbon–carbon bonds in the plane, which offer free π electrons and reactive sites for surface functionalizations. Graphene has attracted the interest of researchers due to their unique physicochemical properties such as strong mechanical strength, acceptable biocompatibility, ease of production, and ease of modification owing to their versatile surface functionalization and ultrahigh surface area characteristics (Lin et al. 2018). Along with graphene, its other derivatives, such as graphene oxide, reduced graphene oxide, and graphene quantum dots, are also explored in various biomedical fields. For the first time, it was isolated by the exfoliation of graphite using an adhesive tape (Geim and Novoselov 2007). Chemical vapor decomposition on metal substrates or thermal decomposition of carbon-based wafer such as silicon carbide wafer in the presence of ultrahigh vacuum conditions, mechanical exfoliation of highly oriented pyrolytic graphite, and chemical and thermal reduction of graphene oxide are some well-known methods for large-scale production of graphene (Bhuyan et al. 2016). Graphene has poor dispersion in liquids which can be overcome by functionalization. Just like CNTs, graphenes have some fundamental properties like visible and NIR photoluminescence, characteristic Raman bands, and photoacoustic and photothermal responses for bioimaging (Choi et al. 2010).

15.3 Applications of Nanoparticles in Different Bioimaging Modalities

15.3.1 Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is an imaging technique that is used to study the structure and function of tissues in medical field (Weissleder 2006; Jun et al. 2008; Waters and Wickline 2008). The basis of MRI depends on the behavior, alignment, and interaction of protons which allow for tissue imaging with an enhanced resolution in both space and time in the presence of an applied magnetic field. By applying a strong magnetic field, protons in the tissues are perturbed from the relaxed state and converted into an image. The weakness of the magnetic signal and the low detector sensitivity are usually overcome by introducing contrast agents (CAs) and amplification. Contrast agents are used to alter/shorten the relaxation parameters, i.e., longitudinal (T1) or transverse (T2), which further enhances the contrast between tissues. MRI contrast agents can help clarify images and allow better interpretation. Efficiency of contrast agent is calculated by its reflexivity over a range of concentrations. The radiation dose is being rid off in MRI and thus offers higher spatial resolution when compared to radionuclide-based imaging (Weissleder 2006; Jun et al. 2008; Weissleder and Imhof 2007). Studies of exploration of various nanoparticles to improve contrast in MRI imaging are further explained.

Magnetic nanoparticles are of considerable importance because of their promising use in magnetic, optical, and electronic devices (Thorek et al. 2008; Shi et al. 2008; Asl 2017; Abd-Elsalam et al. 2019). Magnetic nanoparticles have been used in clinics with great success (Sun et al. 2008; Neumaier et al. 2008; Jun et al. 2008) for more than two decades. Highly superparamagnetic iron oxide is generally used as the core material with dextran (biocompatible polymers) as a coating material (Schulze et al. 1995). Advantages of using iron oxide nanoparticles are their biocompatibility, faster detection rate at moderate concentrations, high saturation magnetization, and relatively less toxicity than optical imaging agents. Paramagnetic substances, such as gadolinium (Gd), are positive contrast agents (T1 CA). Due to Gd limitations, certain degree of toxicity, and decreased efficiency at higher magnetic fields, the research focus has shifted to negative CA such as superparamagnetic iron oxide nanoparticles (SPIONs), a T2 CA in MRI (Veiseh et al. 2010). For active targeting, peptides, antibodies, proteins, and small molecules have been conjugated to SPIONs as contrast agent in MRI, due to their tunable properties and their low toxicity compared with gadolinium (Wunderbaldinger et al. 2002a, b). Wunderbaldinger et al. (2002a) have used dextran–SPION to examine the lymph node metastasis in an experimental murine model using contrast-enhanced MRI. In order to visualize tumors better, Montet et al. (2006) have used magnetofluorescent nanoparticle conjugates targeting normal tissues. Bombesin-labeled magnetofluorescent nanoparticles targeting bombesin receptors present on normal acinar cells of the pancreas leads to a decrease in the T2 signal of normal pancreas tissue, thus enhancing the ability to visualize tumors by MRI. Huh and co-workers (2005) produced iron oxide nanoparticles conjugated with Herceptin to detect breast cancers by MRI. Mn-doped iron oxide nanoparticles have been used for ultrasensitive molecular imaging (Lee et al. 2007). Engineered nanoparticles possessing high magnetism offer improved sensitivity and lower dosing when compared with non-engineered iron oxide contrast agents.

Another type of nanoparticles that have been used in MRI is Fe–Pt nanoparticles. Yang et al. (2010) explored Fe–Pt nanoparticles as possible contrast agents for MRI. Amphiphilic Fe–Pt nanoparticles, which contain both hydrophilic and lipophilic properties, were prepared by high-temperature pyrolysis in a tetraethylene glycol (TEG) medium with oleic acid (OA) as a surfactant. Cell viability studies were carried out on cervical cancer (HeLa) cell lines by taking Fe–Pt nanoparticles to determine the toxic effects. Magnetic properties such as saturation magnetization (Ms) and transverse relaxation time (T2) were also investigated. The MTT assay and transmission electron microscopy (TEM) results depicted that the amphiphilic Fe–Pt nanoparticles were found biocompatible with almost no cytotoxic effect. Magnetic resonance (MR) signal enhancement studies showed clear contrast from the background. It was observed that amphiphilic Fe–Pt nanoparticles could be promisingly used as a $T2$ contrast agent for MRI. Martins et al. (2014) and Carvaldo et al. (2014) reported magnetoliposomes coated with polyethylene glycol (PEG) and loaded with PEGylated SPION as a contrast agent and found PEGylated magnetoliposomes as negative CA for MRI than others. Martínez-González et al. (2016) reported liposomes loaded with hydrophobic iron oxide nanoparticles (SPIONs), i.e., magnetoliposomes as suitable candidates as CAs, especially as a liver CA. Boretti and Castelletto (2016) introduced a nanometric resolution MRI method for noninvasive mapping of functional activity in neuronal networks. Therefore, in the new approach, instead of using SPIONs alone, they can also be encapsulated/embedded in the nanocarrier (liposomes) with a double-function approach in theranostics-like imaging/diagnostics as well as therapy (Carvalho et al. 2017). Recently, chitosan-based SPIONs have been introduced intravenously in orthotopic C6 gliomas in rats which further accumulated in the tumor site, and this retention of nanoparticles resulted in a significant contrast enhancement of the tumor image (Shevtsov et al. 2018).

15.3.2 Computed Tomography

X-ray computed tomography (CT) having optimal cost and broad availability is a commonly used diagnostic imaging tool. X-ray CT helps in visualizing the differences in tissue density and provides image contrast between soft tissues and electron-dense bones. It is often desired to enhance the contrast of the diseased tissue with the use of X-ray contrast agents which increase the contrast between the normal and diseased tissues (Yu and Watson 1999). Commonly used CT contrast enhancers are water-soluble small organic iodinated molecules. The limitations of using these molecules are short imaging times owing to rapid renal clearance and nonspecific vascular permeation (Blaszkiewicz 1994; Yu and Watson 1999; Galperin et al. 2007; Kim et al. 2007). In order to overcome the problems associated with the use of small organic molecules, nanoparticle contrast agents for CT were developed as early as the 1980s, and after that various nanoparticles have been explored in X-ray CT (Cormode et al. 2014; Mahan and Doiron 2018).

CT was earlier not considered to be a molecular imaging technique like various other techniques, viz., magnetic resonance imaging (MRI), nuclear medicine imaging modalities (SPECT, PET), etc. Cai et al. (2007) used colloidal GNPs as a blood-pool contrast agent for X-ray computed tomography in mice. Furthermore, Popovtzer et al. (2008) reported GNPs conjugated with a targeted moiety for the detection of head and neck cancer with a standard clinical CT. Instead of using spherical gold nanoparticles, they used gold nanorods. It is a prerequisite that in CT imaging, the amount of the gold content per unit volume is important regardless of the particle shape and size. Gold nanorods (synthesized by the method of Nikoobakht and El-Sayed 2003), conjugated with UM-A9 antibodies, have been used to target squamous cell carcinoma (SCC). By this study, it was found that the A9-antibody-coated gold nanorods targeted the SCC cells and showed an increased attenuation coefficient (ΔHU; 168–170) when compared to the nontargeted nanorods, non-cancerous cells (normal fibroblast cells), and other cancerous cells (melanoma) (ΔHU; 28–32). The increased X-ray attenuation in targeted SCC cells compared with normal cells confirms to consider molecular X-ray CT imaging as a molecular imaging technique (Popovtzer et al. 2008). Another study which explored gold nanoparticles (1.9 nm) as an X-ray CT contrast agent was explained by Hainfeld et al. (2006) to diagnose tumors in mice. The injected gold nanoparticles were unable to be present in the blood after 24 h, but instead accumulation in the kidney, tumor, liver, and muscle occurs after just 15 min. The gold nanoparticles are removed from the kidneys by means of renal excretion, and no concentrate was found in the liver or spleen, presumably because of the small size of the nanoparticles. Kattumuri et al. (2007) had made use of gum Arabic stabilized gold nanoparticles as a potential biocompatible X-ray CT contrast agent. Besides GNPs, Fe–Pt nanoparticles are also being used as contrast agents for both computed tomography (CT) and MRI as studied by Chou et al. (2010). The research group also reported that NPs were biocompatible with no cytotoxic effect and no significant hemolysis. Moreover, these NPs were binded to a specific site as well as enhanced the contrast by shortening of T2 relaxation.

Van Schooneveld et al. (2010) synthesized PEGylated gold/silica nanoparticles with paramagnetic and fluorescent lipid coating and applied as trimodal contrast agents to allow for nanoparticle-enhanced imaging of macrophage cells in vitro via MRI, CT, and FI and mice livers in vivo via MRI and CT. Cormode et al. (2010) injected a gold high-density lipoprotein nanoparticle as CA for the characterization of macrophage burden, calcification, and stenosis of atherosclerotic plaques and concluded that the used CA gave multicolor CT images with valuable information about atherosclerotic plaques. Moreover, along with X-ray imaging, chemo-photothermal therapy was also performed by using core–shell-structured docetaxel-loaded PLGA–GNPs, showing significant imaging as well as theranostic approach (Hao et al. 2015). Thereafter, researchers used different types of nanoparticles as CAs for the betterment of CT application along with other imaging modalities

(Pan et al. 2012; Xue et al. 2014; Cole et al. 2015; Chhour et al. 2016; Cheheltani et al. 2016; Si-Mohamed et al. 2017).

15.3.3 Positron Emission Tomography

Positron emission tomography (PET) is an imaging technique which depicts three-dimensional images of biological processes in real time. Three-dimensional images of tracers can be obtained by detecting pairs of gamma rays which are emitted by a tracer (represented by a positron-emitting radionuclide) when conjugated to biologically active molecules. PET becomes one of the most promising techniques for the diagnosis of diseases in a noninvasive manner because of having excellent sensitivity and low background noise. PET is a powerful tool for in vivo imaging of human brain function in neurological disorders such as Parkinson's disease, Huntington's disease, multiple sclerosis, and dementias (Meltzer et al. 2003; Herholz et al. 2007; Politis and Piccini 2012; Assimakopoulos et al. 2014; Niccolini et al. 2015; Kato et al. 2016). Carbon-based nanoparticles have been used for PET imaging. Positron-emitting radionuclides can be conjugated to CNTs or even inserted into CNTs for PET imaging. McDevitt et al. (2007) have produced yttrium-86 (^{86}Y)-CNTs covalently attached to multiple copies of DOTA chelates for the solubilization of functionalized CNTs, and the whole-body PET images depicted that ^{86}Y-CNTs have been cleared from the blood within 3 h and distributed majorly to the kidneys, liver, spleen, and bone in mice. In another study, Ruggiero et al. (2010) constructed SWCNTs covalently attached with radio metal–ion chelates (DOPA) and tumor-targeting antibody and used for rapid imaging. Dynamic and longitudinal PET imaging of LS174T tumor-bearing mice demonstrated rapid blood clearance (<1 h) and specific tumor accumulation of the specific construct. PEGylated GO nanoparticles have been used in PET and have shown minimal toxicity when administrated in mice (Yang et al. 2011). Though CNTs are found to be a potential nanomaterial for diagnostic applications, due to their nonbiodegradability nature, CNTs are still not preferred to be used in PET.

Next comes the use of gold nanoparticles in PET imaging. Xie et al. (2010) reported the use radiolabeled gold nanoshells (NSs) with tumor xenografts to produce in vivo PET images. GNPs coated with the radionuclide, (64)Cu and three types of materials, (64)Cu-NS and the controls ((64)Cu-DOTA and (64)Cu-DOTA-PEG2K) were observed for biodistribution and PET imaging. PET images of the rats showed accumulation of (64)Cu-NSs in the tumors and other organs with significant difference from the controls. In another study by Karmani et al. (2013), ^{89}Zr-labeled antibody-targeted GNPs have proved to be a potential probe for cancer imaging and therapy. The use of metal oxide nanoparticles in the application of PET imaging has also been investigated. Perez–Campana and co-workers (2012) reported the activation of ^{18}O-enriched aluminum oxide (Al_2O_3) NPs by irradiation with protons to yield ^{18}F-labeled NPs. Biodistribution studies were carried out in male rats using ^{18}F-labeled NPs which helps in determining the biodistribution pattern in rodents up to 8 h.

Another research was done by the same group in 2013 to activate aluminum oxide (Al_2O_3) NPs by directly irradiating with protons via the $^{16}O(p,\alpha)^{13}N$ nuclear reaction. For biodistribution studies, the accumulation of ^{13}N-labeled NPs with different sizes in different organs was recorded during the first 68 min after administration and showed the uptake of NPs in the brain was very low regardless of the particle size, and low accumulation of NPs (<2%) was observed in the lung for smaller NPs as compared to NPs with larger sizes. Some reports are also available for the use of 18F-fluorodeoxyglucose–PET scans for imaging pancreatic cancer and gastric cancer and also for estimation of perimenopause and emergence of an Alzheimer's in the brain (Ma et al. 2013; Crippa et al. 2014; Grimmer et al. 2016; Mosconi et al. 2017). Radiolabeled iron oxide, another class of NPs, is applied for PET imaging. The iron oxide NPs (IONPs) are differentiated into various classes based on their sizes, viz., standard superparamagnetic iron oxide (SPIO) at 60–150 nm, ultrasmall superparamagnetic iron oxide (USPIO) of approximately 5–40 nm, and monocrystalline iron oxide nanocompounds (MION), a subset of USPIO, ranging from 10 to 30 nm (Xing et al. 2014). Among all, SPIONPs have been selected due to exclusive properties of biocompatibility and intrinsic ability to facilitate surface modification, making them attractive as multifunctional imaging agents. Recent applications of radiolabeled iron oxide nanoparticles for PET imaging and multimodality imaging have been summarized in different comprehensive reviews (Bouziotis et al. 2012; Thomas et al. 2013). Combining PET imaging with the other imaging modalities like X-ray CT or MRI provides the synergistic combination of information (Wang et al. 2014; Riola-Parada et al. 2016; Szyszko and Cook 2017).

15.3.4 Ultrasound Imaging

Ultrasound imaging (USI) is a clinical diagnostic technique that is frequently used because of its distinguished properties, namely, its real-time monitoring capability, low cost, high safety, convenience, and portability (Liu et al. 2011). Ultrasound contrast agents (UCAs) in the form of nanoparticles have been developed for improvement in visualization in US imaging. Mattrey et al. (1982) studied the use of PFOB (perfluoroctylbromide) NPs in US imaging. PFOB NPs have considerably increased the echogenicity of the liver as compared to that of the kidney after 48 h of intravenous infusion and produced an echogenic rim around VX2 carcinoma, which helps in tumor diagnosis. By this study, the authors have considered PFOB NPs to be a promising US contrast material. Lanza et al. (1996) found liquid PFC-filled NPs to be used as new UCAs because of having long circulation half-life and high stability. These NPs present a low intensity of US reflection and require higher concentrations or more binding events, which form the physical basis of the ability of PFOB NPs to serve as UCAs and to produce comparatively high backscatter signal (Marsh et al. 2002; Wickline et al. 2002). Horie et al. (2011) studied the antitumor effects of tumor necrosis factor (TNF-α) by transfection of TNF-α plasmid DNA into solid mouse tumors using the nanobubbles (NBs) and ultrasound gene delivery system. The contrast of the image was enhanced using Sonazoid and a high-frequency US imaging system (40 MHz) to check the difference in tumor size before and after the treatment and found significant reduction in the tumor size. Finally, they concluded the effectiveness of NBs and US for TNF-α gene delivery into tumor cells. Another investigation was done by using halloysite clay nanotubes (HNTs) as promising contrast agents for ultrasound-targeted imaging at a conventional diagnostic frequency of 10 MHz (Conversano et al. 2016). HNTs in the radiofrequency backscatter signals have been used to generate tailored color maps. These were then allowed to superimpose on conventional B-mode echographic images for automated HNT detection having sensitivity up to 60% and specificity above 95% by using HNT concentration of 1.5 mg/mL. HNTs have been found to result in significant diagnostic improvements, enabling nonionizing identification of pathological tissues at cellular level.

15.3.5 Fluorescence Imaging

Fluorescence imaging (FI) has emerged as an evolutionary field that has many significant advancements. This technique has the accumulative availability of fluorescent proteins, dyes, and probes, as well as the development of optical imaging technologies (Ntziachristos 2006). Fluorescence imaging has several advantages like good sensitivity, noninvasive nature, read availability, and comparatively low cost. Because it is an optical technique, it has limitations in terms of tissue penetration depth.

A large number of studies have proved the potential of QDs in the application of fluorescence imaging. Akerman et al. (2002) have used CdSe/Zns QDs coated with PEG for targeting peptides in the lungs of mice. Multifunctional nanoparticle probes based on QDs were formed for in vivo imaging of human prostate cancer in mice, as described by Gao et al. (2004). This new type of coated QDs is based on the encapsulation of PEGylated QDs using an ABC triblock copolymer as a secondary coating layer, further functionalized with a tumor-targeting antibody to prostate-specific membrane antigen. Cai et al. (2006) have conjugated QDs with peptides for targeted in vivo imaging of tumors. As observed from NIR fluorescence images, they showed that QDs labeled with arginine–glycine–aspartic acid (RGD) peptide had selectively target the αvβ3-positive tumor vasculature in a murine xenograft model. Though significant accumulation in the liver, bone marrow and lymph nodes were found, after 6 h of injection of QDs, then also high tumor contrast was there. Distribution of four QDs with different surface coatings was studied by Ballou et al. (2004), and it was observed that the QDs were fluorescent for at least 4 months in vivo. Tada et al. (2007) has chased single QDs coated with monoclonal anti-HER2 antibody using a high-speed confocal microscope in the tumors of living mice in the dorsal skinfold chamber. QD-based contrast agent for brain imaging has been developed by Gao et al. (2008). Surface modification of QDs using poly(ethylene glycol)–poly(lactic acid) was carried out which was then functionalized with wheat germ agglutinin. The agent was delivered to the brain by means of intranasal administration, and accumulation in the brain remained for >4 h and was cleared after 8 h of administration. Deliberate addition of different components like gadolinium and manganese in QDs leads to the formation of multimodal imaging agents (Yong 2009).

Jin et al. (2008) have produced hybrid QDs with the careful incorporation of Gd^{3+} in QDs to achieve dual-mode (fluorescence/magnetic resonance) imaging. In the same way, Yong (2009) have produced manganese-doped QDs as multimodal targeted probes for pancreatic cancer imaging. To determine the location of anti-claudin, anti-mesothelin, or anti-PSCA-coated QDs to pancreatic cancer cells, confocal spectroscopy was used. The use of Fe–Pt nanoparticles for fluorescence imaging and MRI was studied by Lai et al. (2012). Fe–Pt nanoparticles were formed by a method using high-temperature chemical reduction. The nanoparticles were then coated with silica using a microemulsion method to improve biocompatibility and bioconjugation. This made it easier to incorporate fluorescent dye fluorescein isothiocyanate (FITC) into the silica shell. The cytotoxicity of Fe–Pt and Fe–Pt/SiO_2/FITC nanoparticles was determined by MTT assay using a human cervical cancer cell line (HeLa) and was found nontoxic. Confocal laser microscopy was used to examine the intracellular localization of Fe–Pt/SiO_2/FITC nanoparticles in HeLa cells after staining with a red fluorescent dye, and the fluorescence was observed after 12 h of incubation. These results showed the potential use of Fe–Pt/SiO_2/FITC nanoparticles for dual fluorescence and MR imaging. In another study carried out by Zhang et al. (2016), fluorescent SNPs were developed for application in both in vitro and in vivo fluorescence bioimaging. They are easy to handle, biocompatible in nature, less toxic, and highly hydrophilic and exhibit good optical transparency. Due to these properties, SNPs are considered to be suitable substrates for the fabrication of fluorescent probes and thus can be used in the imaging of living cells.

15.3.6 Photoacoustic Imaging (PAI)

PAI is a new method that has taken the advantages of the same optical properties as that of fluorescence imaging. Tissues are firstly irradiated with visible or near-infrared light, resulting in adiabatic expansion, and thus pressure waves are produced, which in turn are measured and used to construct an image. In cases where depth of penetration is found lower and there is a lack of natural contrast between tissues, contrast agents in the form of various nanoparticles are used (Wu et al. 2014). Zerda et al. (2008) first took photoacoustic images in a tumor mouse model, using SWNTs as the contrast agent. Yang et al. (2010) studied four different types of nanoparticles that can be used as photoacoustic contrast agents in photoacoustic imaging. They focused mainly on gold nanoshells, gold nanorods, gold nanocages, and indocyanine green (ICG)-doped nanoparticles. Their studies found that among the four kinds of nanoparticles employed in PAI so far, nanorods were appropriate optical absorbers. Au nanocages also have similar optical absorption as Au nanorods. In addition, nanocages were found capable of encapsulating drugs and ICG-based nanoparticles, which depends on the fact that ICG is the FDA-approved dye for routine clinical use. Kim et al. (2009) reported the growth of GNPs on the surface of CNTs and utilized this conjugate as a photoacoustic contrast agent for in vivo imaging and for killing cancer cells via a photothermal effect. Chanda et al. (2011) explored the use of cinnamon phytochemicals as an AuNP capping agent to increase uptake of particles to cancer cells. The results showed linear photoacoustic response from untreated cells, while treated cells showed a time-variant signal, which indicates the particle uptake and particle contrast ability. In another study, Jing et al. (2014) used the fluorescent dye Prussian blue as a coating to enhance the photoacoustic signal. Testing of particles was carried out in agar gels as well as mice using a 765 nm laser. In the absence of tissue, high resolution was found, while an increasing loss of clarity was evident up to ~4.3 cm. Cheheltani et al. (2016) has encapsulated AuNP into polydi (carboxylatophenoxy) phosphazene (PCPP) nanospheres and found that the formulated particles exhibited high CT contrast, while the absorbable wavelengths can be adjusted changing the size or amount of AuNP. Photoacoustic imaging is an emerging field, and researchers use this as a guided technology for photodynamic therapy and photothermal therapy using different PA agents conjugated with different types of nanomaterials (Wang et al. 2016; Xie et al. 2016; Gao et al. 2017; Wu et al. 2017). Photoacoustic imaging is still a new modality imaging technique, further work on the use of different nanoparticles is being carried out to completely understand the parameters of photoacoustic imaging.

15.4 Conclusion

Nanomaterial drastically inflates the proficiencies of conventional methods of imaging owing to their high surface area, controllable size, and ease in surface functionalization. Different types of molecules including small organic dyes, radioisotopes, metal ions, inorganic nanoparticles, and even the source of microbubbles can be easily conjugated to allow an enhanced imaging performance with high stability of imaging agents before delivery to the target cells or organs. In the past few years, lots of studies have been done on the use of nanomaterial for bioimaging applications. However, most of studies are in their infancy stage within finite prospects, and only few have got clinical successes. For in vivo applications, the issues like biocompatibility, systemic toxicity, and unwanted accumulation in the body have to be considered. Imaging efficiencies are also an important factor for bioimaging, which can be improved by the conjugation of targeting ligands such as antibody and peptides, to secure high colloidal stability in the bloodstream. Thus, more efforts are still needed to be done in the near future for the promotion of nanomaterial advances in bioimaging applications.

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Chapter 16
Green Engineering of Silver Nanoparticles to Combat Plant and Foodborne Pathogens: Potential Economic Impact and Food Quality

Maluta Steven Mufamadi and Rofhiwa Bridget Mulaudzi

Contents

M. Mufamadi (✉)
NABIO Consulting (Pty) Ltd , Pretoria, 0183, South Africa

R. B. Mulaudzi
Agricultural Research Council (ARC),Vegetable and Ornamental Plants
Africa Private Bag X293, Pretoria, 0001, South Africa

Romukhu (Pty)Ltd, Doornpoort, Pretoria, 0186, South Africa

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16.1 Introduction

Plant diseases are the major economic burden in agricultural food production, caused by bacteria, viruses, and fungi. Most plant diseases, which are caused by bacteria, can cause severe economic damage from crop losses due to spots, mosaic patterns, or pustules on leaves and fruits leading to the death of plants. Some bacteria cause hormone-based distortion of leaves and shoots; others cause crown gall, which is a proliferation of plant cells that produces swelling at the intersection of stem and soil and roots (Nivas et al. 2016).

The use of synthetic chemicals has been found to be effective in controlling plant diseases; however, the use of these chemicals induces genetic resistance in fungal and bacterial populations and creates hazardous environment for both human beings and other flora and fauna because of their nonbiodegradable nature. Therefore, the protection of plants from pathogens remains a major concern of agricultural scientists. Technologies such as bacteriophages and systemic acquired resistance have been under investigation for several years to manage plant disease; these technologies have been showing promising outcomes in managing plant diseases (Obradovic et al. 2005; Huang et al. 2012). According to Ocsoy et al. (2013), bacteriophages pose a challenge to field conditions due to limited phage viability and the specific environmental requirements for their multiplication.

Economic losses arising from crop diseases caused by phytopathogenic organisms are principally associated with yield reductions affecting crop quality and safety as well as undermining both consumer confidence and profitability to the producers (Kavitha and Satish 2011). Control of plant diseases is very critical to the reliable production of food, and it provides significant reductions in agricultural use of land, water fuel, and other inputs (Pal and Gardener 2006). Integrated Pest and Disease Management (IPDM) has recognized the importance of medicinal plants and their derivatives (extracts, essential oils, and decoctions) in crop protection (Ragsdale 2000). The potential of medicinal plants as source for new botanicals, fungicides, or bactericides is still largely unexplored. Exploitation of naturally available chemicals from plants, which retards the reproduction of undesirable microorganisms, would be a more realistic and ecologically sound method for plant protection and will play a prominent role in the development of future commercial pesticides and crop protection strategies (Gottlieb et al. 2002).

According to Aromal and Philip (2012), plant crude extract contains novel secondary metabolites such as phenolic acid, flavonoids, alkaloids, and terpenoids in which these compounds are mainly responsible for the reduction of ionic into bulk metallic nanoparticle formation. Kuppusamy et al. (2016) reported that primary and secondary metabolites are constantly involved in the redox reaction to synthesize eco-friendly nanosized particles. Biological methods of nanoparticle synthesis using microorganisms, enzymes, fungi, and plants extracts have been suggested as possible eco-friendly alternatives to chemical and physical methods (Ponneerselvam et al. 2012; Prasad et al. 2016, 2018a; Abdel-Aziz et al. 2018). Synthesis of nanoparticles using plant extracts can be beneficial over other biological processes by eliminating the elaborate processes of maintaining microbial cultures (Ponneerselvam et al. 2012; Prasad 2014; Shankar et al. 2004).

Foodborne diseases encompass a wide spectrum of illnesses and are a growing public health hazard worldwide. They are the result of ingestion of foodstuffs contaminated with microorganisms or chemicals. Foodborne diseases have been noticed as serious threats to public health all over the world. In foodborne pathogen studies, four major pathogens have emerged significantly important in terms of human health and disease. These include *Escherichia coli* O157:H7, *Listeria monocytogenes*, *Salmonella typhimurium*, and *Vibrio parahaemolyticus.* These organisms have frequently been associated with food products and linked to a number of human illness cases (Zarei et al. 2014). The worldwide statistics on foodborne diseases published for 2011–2012 by the Centers for Disease Control and Prevention reported a total of 1632 outbreaks, 29,112 affected patients, 1750 hospitalizations, and 68 deaths. *Salmonella* (31%), *Listeria* (28%), *Campylobacter* (5%), and *Escherichia coli* O157:H7 (3%) pathogens are reported to cause some of the foodborne diseases and eventual death (Inbaraj and Chen 2016).

The impact of foodborne disease is a significant economic and clinical issue, despite recent advances in food safety (Billington et al. 2014). It has been concluded by Joint Food and Agriculture Organization/World Health Organization Expert committee on food safety that illness due to contaminated food was perhaps the most widespread health problem in the contemporary world and important cause of reduced economic productivity (Käferstein et al. 1997). Reducing the occurrence of foodborne illness through the use of rapid, cost-effective detection procedures and new ways to control pathogens are the focus of much current research (Billington et al. 2014).

Nanotechnology is an emerging field of interdisciplinary research that includes all spheres of science starting from physics, chemistry, biology, and especially biotechnology (Natarajan et al. 2010), which collectively describes the technology and science involving nanoparticles. Nanoparticles are a group of materials synthesized from a number of metals or nonmetal elements with distinct features and extensive applications in different fields of science and medicine (Matei et al. 2008). Nanoparticles also have potential biological applications, such as biosensing, catalysis, drug delivery, imaging, nanodevice fabrication, and for use as antimicrobial agents and in medicine (Ghosh et al. 1996; Geddes et al. 2003; Nair and Laurencin 2007; Jain et al. 2008; Sharma et al. 2009; Zargar et al. 2014; Prasad et al. 2016, 2018a, b; Patra and Baeke 2017).

Green synthesis of metal nanoparticles has been achieved using environmentally acceptable solvents from plant extracts has been achieved with the benefit of rapid, low-cost, eco-friendly, and a single-step method for biosynthesis process (Ponneerselvam et al. 2012; Huang et al. 2007). Plant extracts have recently been used for green synthesis of nanoparticles, since they are rich in bioactive compounds. The potential of biomolecules present in plant extracts to reduce metal ions to NPs in a single-step green synthesis process is very important (Benakashani et al. 2016). Several metal ions, such as Ag^+, Au^{3+}, Zn^{2+}, and Cu^{2+}, have been used to inactivate bacterial growth; among the different types of nanoparticles, Ag NPs have been used as effective biocides against a variety of pathogens, fungi, and viruses

(Ocsoy et al. 2013). Ag NPs release Ag^+ ions that interact with the thiol groups in bacterial proteins and affect the DNA replication, resulting in the destruction of bacteria (Marini et al. 2007). Additionally, nanoparticles have been shown to have potential antibacterial activity and significantly higher synergistic effects when applied with many antibiotics (Devi and Joshi 2018; Aziz et al. 2015, 2016).

This chapter reviews the latest research development and mechanism of action during green synthesis of silver nanoparticles (Ag NPs) utilizing of plants extract, the antimicrobial activity, and mechanism of action of Ag NPs against agriculture (phytopathogens) and foodborne pathogens. Second, the benefits of using green synthesis of Ag NPs as new antimicrobial agent are explored. Finally, we highlight the potential impacts of plant-mediated synthesized Ag NPs on agriculture and food sector and economic benefits in sub-Saharan Africa (SSA) countries.

16.2 Green Synthesis of Silver Nanoparticles Using Plant Extract

16.2.1 Plant Broth Preparation from Plant Extract

Different plant materials have been used for the preparation of plant broth for green synthesis of Ag NPs such as seeds, roots, stems, leaves, flowers, and fruits (Phanjom et al. 2012; Prasad 2014; Ahmed et al. 2016; Dhayalan et al. 2017; Khan et al. 2018).

In order to prepare plant broth for green syntheses of Ag NPs, the following simple steps have to be pursued:

- *Step 1*: Collection of plant materials is the first step for the preparation of plant broth from plant materials.
- *Step 2*: Washing step, part 1; in this step, plant materials are washed with tap water to remove epiphytes and necrotic plants. This process can be done twice or more.
- *Step3*: Washing step, part 2; this is another washing step; however, in this step, plant materials are washed with sterile distilled water in order to remove any debris or potential contaminants.
- *Step 4:* Drying stage; in this stage, materials are kept in the shade for 10–15 days until they dried; this is done in order to protect degradation of plant materials.
- *Step 5*: Preparation of plant extract/powder; in this step, plant materials are blended with domestic blender in order to obtain dried powder.
- *Step 6*: Preparation of plant broth; in order to prepare plant broth from dried powder, 10 g of powder or plant extract was boiled in 100 ml of deionized water or using sunlight as the primary source of energy.
- *Step 7*: Filtration; in this step all insoluble materials are filtered out using microfilter until all insoluble materials are no longer visible in the plant broth (Fig. 16.1).

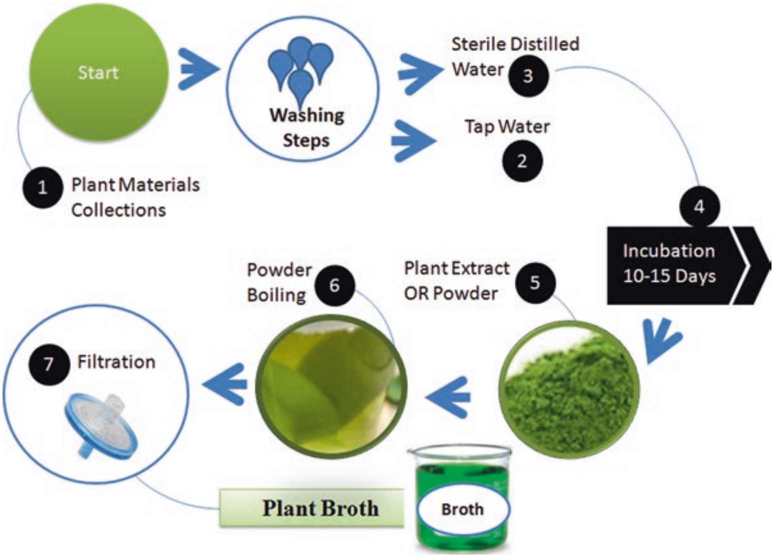

Fig. 16.1 Schematic illustration of seven (7) steps for preparation of plant broth from plant extract

16.2.2 Single-Step Method for Green Synthesis of Silver Nanoparticles Using Plant Extract

Green synthesis is a simple synthesis technique that utilizes microorganisms and plant extract to form metallic nanoparticles with different sizes and shapes. This technique does not require any chemical reducing agent for the formulation of metal nanoparticles, because they contain highly toxic substances (Roy and Das 2015).

Single-step technique for the synthesis process of Ag NPs involved the mixing 1 mM final concentration of silver nitrate ($AgNO_3$) solution and plant broth (plant extract) through magnetic stirrer at room temperature or using sunlight (Bindhani and Panigrahi 2015). The formation of Ag NPs is confirmed by color change in the mixture due to the reduction of pure Ag^+ ions to zero valent state Ag 0 just after 2–5 minutes (Fig. 16.2). UV-visible spectra analysis showed a strong surface plasma resonance and absorption property that confirmed the formation of nanoparticles. The shape, size, surface area analysis, morphology, oxidation state, and polydispersity of Ag NPs were characterized using various techniques such as dynamic light scattering (DLS), scanning electron microscopy (SEM), transmission electron microscopy (TEM), auger electron spectroscopy (AES), X-ray diffraction (XRD), low energy ion scattering (LEIS), energy dispersive spectroscopy (EDS), and Fourier-transform infrared spectroscopy (FTIR) (Kumar et al. 2007; Aguilar-Mendez et al. 2010; Banerjee et al. 2014; Park 2014; Bindhani and Panigrahi 2015; Lateefa et al. 2016; Joshi et al. 2007; Joshi et al. 2018).

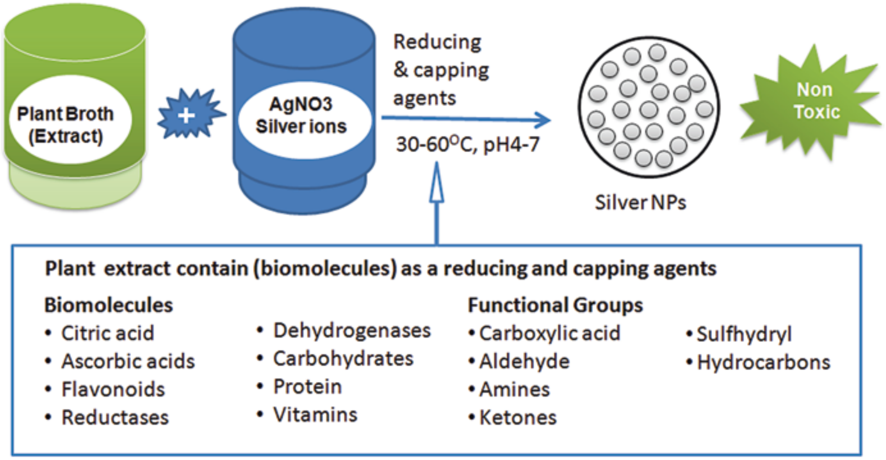

Fig. 16.2 Schematic illustration of green synthesis of silver nanoparticles from plant extracts (Gholami-Shabani et al. 2017)

16.2.3 The Mechanism of Silver Nanoparticle Synthesis Using Plant Extracts

The mechanism of synthesis of Ag NPs using plant extracts is influenced by biomolecules such as flavonoids, protein, vitamins, citric acid, ascorbic acids, carbohydrates, carboxylic acids, aldehydes, hydrocarbons, amides, and ketones (Fig. 16.2). The reduction of pure Ag (+) ions into Ag(0) nanoparticles is could be achieved by blending of silver ions together with plant extracts, which can act as reducing and stabilizing agents (Prabhu and Poulose 2012; Kulkarni and Muddapur 2014). A study conducted by Tran et al. (2013) showed that the presence of carbonyl group of amino acid and proteins facilitated the reduction and capping of metal ions to form Ag NPs that are very stable. Another study conducted by Makarov et al. (2014) showed that the presence of free aldehyde group of glucose used to facilitate ion reduction during the formation of Ag NPs. Roopan et al. (2013) indicated that the presence of hydrocarbons as a stabilizing agent influenced the formation of stable Ag NPs. The concentration of $AgNO_3$ and different experimental environments (e.g., temperature and pH) also shown to govern ion reduction process during nanoparticle synthesis. The temperature improves the reaction rate and efficiency of nanoparticle synthesis. Different pH values of the biomolecules from various plant extracts showed to influence capping process during nanoparticle formation (Makarov et al. 2014; Mohammadlou et al. 2016).

16.2.4 Green Synthesis Approaches to Synthesis of Silver Nanoparticles

Many plant extracts have been used for green synthesis of Ag NPs (Table 16.1), such as *Moringa oleifera* (Moodley et al. 2018), Buchu plant extracts (Chiguvare et al. 2016), stem bark hydrosol of *Acacia mearnsii* (Avoseh et al. 2017), root bark aqueous extract of *Annona muricata* Linn (Ezealisiji et al. 2017), plant extract from *Ziziphus spinachristi* and *Garcinia kola* (Abalaka et al. 2017), aqueous leaf extract of *Costus afer* (Elemike et al. 2017), and pod extract of *Cola nitida* (Lateef et al.

Table 16.1 Plant-mediated synthesis of silver nanoparticles

No.	Plants	Extracts	Size of NPs (nm)	Shape of NPs	References
1	*Moringa oleifera*	Leaf	9–11	Spherical	Moodley et al. (2018)
2	*Momordica charantia*	Stem	27.81 ± 1.64	Quasi-spherical	Akinsiku et al. (2018)
3	*Aloe vera*	Plant	3–14	Spherical	Vélez et al. (2018)
4	*Curcuma amada*		160–240	Spherical	Khairunnisa and Anjana (2018)
5	*Imperata cylindrica*	Leaf	22–37	Spherical	Bonnia et al. (2018)
6	*Ocimum tenuiflorum* (Tulsi)	Leaf	5–10	Spherical	Singh et al. (2018)
7	*Jatropha curcas*	Leaves	17.12 ± 2.9	Quasi-spherical	Francis et al. (2018)
8	*Hydnocarpus pentandra*	Leaf	141–202	Spherical	Kumar et al. (2018)
9	*Wedelia chinensis*	Leaf	31.68	Spherical	Das et al. (2018)
10	*Ocimum sanctum and Ocimum americanum*	Leaf	40–95	Spherical	Yadav et al. (2018)
11	*Coriandrum sativum*	Leaf	6.45	Spherical	Khan et al. (2018)
12	*Monotheca buxifolia*	Plant	40–78	Spherical	Anwar et al. (2018)
13	*Nelumbo nucifera* (Lotus)	Vegetable	12.9 ± 3.7	Quasi-spherical	He et al. (2018)
14	*Buddleja globosa*	Plant	16	Spherical	)
15	*Bacopa monnieri, Coleus blumei, Cichorium intybus*		40.3, 5.05, 3.16	Spherical	Badrelden et al. (2018)
16	*Phyllanthus acidus*	Leaf	65–250	Spherical	Sowmya et al. (2018)
17	*Echinochloa crus-galli* (waste grass)	Grass	15	Quasi-spherical	Khatami et al. (2018)
18	*Costus afer*	Leaf	20	Spherical	Elemike et al. (2017)
19	*Origanum vulgare*		2–25	Spherical	Shaik et al. (2018)
20	*Mint*	Leaf	26	Spherical	Aziz and Jassim (2018)
21	*Embelia ribes*	Seed	20–30	Spherical	Dhayalan et al. (2017)

(continued)

Table 16.1 (continued)

No.	Plants	Extracts	Size of NPs (nm)	Shape of NPs	References
22	*Agathosma betulina* (Buchu plant)	Leaf	19.95 ± 7.76	Spherical	Chiguvare et al. (2016)
23	*Thevetia peruviana*	Leaf	18.1	Spherical	Oluwaniyi et al. (2016)
24	*Pelargonium endlicherianum*	Root	Different size	Spherical	Karatoprak et al. (2017)
25	*Millettia pinnata*	Flower	16–38	Spherical	Rajakumar et al. (2017)
26	*Pedalium murex*	Leaf	50	Spherical	Anandalakshmi et al. (2016)
27	*Centella asiatica*	Leaf	3–30	Spherical	Vuong et al. (2017)
28	*Cerasus serrulata*	Leaf	10–50	Spherical	Karthik et al. (2016)
29	*Saraca indica*	Leaf	23 ± 2	Spherical	Perugu et al. (2016)
30	*Hydrocotyle asiatica*	Leaf	21	Spherical	Devi et al. (2016)
31	*Cucumis sativus*	Fruit	8–10	Spherical	Roy et al. (2015)
32	*Cydonia oblonga*	Leaf	38	Cubic	Zia et al. (2016)
33	*Euphorbia amygdaloides*	Plant	7–20	Spherical	Cicek et al. (2015)
34	*Trachyspermum ammi*	Seed	36	Cubic	Chouhan and Meena (2015)
35	*Emblica officinalis*	Fruit	10–70		Ramesh et al. (2015)
36	*Syzygium alternifolium*	Fruit	4–48	Spherical	Yugandhar et al. (2015)
37	*Eucalyptus globulus*	Leaf	1.9–4.3 and 5–25	Spherical	Ali et al. (2015)
38	*Phlomis*	Leaf	19–30	Spherical	Allafchian et al. (2016)
39	*Alpinia calcarata*	Root	5–15	Spherical	Pugazhendhi et al. (2015)
40	*Leptadenia reticulata*	Leaf	50–70	Spherical	Swamy et al. (2014)
41	*Ocimum sanctum*	Leaf	18	Spherical	Ramteke et al. (2013)
42	*Ixora coccinea*	Flower	5–10	Spherical	Nalvolthula et al. (2015)
43	*Psoralea corylifolia*	Seed			Sunita et al. (2014)
44	*Tithonia diversifolia*	Leaf			Tran et al. (2013)
45	*Memecylon edule*	Leaf	20–50	Hexagonal	Elavazhagan and Arunachalam (2011)
46	*Santalum album*	Leaf	80–200	Spherical	Swamy and Prasad (2012)
47	*Syzgium cumini*	Leaf	100–160	Spherical	Prasad et al. (2012)
46	*Syzgium cumini*	Bark	20–60	Spherical	Prasad and Swamy (2013)
47	*Nicotiana tabaccum*	Leaf	8		Prasad et al. (2011)
48	*Carissa Carandas*	Berry	10–60		Joshi et al. (2018)
49	*Trianthema decandra*	Root	10–50	Hexagonal	Geethalakshmi and Sarada (2010)

2016). Moodley et al. (2018) reported green synthesis of Ag NPs from the leaf extracts of *Moringa oleifera*. The study demonstrated the use of sunlight as the primary source of energy during the reaction mixture of 1 mM aqueous $AgNO_3$ and aqueous plant extract. The FTIR study confirmed the presence of biomolecules from the extract to be flavones, polysaccharides, and terpenoids. The biomolecules have been shown to be responsible for both reduction and capping of silver ions during the formation of Ag NPs. The formation of Ag NPs was confirmed by color change from initial reagent yellow solutions to dark brown mixture solution and validated by surface plasmon resonance peak between 450 nm and 440 nm. The nanoparticle sizes were confirmed by X-ray diffraction analysis and DLS and were found to have particle size ranging from 3 to 50 nm. Chiguvare et al. (2016) have reported a green synthesis of Ag NPs from Buchu plant extracts from South Africa. Phytochemical screening of the crude using FTIR revealed the presence of proteins, flavonoids, alkaloids, and saponins. The presence of phytochemicals facilitated the reduction of silver ions during the formation of Ag NPs. The TEM analysis confirmed the morphology of Ag NPs as spherical in shape and particles size in a range between 19.95 and 7.76 nm, respectively. Avoseh et al. (2017) demonstrated a rapid green synthesis of Ag NPs using stem bark hydrosol of *Acacia mearnsii* within 15 minutes at 60 °C. The presence of plant extract facilitated ion reduction and capping process during the formation of Ag NPs. TEM images confirmed that the presence of spherical Ag NPs with the diameter in the range of 19.95 ± 7.76 nm. Ezealisiji et al. (2017) also reported green synthesis of Ag NPs using the root bark aqueous extract of *Annona muricata* with an average particle size of 22 ± 2 nm. In this study, Malvern Nano ZS was used to reveal zeta potential of – 27.90 ± 0.01 mV, a negative surface charge, and the polydispersity index (PDI) of 0.44 ± 0.02. Abalaka et al. (2017) reported synthesis of Ag NPs using plant extract from *Ziziphus spinachristi* and *Garcinia kola.* The plant extract acted as reducing and capping agent; however, in this study, hyaluronic acid was added to enhance particle stability and to prevent aggregation during synthesis. The presence of nanoparticles, particle size, and shape was determined by TEM. Elemike et al. (2017) reported synthesis of Ag NPs employing aqueous leaf extracts of *Costus afer* with a mean diameter of 20 nm. Loo et al. (2012) reported the synthesis of Ag NPs using tea leaf extract of Chinese tea from *Camellia sinensis*, *with* a particle size of 4 nm. Lateef et al. (2016) demonstrated the synthesis of Ag NPs employing pod extracts of *Cola nitida*. The formation of Ag NPs was observed by the color change in the solution from yellow brown to dark brown. The presence of nanoparticles was confirmed by UV-visible spectroscopy and TEM images with a spherical shape and the diameter in a range between 12 and 80 nm. Yadav et al. (2018) reported the synthesis of spherical Ag NPs with a size ranging from 40 to 95 nm using leaf extract of *Ocimum sanctum* and *Ocimum americanum.* Sowmya et al. (2018) reported synthesis of Ag NPs from leaf extract of *Phyllanthus acidus.* The physicochemical characterization revealed the formation of Ag NPs with a spherical shape, and the average size ranged from 65 to 250 nm. Very recently, Singh et al. (2018) reported synthesis of Ag NPs using dried tulsi leaves. The catalytic activity during the formation of Ag NPs was evaluated through the reduction of 4-nitrophenol to 4-aminophenol in alkaline medium. The formation Ag NPs was revealed by UV-visible spectrum with peak at 430 nm and TEM image with the average diameter of 5–10 nm. The study conducted by Balashanmugam et al. (2016) showed synthesis of Ag NPs to be influenced by different physicochemical conditions. Highly stable Ag NPs were synthesized with 1.0 mL of *C. roxburghii* leaf extract and 1.0 mM AgNO3 (pH 7.0) at 37 °C. The synthesized Ag NPs were characterized by XPS, DLS, and ZETA potential. In DLS and ZETA potential analysis, the average size of Ag NPs was 35 nm, and the zeta potential was −18.3 mV. The studies by Chahardooli et al. (2014) showed green synthesis of Ag NPs characterized by UV-visible spectroscopy gave surface plasmon resonance for synthesized Ag NPs peak at 415–445 nm. Further, the Ag NPs showed an effective antibacterial activity toward plant pathogenic bacteria (*Pectobacterium carotovorum*, *Ralstonia solanacearum*, *Erwinia amylovora*, and *Xanthomonas citri*). The synthesized Ag NPs were characterized using UV-visible spectroscopy, dynamic light scattering spectroscopy (DLS), Fourier-transform infrared spectroscopy (FTIR), and scanning electron microscopy. The DLS study revealed the surface charge of the resulting nanoparticles that was highly negative, i.e., −25.0 ± 7.84 mV, and the size was 74.56 ± 0.46 nm. The phytochemical and FTIR analysis confirmed the role of water-soluble phyto-compounds for the reduction of silver ions to silver nanoparticles. The biosynthesized Ag NPs were characterized by UV-visible spectrophotometry with surface plasmon resonance at 450 nm followed by the analysis using scanning electron microscope, X-ray diffraction, Fourier-transform infrared spectroscopy, and thermogravimetric analysis.

16.2.5 The Advantages of Using Green Synthesis of Silver Nanoparticles

Metallic nanoparticle synthesis using green chemistry route has recently received a lot of attention as nanofactories over the conventional methods. The conventional methods such as chemical and physical synthesis involving toxic chemicals are harmful to humans and the environment (Patra and Baek 2014). The use of plant extracts and microorganisms toward biosynthesis of Ag NPs promises to overcome setbacks associated with conventional synthesis. Green synthesis for the formation of Ag NPs employs aqueous plant extracts as reducing and stabilizing agents during the synthesis of Ag NPs (Suna et al. 2014; Sadeghi and Gholamhoseinpoor 2015; Mohammadlou et al. 2016). This approach offers simplicity, rapid synthesis, and inexpensive biological procedure for nanoparticle fabrication and is environment friendly and nontoxic (Ahmed et al. 2016). Additionally, green synthesis approaches are easy to scale up for large-scale production of nanoparticles and are economically viable. Although plant and microbiological approach promises to overcome the setbacks associated with conventional methods during metallic nanoparticle synthesis, the use of plant extract during green synthesis is considered to be more advantageous and safer over microorganism approach. During metallic nanoparticle synthesis, plant extracts are able to reduce and cap metal ions faster than bacteria, fungi, and viruses (Iravani 2011). Additionally, microorganisms are associated with biohazards and have setbacks toward nanoparticle isolation and identification. The approach is not eco-friendly particularly toward maintaining cell culture processes for microorganisms (Kalishwaralal et al. 2010; Roy and Das 2015). The toxicity of Ag NPs is shown to influence the type of plant extract used and also by nanoparticle size, concentration, dosage, pH of the medium, and exposure time to pathogens (Banerjee et al. 2014; Das et al. 2018; Kumar et al. 2018). In addition, green synthesis of Ag NPs is biocompatible to the human cell line and nontoxic to mammalian cells (Ahmed et al. 2016). The study conducted by Balashanmugam et al. (2016) showed synthesis of Ag NPs to be influenced by different physicochemical conditions. Highly stable Ag NPs were synthesized with 1.0 mL of *C. roxburghii* leaf extract and 1.0 mM $AgNO_3$ (pH 7.0) at 37 °C. The synthesized AgNPs were characterized by XPS, DLS, and ZETA potential. In DLS and ZETA potential analysis, the average AgNPs size was 35 nm, and the zeta potential was −18.3 mV. Chahardooli et al. (2014) reported green synthesis of Ag NPs using *Protium serratum* leaf extract. UV-visible spectroscopy confirmed the formation of Ag NPs with surface plasmon resonance peak at 415–445 nm. The synthesized Ag NPs were characterized using UV-visible spectroscopy, dynamic light scattering spectroscopy (DLS), Fourier-transform infrared spectroscopy (FTIR), and scanning electron microscopy. The DLS study revealed the surface charge of the resulting nanoparticles that was highly negative, i.e., −25.0 ± 7.84 mV, and the size was 74.56 ± 0.46 nm. The phytochemical and FTIR analysis confirmed the role of water-soluble phyto-compounds for the reduction of silver ions to silver nanoparticles. The biosynthesized AgNPs were characterized by UV-visible spectrophotometry with surface plasmon resonance at 450 nm followed by the analysis using scanning electron microscope, X-ray diffraction, Fourier-transform infrared spectroscopy, and thermogravimetric analysis. The AgNPs displayed moderate antibacterial activity (9.26–11.57 mm inhibition zone) against all five foodborne pathogenic bacteria. Patra and Baeke (2017) reported biosynthesis of Ag NPs using the aqueous extract of corn leaf waste of *Zea mays*. Ag NPs were characterized by UV-visible spectrophotometry with surface plasmon resonance at 450 nm followed by the analysis using scanning electron microscope, X-ray diffraction, Fourier-transform infrared spectroscopy, and thermogravimetric analysis.

16.3 Plant and Foodborne Pathogens

Pathogenic microorganisms affecting plant health are a major and chronic threat to food production and ecosystem stability worldwide. As agricultural production intensified over the past few decades, producers became more and more dependent on agrochemicals as a relatively reliable method of crop protection helping with economic stability of their operations. However, increasing use of chemical inputs causes several negative effects, i.e., development of pathogen resistance to the applied agents and their nontarget environmental impacts (Compant et al.

2005). Foodborne pathogens are also posing a big threat to the public health and food security. Bacteria, fungi, viruses, and parasites are the main cause of foodborne disease worldwide. *Salmonella typhimurium*, *Escherichia coli, Listeria monocytogenes, Vibrio parahaemolyticus, Vibrio cholera, Pseudomonas aeruginosa,* and *Streptococcus pyogenes* are the major bacterial pathogens that cause foodborne illness. Current traditional antibacterial and disinfection agents are facing the challenge of bacterial resistance, which result in food spoilage and outbreaks with high mortality. *Escherichia coli* O157:H7 has been reported to be resistant to ampicillin and *Streptococcus pyogenes* resistant to erythromycin (Armstrong et al. 1996; Jay 2000; Lara et al. 2010). In the agriculture and food industry, microbial pathogens are threatening food production, food quality, and food security by failing to protect plant crops, maintaining food quality, and shortening food shelf life (Tareq et al. 2017; Prasad et al. 2017). Therefore, there is an urgent need to develop a new generation of antimicrobial agents that are effective against both plant and foodborne pathogens. In sub-Saharan Africa countries, where the economy of the majority of the countries is heavily dependent on agriculture and food production, and where there are no appropriate systems to deal with foodborne disease outbreaks or advanced analytical tools to analyze food samples, developing a new generation of antimicrobial agents is an issue of high priority. Ag NPs promise to overcome challenges associated with plant and foodborne pathogens by offering an effective antimicrobial agent that could protect crops, extend food shelf life, and maintain food quality for a longer period (Lara et al. 2010; Zandi et al. 2013; Rajeshkumar and Malarkodi 2014; Zarei et al. 2014; Tareq et al. 2017).

16.4 Antimicrobial Activity of Silver Nanoparticles on Plant and Foodborne Pathogens

Green synthesis of Ag NPs promises to offer an effective antimicrobial agent against plant and foodborne pathogens (Jo et al. 2009). According to Jo et al. (2009) and Conrad et al. (1999), silver particles display multiple modes of inhibitory action to microorganisms, it may be used for controlling various plant pathogens in a relatively safer way compared to synthetic fungicides (Park et al. 2006). Ag NPs exhibit new or improved properties depending upon their size, morphology, and distribution, which can be achieved through different (physical and chemical) methods that are employed for the synthesis of metal nanoparticles (Shankar et al. 2004; Panacek et al. 2006). Krishnaraj et al. (2012) tested the inhibitory effect of fungal plant pathogens, namely, *Alternaria alternata, Sclerotinia sclerotiorum, Macrophomina phaseolina, Rhizoctonia solani, Botrytis cinerea,* and *Curvularia lunata* using different concentrations of Ag NPs. Interestingly, 15 mg concentration of Ag NPs showed excellent inhibitory activity against all the tested pathogens. Thus, the obtained results clearly suggest that Ag NPs may have important applications in controlling various plant diseases caused by fungi. Balashanmugam et al. (2016) exhibit no antifungal activity using Ag NPs comparing with the conventional antifungal drug amphotericin B against all the tested plant fungal pathogens *R. solani, Fusarium oxysporum,* and *Curvularia* sp. Chahardooli et al. (2014) showed good antibacterial activity against the foodborne pathogens *Pseudomonas aeruginosa* (74.26 ± 0.14 μg/ml), *Escherichia coli* (84.28 ± 0.36 μg/ml), and *Bacillus subtilis* (94.43 ± 0.4236 μg/ml). This finding displayed the potential use of *Protium serratum* leaf extract as a good bioresource for the biosynthesis of Ag NPs and their implementation in diverse applications, specifically as antibacterial agent in food packaging and preservation to combat against various foodborne pathogenic bacteria (Mohanta et al. 2017). Menon et al. (2017) synthesized silver nanoparticles by using the medicinal plant *Acalypha indica*, which was characterized using various advanced tools with the help of UV-visible spectrophotometer. The food pathogen strain *Aspergillus fumigates* showed ZOI (Zone of inhibition) of 133% at 75 μl of concentration proving that Ag NPs can act effectively against this strain when compared to other strains even at low concentrations. The study concluded that Ag nanoparticle can be used for therapeutic purposes and for large-scale synthesis in food industries for food preservation or packaging. Patra and Baeke (2017) evaluated synthesized Ag NPs for their antibacterial activity against foodborne pathogenic bacteria (*Bacillus cereus* ATCC 13061, *Listeria monocytogenes* ATCC 19115, *Staphylococcus aureus* ATCC 49444, *Escherichia coli* ATCC 43890, and *Salmonella Typhimurium* ATCC 43174). The anticandidal activity of Ag NPs was evaluated against *Candida* species (*C. albicans* KACC 30003 and KACC 30062, *C. glabrata* KBNO6P00368, *C. geochares* KACC 30061, and *C. saitoana* KACC 41238). The AgNPs displayed moderate antibacterial activity (9.26–11.57 mm inhibition zone) against all five foodborne pathogenic bacteria. When Ag NPs were mixed with standard antibacterial or anticandidal agent, they displayed strong synergistic antibacterial (10.62–12.80 mm inhibition zones) and anticandidal activity (11.43–14.33 mm inhibition zones). The findings of Patra and Baeke highlighted the potential use of maize industrial waste materials in the synthesis of Ag NPs and their utilization in various applications, particularly as an antibacterial substance in food packaging, food preservation to protect against various dreadful foodborne pathogenic bacteria together with its biomedical, pharmaceutical-based activities. Chahardooli et al. (2014) displayed moderate antibacterial activity (9.26–11.57 mm inhibition zone) against all five foodborne pathogenic bacteria using green synthesis of Ag NPs using *Protium serratum* leaf extract.

Table 16.2 shows the effect of Ag NPs against other microbes. Emamifar et al. (2011) showed antimicrobial effect and improved preservation of orange juice storage for more than 112 days against bacteria strain, *Lactobacillus plantarum.* Min et al. (2009) showed sclerotial germination and growth inhibition against plant pathogens, *Sclerotinia minor* and *Sclerotinia sclerotiorum.* Mahdizadeh et al. (2015) showed mycelial growth inhibition caused by plant pathogen, *Macrophomina phaseolina.* Lara et al. (2010) exhibited bactericidal effect against multidrug-resistant bacteria, namely, *Listeria monocytogenes, Escherichia coli* O157:H7, *Salmonella typhimurium*, and *Vibrio parahaemolyticus*. Zarei et al. (2014) showed antibacterial effects on four important foodborne pathogens, namely, *Listeria monocytogenes, Escherichia coli*

Table 16.2 Effect of plant-mediated silver nanoparticles against plant and foodborne pathogens

Purpose	Pathogens	Microbial strain	Antimicrobial activity	References
Plant disease control *[Pathogens]*	*Macrophomina phaseolina*	Fungi	Mycelial growth inhibition	Mahdizadeh et al. (2015)
	Sclerotinia minor and *Sclerotinia sclerotiorum*	Fungi	Sclerotial germination and growth inhibition	Min et al. (2009)
	Bacillus megaterium	Bacteria	Effective against agricultural pathogens	Tareq et al. (2017)
Foodborne diseases control *[Pathogens]*	*Escherichia coli, Salmonella typhi,* and *Pseudomonas aeruginosa*	Bacteria	Antibacterial against foodborne and human pathogens	Abalaka et al. (2017)
	Listeria monocytogenes, Escherichia coli O157:H7, Salmonella typhimurium, and *Vibrio parahaemolyticus*	Bacteria	Antibacterial effects on four important foodborne pathogens	Zarei et al. (2014)
	Pseudomonas aeruginosa, Escherichia coli O157:H7, and *Streptococcus pyogenes*	Bacteria	Exhibited bactericidal effect against multidrug-resistant bacteria	Lara et al. (2010)
	Pseudomonas aeruginosa, Escherichia coli, and *Bacillus subtilis*	Bacteria	Act as antibacterial agent in food packaging and preservation	Mohanta et al. (2017)
	Lactobacillus plantarum	Bacteria	Showed antimicrobial effect and improved preservation of orange juice storage for more than 112 days	Emamifar et al. (2011)
	Aspergillus niger, Aspergillus flavus, Aspergillus fumigates	Fungi	Showed antifungicidal activity, and potential to use for food preservation and packaging	Menon et al. (2017)

O157:H7, Salmonella typhimurium, and *Vibrio parahaemolyticus.* Abalaka et al. (2017) demonstrated the antibacterial against both foodborne and human pathogens such as *Escherichia coli*, *Salmonella typhi, and Pseudomonas aeruginosa.*

16.4.1 Mechanisms of Action of Silver Nanoparticles on Microbial Pathogens

Silver ion is known to have microbial effect on a broad range of microorganisms (Bragg and Rainnie 1974; Brown and Smith 1976; Liau et al. 1997); however, the mechanisms of action of Ag NPs on microbes to cause the microbicidal effect is only partially understood (Richards 1981; Russell and Hugo 1994; Matsumura et al.

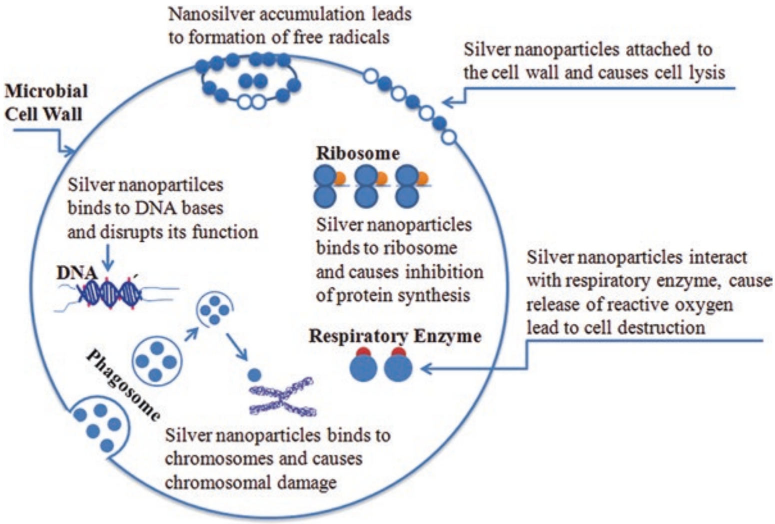

Fig. 16.3 Mechanism of action of Ag NPs on microbes (Prabhu and Poulose 2012)

2002; Morones et al. 2005; Kim et al. 2007; Feng et al. 2008; Dallas et al. 2011; Nasrollahi et al. 2011). Some hypotheses suggest that Ag NPs attached to cell wall cause cell lysis, resulting in structural damage, and cause disturbance to its proper functioning that can lead to the termination of microbial cell life (Rai et al. 2009). Figure 16.3 shows different bactericidal and fungicidal mechanisms using Ag NPs. The study by Morones et al. (2005) showed bactericidal effects employing Ag NPs with size range between 1 and 10 nm against *E. coli, P. aeruginosa,* and *S. typhus*. The study showed the accumulation of Ag NPs on the surface of the cell membrane leads to the formation of free radicals, which increased membrane permeability and make it porous resulting into cell death. In addition, Ag NPs were able to penetrate inside the bacteria and bind to DNA bases and disrupt bacteria functions such as DNA replication, respiratory chain, and cell division ultimately leading to cell death (Dallas et al. 2011; Aziz et al. 2014, 2015, 2016). Another study by Prabhu and Poulose (2012) showed another mechanism by which the cells die using Ag NPs; in this study, cell death was showed to be influenced by Ag NPs that bind to ribosome and cause inhibition of protein. Also, it was proposed that Ag NPs enter the cell membrane and interact with respiratory enzyme, cause release of reactive oxygen, and lead to cell damage (Inoue et al. 2002; Choi and Hu 2008). In another study by Kumar et al. (2017), it was proposed that Ag NPs enter into fungal cell membrane and nucleus through phagosome process, then binds to chromosomes and cause chromosomal damage. Many studies showed that the microbial properties of Ag NPs to be more effective and influenced by nanoparticle size. Nanoparticles with a diameter of 1–10 nm are shown to have direct interaction with the cellular components such as cell membrane, DNA, protein, enzymes, and chromosomes, and also have an effect on microbial growth ultimately leading to cell death.

16.5 The Potential Benefits of Using Green Synthesis of Silver Nanoparticles in Agriculture and Food Sectors

Applications of nanotechnology in agriculture and the food sector have many benefits. Nanotechnology has many potential benefits in improving food quality and safety, reduction of agricultural inputs, and enrichment of absorbing nanoscale nutrients from the soil (Prasad et al. 2017; Sangeetha et al. 2017a, b). Furthermore, Prasad et al. (2017), Gruère (2012), Mukhopadhyay (2014), Prasad et al. (2014) explain that agriculture, food, and natural resources are a part of those challenges like sustainability, susceptibility, human health, and healthy life; therefore, the importance of nanomaterials in agriculture is to reduce the amount of spread chemicals, minimize nutrient losses in fertilization, and increase yield through pest and nutrient management. In the food industry, Ag NPs promises to overcome the followings setbacks: disinfection during food processing, packaging materials, preservation, food additives, and supplements. In agriculture, nanomaterials can also be used to control agricultural pathogens and protect crops and seeds (Bhattacharyya et al. 2016; Ismail et al. 2017; Gupta et al. 2018). In healthcare, nanomaterials such as Ag NPs promised to impact in medical health device, diagnostic devices, and pharmaceuticals (Zandi et al. 2013). Microbial resistance to current antibiotics and disinfection agents resulting into food spoilage due to foodborne pathogens pose threat to the public health and food security. Therefore, there is an urgent need to develop a new generation of antimicrobial agents that are effective against foodborne pathogens (Parihar et al. 2008; Rajeshkumari and Malarkodi 2014; Zarei et al. 2014).

Green synthesis of Ag NPs are very much stable, environment friendly, biocompatible to the human cell line, and have a low systemic toxicity to humans (Ahmed et al. 2016; Aziz et al. 2019). In food industries, Ag NPs gain attention due to the excellent antimicrobial and antioxidant properties and have been used in food process, food packaging materials, preservation, and also as disinfectant agents. As a disinfectant agent, Ag NPs showed significant effect against foodborne pathogens such as *Escherichia coli* O157:H7, *Listeria monocytogenes*, *Salmonella typhimurium,* and *Vibrio parahaemolyticus* (Zarei et al. 2014). However, *L. monocytogenes,* Gram-positive bacteria, show some resistance against Ag NPs when compared to Gram-negative bacteria such as *E. coli* O157:H7. The study agreed with Kim et al. (2007) that suggested that the effect of Ag NPs as antibacterial agent could be influenced by differences in bacterial cell walls; Gram-negative bacteria have thin cell walls and Gram-positive bacteria have thick cell walls. In addition, Ag NPs could be used for cleaning equipments and surface areas in food-related environments. In the food packaging industry, the presence of Ag NPs showed to have bactericidal effect against foodborne pathogenic bacteria such as *Bacillus subtilis*, *Klebsiella planticola, Klebsiella pneumoniae, Serratia nematodiphila,* and *Escherichia coli* (Rajeshkumari and Malarkodi 2014). The study conducted by Rajeshkumari and Malarkodi (2014) showed the bactericidal effect against foodborne pathogenic bacteria such as *Bacillus subtilis*, *Klebsiella planticola, Klebsiella pneumoniae, Serratia* *nematodiphila,* and *Escherichia coli* at a high (750 μl) concentration of Ag NPs. As a result, Ag NPs could be used during surface coating of packing material to improve the lifespan of food products and ensure food safety by eliminating bacterial pathogens in food products. Zandi et al. (2013) showed improvement in food quality post-harvest, food preservation, and increased storage life for more than 10–12 days (Zandi et al. 2013). Emamifar et al. (2011) showed antimicrobial effect on the inactivation of *Lactobacillus plantarum* in orange juice stored in packaging materials made up of nanocomposite films containing Ag NPs over a period of 112 days. A recent study by Menon et al. (2017) showed the antifungal activity employing green-synthesized Ag NPs using plant extract against the food pathogens such as *Aspergillus niger, Aspergillus flavus* and *Aspergillus fumigatus.* The study showed significant maximum inhibition of *Aspergillus fumigatus* at 75 μl of Ag NPs. Due to antioxidant properties and fungicidal activity, green synthesis of Ag NPs have the potential to prevent food spoilage caused by foodborne pathogens such as fungi.

16.6 Nanotechnology in Agriculture and the Food Sector: Potential Economic Impact

As silver possesses antibacterial and antifungal properties, Ag NPs have been incorporated into more than 200 consumer products, including clothing, cosmetics, ceramics, car paints, and medical products. According to the Lux Research report 2015 estimates that nanoproducts to have markets value of USD 2.84 trillion (Lux Research 2004; Smith 2008). However, nanoproducts in the agrifood sector are facing challenges when it comes to consumer acceptance; this could be due to risks not clearly communicated to the consumers and uncertainty around nanomaterial toxicity.

In SSA, nanotechnology ensures to impact on low- and middle-income countries, particularly in agriculture and the food sectors. Majority of SSA countries' economics are heavily dependent on agriculture and food production. However, agricultural pathogens affecting plant health and foodborne pathogens are associated with food wastage, which posed threat to food production, quality, food security, and Africa's economic growth (Cozzini et al. 2008; Kiaya 2014). The report compiled from national workshop by Nanotechnology Research Group at Nigeria's Ladoke Akintola University of Technology indicates that inadequate funding on nanotechnology research is a major challenge for nanotechnology development in Africa. In addition, the report also indicates that African countries are too slow in embracing nanotechnology despite the potential benefits it has toward the continent (Rateng 2017). Therefore, African countries need urgently to look at their nanotechnology strategies in order to strengthen Africa's competitive position in nanotechnology and in order improve the food quality and improve their economy.

16.7 Conclusion

Plant and foodborne diseases pose immense threat to the agricultural food production, food quality, and economic growth for developing countries, particularly for regions such as SSA. Nanotechnology is an emerging technology that is promising to the development of a new generation of antimicrobial agents to fight and prevent disease at atomic scale and molecular level. The use of Ag NPs as a new generation of antimicrobial agents enables the inhibition of harmful pathogens to grow, multidrug-resistant bacteria, antioxidant property, improve food quality, packaging, storage, and plant disease control. The generation of Ag NPs using plant extracts promises to offers inexpensive, rapid, environment friendly, and biocompatible to human cell line and low systemic toxicity to humans. In addition, green synthesis approaches are easy to scale up for large-scale production of nanoparticles. Although, green synthesis promises nanotherapy with low toxicity, there is a need for the analysis of commercial viability and economic value associated with the use of nanoparticles generated through plant extracts. Further, in-depth study on the mechanism of action and the properties of Ag NPs against antibacterial and antifungal agents in the mammalian immune system is required. SSA countries need to begin prioritizing on nanotechnology in order improve their agricultural food production and food quality and for their economic growth.

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