MINI-REVIEW

Biological synthesis of metallic nanoparticles (MNPs) by plants and microbes: their cellular uptake, biocompatibility, and biomedical applications

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Abstract

Metallic nanoparticles (MNPs) with their diverse physical and chemical properties have been applied in various biomedical domains. The increasing demand for MNPs has attracted researchers to develop straightforward, inexpensive, simple, and eco-friendly processes for the enhanced production of MNPs. To discover new biomedical applications first requires knowledge of the interactions of MNPs with target cells. This review focuses on plant and microbial synthesis of biological MNPs, their cellular uptake, biocompatibility, any biological consequences such as cytotoxicity, and biomedical applications. We highlighted the involvement of biomolecules in capping and stabilization of MNPs and the effect of physicochemical parameters particularly the pH on the synthesis of MNPs. Recently achieved milestones to understand the role of synthetic biology (SynBiol) in the synthesis of tailored MNPs are also discussed.

Keywords Plant and microbial synthesis · Metallic nanoparticles · Biocompatibility · Cellular uptake · Cytotoxicity · Biomedical applications

Introduction

Different physiochemical methods including aerosol technologies, laser ablation, ultraviolet irradiation, lithography, photochemical reduction, and ultrasonic have been developed for the synthesis of metallic nanoparticles (MNPs), which require the use of reactive and toxic chemicals causing disruptive effects on the ecosystem. Therefore, scientific community is continuously trying to develop environment friendly, cost-efficient, and straightforward biological processes for the synthesis of MNPs. Like other scientific endeavors, inspiration has been taken from nature where different forms of nanostructures such as encapsulin, dodecameric (Dps), and ferritins

are performing vital role in biomineralization of metals. Richard Feynman described the basic idea of nanotechnology in a lecture entitled "there is plenty of room at the bottom" at the American Institute of Technology in 1959. MNPs vary in their physicochemical properties with the variation in size from 0.1–1000 nm. Generally, MNPs are synthesized using two approaches including bottom-up and top-down (Fawcett et al. 2017; Schöbel et al. 2017; Zhang and Liu 2017). In the bottom-up approach, atoms and molecules assemble to form nanostructures, whereas in the top-down approach, bulk materials are broken down to nano-sized particles (Fig. 1). Preferably, the bottom-up approach has been practiced for the biological synthesis of MNPs.

Biological synthesis of MNPs by using microbes and plants is simple, straightforward, and eco-friendly approach (Varma 2012; Zeth et al. 2016). The use of unicellular microorganisms and multicellular plant tissue extracts for the synthesis of MNPs has been reported as a facile and inexpensive approach (Maliszewska 2011; Ovais et al. 2018; Rajesh et al. 2012). Microorganisms can produce MNPs both intracellularly as well as extracellularly. However, extracellular synthesis of MNPs is easy and cost-efficient. Unicellular magnetotactic bacteria are known for their natural ability to produce magnetite (Fe_3O_4) (Descamps et al. 2016; Marcano et al. 2017).

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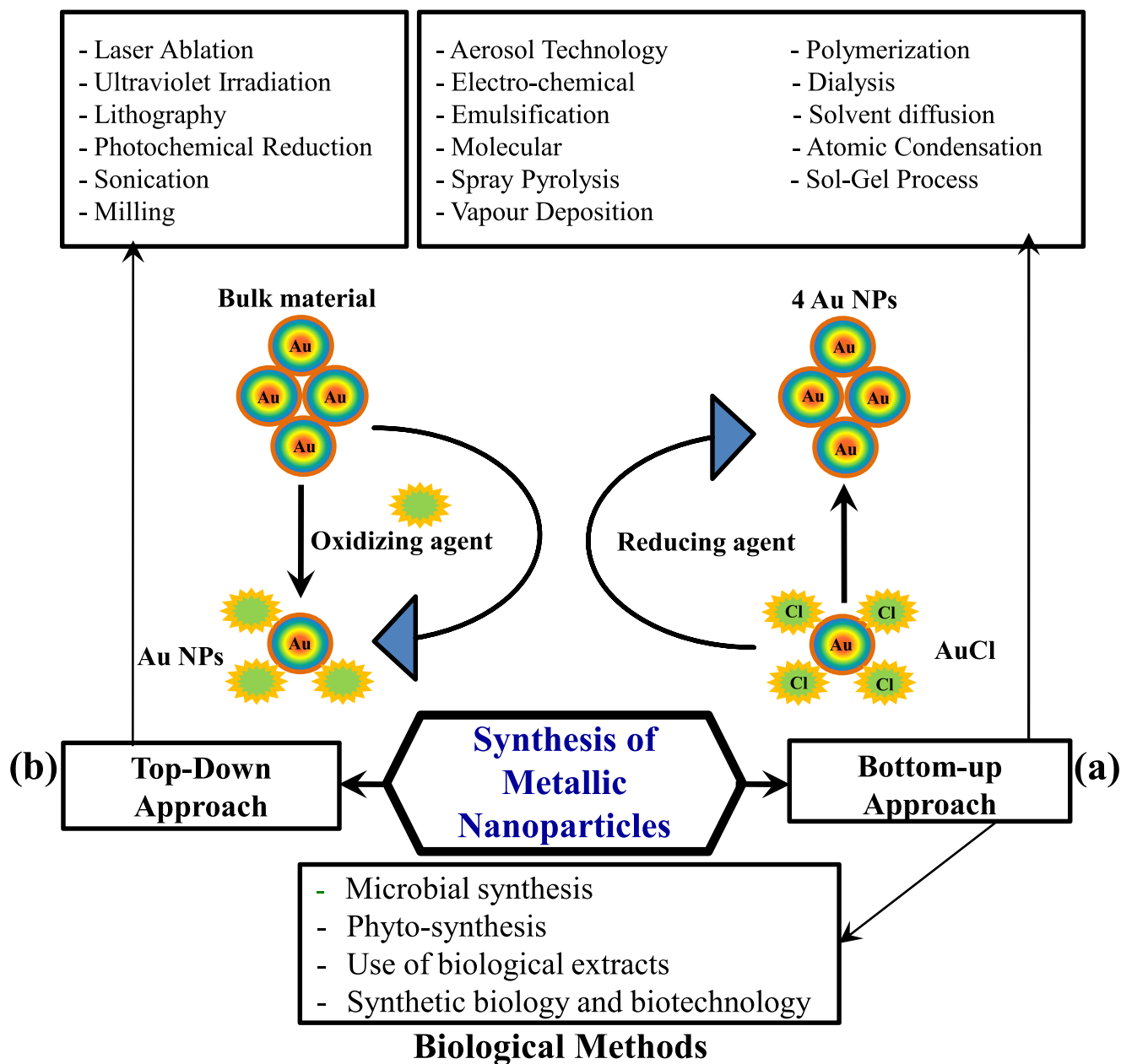
Physicochemical Methods

- Laser Ablation
- Ultraviolet Irradiation
- Lithography
- Photochemical Reduction
- Sonication
- Milling

- Aerosol Technology
- Electro-chemical
- Emulsification
- Molecular
- Spray Pyrolysis
- Vapour Deposition

- Polymerization
- Dialysis
- Solvent diffusion
- Atomic Condensation
- Sol-Gel Process

Bulk material

4 Au NPs

Oxidizing agent

Reducing agent

Au NPs

AuCl

Synthesis of Metallic Nanoparticles

(b) **Top-Down Approach**

Bottom-up Approach **(a)**

- Microbial synthesis
- Phyto-synthesis
- Use of biological extracts
- Synthetic biology and biotechnology

Biological Methods

Fig. 1 The (**a**) bottom-up and (**b**) top-down approaches for the synthesis of metallic nanoparticles (MNPs) using conventional physiochemical and relatively new eco-friendly biological methods

Also, the extract of different plant tissues has been extensively used for the synthesis of MNPs (Ankamwar et al. 2017; MubarakAli et al. 2011). Plant and microbial-mediated synthesis of MNPs is a bottom-up approach where oxidation and reduction are the two principle reactions involved in the formation of nanoparticles. Biomolecules such as proteins, phenolic compounds, sugars, polysaccharides, and others are considered to be responsible for the conversion of charged metallic ions to their zero-valent nano-forms (Ovais et al. 2018).

Even though many advancements have been made in the synthesis and use of MNPs, much is yet unknown about the toxicity induced by MNPs. Based on the available knowledge, the use of biologically synthesized MNPs in biomedical sciences is safer than those produced by traditional physicochemical approaches (Ahmed et al. 2016; Duan et al. 2015). The better biocompatibility of BMNPs is due to the encapsulation of metallic core of the nanoparticles with non-toxic biomolecules. Due to this reason, synthesis of MNPs using biological and biotechnological approaches opened a new paradigm for the production of biocompatible, non-toxic, reproducible, easy scaling-up, and well-defined nanostructures. In the recent era, there is a growing interest among the scientific

community to develop synthetic biology (SynBiol) techniques to produce tailored BMNPs (Giessen and Silver 2016; Maddinedi et al. 2017; Roopan et al. 2013). Furthermore, metabolic alleyways can be designed, assembled, and integrated within a cell using biotechnological tools. Specifically, microorganisms, plants, and nonhazardous biocompatible agents (Mirzaei and Darroudi 2017; Narayanan and Sakthivel 2010; Wang et al. 2017) having biogenic origin have been explored as a potential resource for the biosynthesis of MNPs (Fig. 2).

This review provides ease for the readers to understand the process of plant and microbial synthesis of biological MNPs and the effect of experimental factors affecting the process. Recently, the role of synthetic biology in the synthesis of tailored MNPs has been described. We highlighted existing knowledge regarding interaction of MNPs with cells, in particular, how the unique properties of MNPs influence their cellular uptake and cytotoxicity. Furthermore, biocompatibility of plant and microbe-assisted synthesized biological MNPs with their biomedical applications has been elaborated.

Microbial synthesis of MNPs

Microbes have immense potential for the synthesis of environmentally benign MNPs, without using conventional physical as well as chemical approaches. Microbes have the capability biomineralized inorganic minerals either intracellularly or extracellularly to produce materials of different size and morphologies at nano-scale (Fig. 3). Microbes are ubiquitously present that can quickly acclimatize themselves in the environment and show resistance to the toxic metals. Microbial

resistance against toxic metals is based on two basic approaches: (1) chemical detoxification and (2) ionic efflux from the cell that might be concentration gradient or energy dependent. These functions are actively carried out by the membrane proteins functioning as chemiosmotic cations, ATPase, and anti-transporters. Microbes can produce MNPs both intracellularly as well as extracellularly. Briefly for the extracellular synthesis of MNPs, under optimum conditions, targeted microbe is grown in a rotary shaker for 1–2 days, the biomass is removed through centrifugation, and the supernatant is collected. Subsequently mixing the filter-sterilized metallic salt solution and cell-free culture supernatant in a particular ration followed by incubation at optimal temperature will produce MNPs. Contrastingly, for the synthesis of intracellular MNPs, the microbial biomass is collected after centrifugation following thorough washing with sterilized water, then the biomass is dissolved in a filter-sterilized metallic salt solution. The reaction mixture is incubated and monitored for a visual change of the color. After repeated cycles of sonication, the biomass is removed by centrifugation and the synthesized MNPs are measured using a UV-spectrophotometer. Ultrasonication helps to break the microbial cell wall/membrane and allow the MNPs to move out of the cell. Extracellular synthesis of MNPs is considered as an inexpensive, rapid, and scalable approach because it eliminates the processing steps, including sonication, centrifugation, and washing required in the case of intracellular synthesis and recovery of MNPs.

Microbes, including fungi, yeast, virus, and bacteria have been studied for intra- and extracellular synthesis of MNPs (Table 1) (Chen et al. 2015; Priyadarshini et al. 2013). Recently, different bacterial types such as *Vibrio*
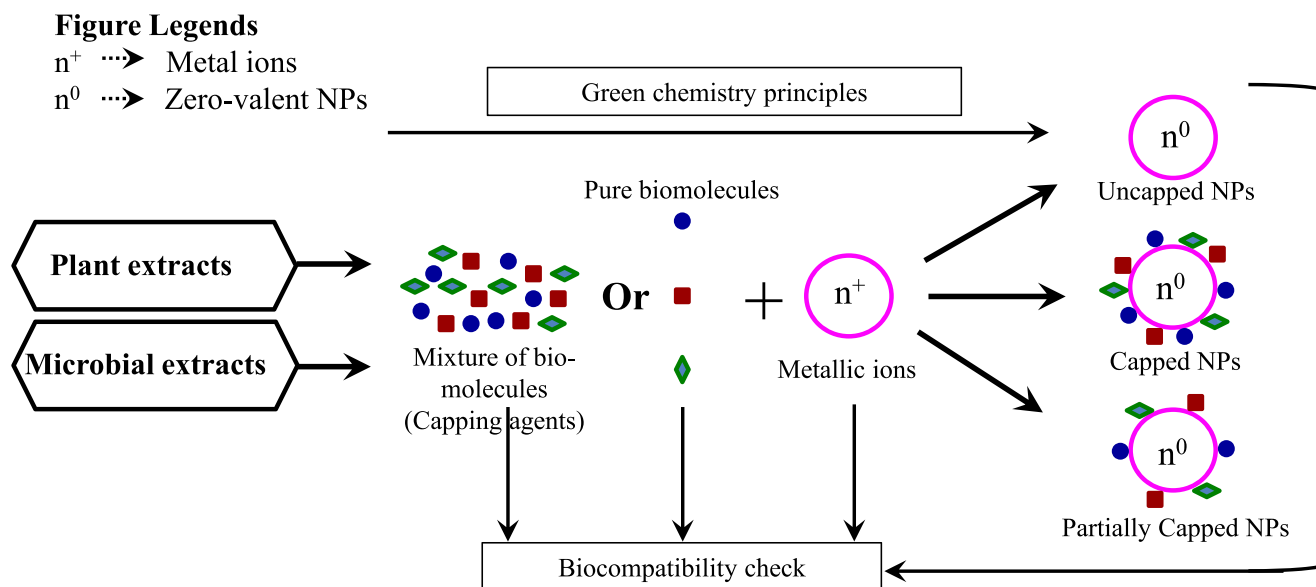

Figure Legends
n⁺ ┅➤ Metal ions
n⁰ ┅➤ Zero-valent NPs

Fig. 2 A step-by-step description of plant and microbial synthesis of MNPs. Different forms of synthesized MNPs and stages where demonstration of biocompatibility tests is essential
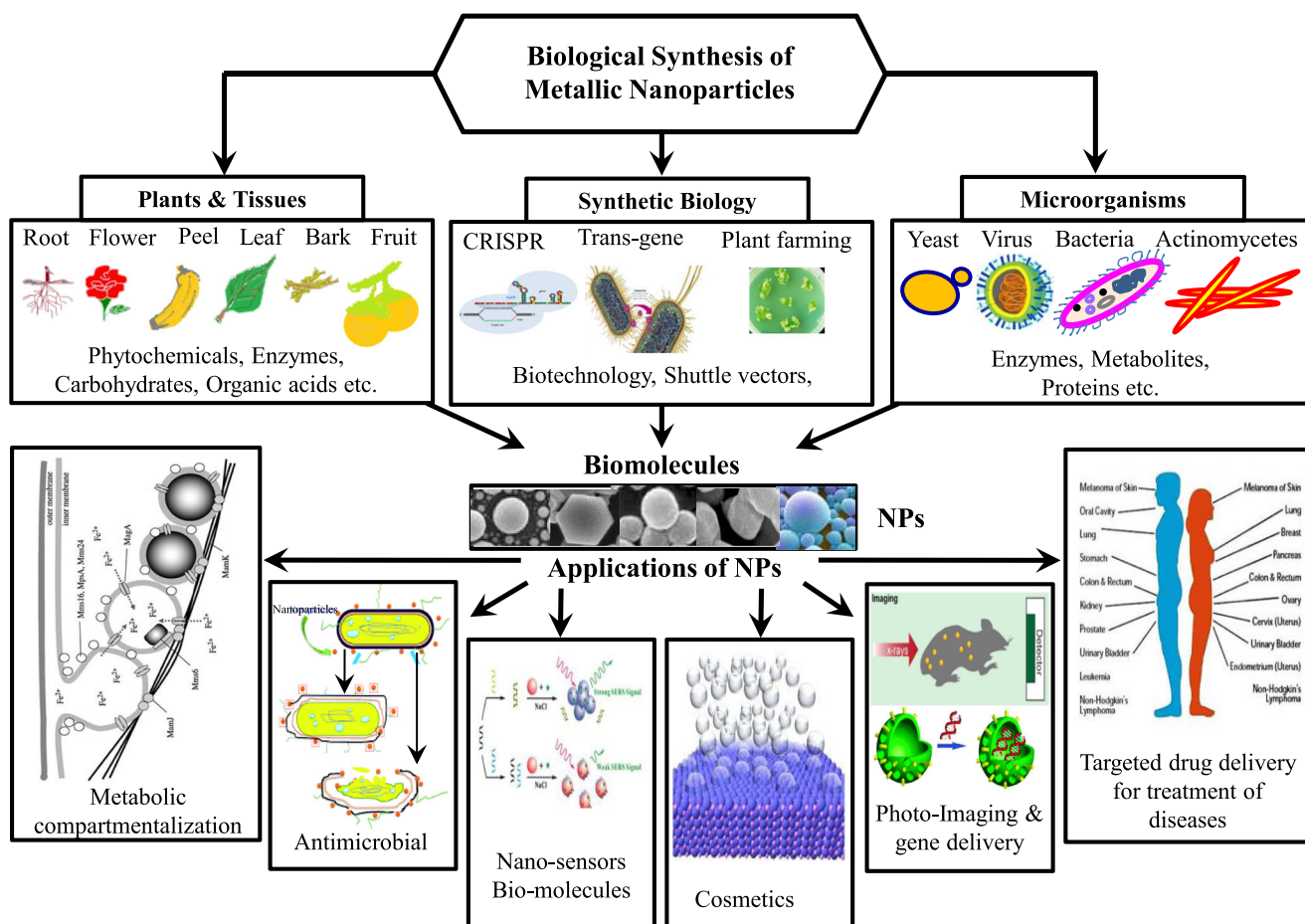
Fig. 3 Synthesis of MNPs through microbes, plants, and synthetic biology and their biomedical applications

parahaemolyticus (Elayaraja et al. 2017), *Bacillus methylotrophicus* (Wang et al. 2016), *Pseudomonas deceptionensis DC5* (Jo et al. 2016), *Rhodococcus* spp. (Otari et al. 2015), and *Shewanella oneidensis* MR-1 (Ishiki et al. 2017) have been studied for the synthesis of gold and silver NPs. Similarly, some reports have been published showing the potential of *Bacillus flexus*, *Staphylococcus lentus*, *Escherichia coli*, *Magnetospirillum gryphiswaldense*, and *Rhodospirillum rubrum* to produce MNPs (Apte et al. 2016; Das et al. 2014; Kushwaha et al. 2015; Priyadarshini et al. 2013). Furthermore, SynBiol represents a step forward for biotechnologically sustainable production of tailored MNPs (Lin et al. 2012) such as magnetite (Fe$_3$O$_4$) nanostructures (Kolinko et al. 2014). A range of bacterial genera including *Lactobacillus*, *Brevibacterium*, *Pseudomonas*, *Rhodobacter*, *Weissella*, *Rhodococcus*, *Bacillus*, *Corynebacterium*, *Pseudomonas*, *Aeromonas*, *Klebsiella*, *Enterobacter*, *Escherichia*, *Shewanella*, *Streptomyces*, *Sargassum*, *Trichoderma*, *Rhodopseudomonas*, *Desulfovibrio*, *Plectonema boryanum*, and *Pyrobaculum* have been reported for the synthesis of MNPs (Li et al. 2011).

Mycosynthesis of MNPs has been explored by utilizing diverse metabolites of fungi showing enhanced oxidation/reduction potential and better bioaccumulation potential with

straightforward eco-friendly method (Castro-Longoria 2016; Kashyap et al. 2017; Kitching et al. 2016). Three different phenomena including electron shuttle quinones, the activity of nitrate reductase, and the combination of both have been reported for the myco-mediated synthesis of MNPs (Alghuthaymi et al. 2015). Different enzymes such as nitrate reductase in case of *Penicillium* sp. and NADPH-dependent reductases of *Fusarium oxysporum* have been reported for the formation of different MNPs (Kumar et al. 2007). Although, few reports are available showing the involvement of actinomycetes in the formation of MNPs (Sanjenbam et al. 2014). However, there is room to explore the potential of actinomycetes for the synthesis of stable and monodispersed MNPs. Synthesis of copper, zinc, and silver NPs using reductase enzyme obtained from *Streptomyces* sp. have been reported for the synthesis of MNPs (Undabarrena et al. 2017). The yeast has also been studied for the synthesis of MNPs on a large scale with simple downstream methods (AbdelRahim et al. 2017; Apte et al. 2013; Barabadi et al. 2017; Mourato et al. 2011; Waghmare et al. 2015; Yang et al. 2016).

Tobacco mosaic virus (TMV)-mediated synthesis of iron oxide were achieved due to the involvement of amino acids such as aspartate, and glutamate present on the external

Table 1 Microbial synthesis of metallic nanoparticles (MNPs) and their applications

Microorganism	MNPs	Place of MNPs synthesis	Size of the MNPs	Morphology of the MNPs	Applications of the MNPs	Reference
Bacteria						
V. parahaemolyticus	Silver	Extracellular	200 nm	Cubic- and spherical shapes	Antivibriocidal activity against shrimp pathogens	(Elayaraja et al. 2017)
Bacillus licheniformis Mo9	Silver NPs	Extracellular	10–30 nm	Spherical	Antibacterial, dye degradation	(Momin et al. 2019)
Bacillus methylotrophicus	Silver	Extracellular	10–30 nm	Spherical	Antimicrobial activity	(Wang et al. 2016)
Aeromonas hydrophila	ZnO	ND	57.72 nm	Spherical, irregular edges	Antibacterial and antifungal	(Jayaseelan et al. 2012)
Rhodococcus sp.	Silver	Intracellular	5–50 nm	Spherical	Bactericidal and bacteriostatic activity	(Otari et al. 2015)
Shewanella oneidensis MR-1	Gold	Extracellular	10 nm	Spherical	Antibacterial	(Ishiki et al. 2017)
Bacillus sp.	Silver	In periplasmic space and on surface of the cell	5–15	Spherical	ND	(Pugazhenthiran et al. 2009)
Bacillus flexus	Silver	Extracellular	12 and 65 nm	Spherical, triangular	Antibacterial activity against clinical pathogens	(Priyadarshini et al. 2013)
Bacillus sp.	Silver	Extracellular and intracellular	42–92 nm	Spherical	Antibacterial	(Das et al. 2014)
Fungus						
Rhizopus oryzae	Gold	Extracellular	16–52 nm	Spherical and flower like	Biomedical	(Kitching et al. 2016)
Fusarium oxysporum	Silver	Extracellular	5–15 nm	Variable (spherical and triangular)	ND	(Ahmad et al. 2003a)
Macrophomina phaseolina	Ag/AgCl	Extracellular	5–30 nm	Spherical	Bactericidal	(Spagnoletti et al. 2019)
Aspergillus fumigatus	Silver	Extracellular	5–25 nm	Spherical and triangular	ND	(Bhainsa and D'Souza 2006)
Actinomycetes						
Streptomyces sp. VITPK1	Silver	Extracellular	20–45 nm	Rectangular	Antifungal against *Candida* species	(Sanjenbam et al. 2014)
Rhodococcus sp.	Gold	Intracellular	5–15 nm	ND	ND	(Ahmad et al. 2003b)
Yeast						
Rhizopus stolonifer	Silver	Extracellular	2.56–3.06 nm	Cubic	Antibacterial	(AbdelRahim et al. 2017)
Yeast strain MKY3	Silver	Extracellular	2–5 nm	Circular and hexagonal	ND	(Kowshik et al. 2002)
Rhodotorula sp. strain ATL72	Silver	ND	8.8–21.4 nm	Spherical and oval	Antibacterial and antifungal	(Soliman et al. 2018)
Candida utilis NCIM 3469	Silver	Extracellular	20–80 nm	Spherical	Antibacterial	(Waghmare et al. 2015)
Yarrowia lipolytica NCYC 789	Silver	Extracellular	15 nm	Spherical	Antibiofilm	(Apte et al. 2013)
Extremophilic yeast	Silver and gold	Extracellular	Silver, 20 nm; gold, 30–100 nm	Irregular	Antibiofilm	(Mourato et al. 2011)
Virus						
Tobacco mosaic virus	SiO_2, Fe_2o_3, CdS, and PbS	On surface	CdS, 5 nm: PbS, 30 nm: Fe_2o_3, 2 nm	Disordered, prismatic and film respectively	ND	(Shenton et al. 1999)

Table 1 (continued)

Microorganism	MNPs	Place of MNPs synthesis	Size of the MNPs	Morphology of the MNPs	Applications of the MNPs	Reference
Cowpea mosaic virus (CPMV)	Cobalt, nickel, iron, platinum, cobalt-platinum, and nickel-iron	On surface	≤35 nm	ND	ND	(Aljabali et al. 2010)
Tobacco mosaic virus (TMV)	Nickel and Cobalt	Central channel	3 nm	Nanowires	ND	(Knez et al. 2003)
M13 bacteriophage	Titanium oxide	On surface	2–40 nm	Wire film	Mesoporous Semiconducting networks	(Chen et al. 2015)

ND not determined

surface of the virus (Shenton et al. 1999). The capsids of genetically engineered viruses were also investigated as biotemplates for the synthesis of nanostructures of titanium and quantum dot nanowires (Chen et al. 2015). Furthermore, some biological molecules such as amino acids, polyphosphates, and fatty acids were applied as a template for the synthesis of semiconductor nanoparticles. Some other biological approaches are also available for green synthesis of nanostructures, including protein cages (Palchoudhury et al. 2017; Uchida et al. 2015), DNA (Lodha et al. 2017; Vial et al. 2017), biolipid cylinders (Charcosset 2016), multicellular superstructures (Mann et al. 1997), and viroid capsules (Chen et al. 2015), which have been applied for the template-mediated formation of MNPs.

Phyto-mediated synthesis of MNPs

Phytonanotechnology is also an environment friendly, rapid, cost-effective, stable, and straightforward approach for the synthesis of MNPs (Fig. 3). Phytonanotechnology has many advantages such as the use of a universal solvent (water) as a reducing medium, scalability, biocompatibility, lack of pathogenicity, and medical applicability of phyto-synthesized MNPs (Noruzi 2015). Thus, the non-toxic nature of plant-derived materials seems to be suitable to accomplish the high demand for the synthesis of MNPs with applications in biomedical areas. Gold and silver NPs were successfully synthesized by using fruit, leaf, root, and bark extracts of aquatic and herbal plants (Ankamwar et al. 2017; Mittal et al. 2013; Salari et al. 2016; Singh et al. 2016). Different plant tissues, such as roots, stems, bark, leaves, flowers, fruits, and seed extracts have been exploited for the synthesis of various MNPs (Table 2) (Bankar et al. 2010; Dhand et al. 2016; Edison et al. 2016; Gogoi et al. 2015; Jafarirad et al. 2016; Malaikozhundan et al. 2017; Mo et al. 2015; Murugan et al. 2015; Rajakumar et al. 2017; Rajan et al. 2017; Rao et al. 2016; Tahir et al. 2017; Wang et al. 2014).

The process of phyto-mediated synthesis of MNPs is simple and proceeds from washing the plant tissues, cutting into small pieces, crushing, and heating in boiling water to extract plant biomolecules out of the cell. Subsequently, purification of the extract can be performed through centrifugation and filtration process. Synthesis of MNPs can be carried out by mixing the metallic salt solution and plant extract in particular ratios followed by incubation of the reaction mixture at ambient temperatures. The change in color of the reaction mixture is the visual indication of MNP synthesis. Usually, red-colored gold and transparent silver salt solutions change to purple and brown respectively when mixed with plant extracts. Synthesized MNPs can be extracted out of the solution through centrifugation of the nanoparticles suspension at high-speed such as 22,000-24,000g for 30 to 40 min. Unreacted metallic ions and small biomolecules can be removed

Table 2 Plant-mediated synthesis of metallic nanoparticles (MNPs) and their applications

Type of the plant	MNPs	Plant tissues used to prepare an extract	Size of the MNPs	Morphology of the MNPs	Applications of the MNPs	Reference
Fruit peel extract						
Banana	Gold	Peel	300 nm	Disordered spherical and wires	Antimicrobial	(Bankar et al. 2010)
Annona squamosa	TiO$_2$	Peel	23 ± 2	Spherical	ND	(Roopan et al. 2012)
Mango	Silver	Peel	7–27 nm	Cubic	Antibacterial onto non-woven fabrics	(Yang and Li 2013)
Solanum melongena	Gold and silver	Peel	AuNPs = 29 nm, AgNPs = 92.4 nm	Spherical	Antibacterial property of AgNPs	(Das and Bhuyan 2019)
Fruit extract						
Aqueous Cordia myxa	Gold	Fruit	20–50 nm	Pentagonal, hexagonal, and icosahedron	Medical	(Ankamwar et al. 2017)
Rosa canina	Zinc oxide	Fruit	11.3–13.3 nm	Spherical	Antibacterial and biomedical application	(Jafarirad et al. 2016)
Tanacetum vulgare	Silver and gold	Fruit	10–40 nm	Spherical, triangular, and hexagonal	ND	(Dubey et al. 2010)
Flower extract						
Millettia pinnata	Silver	Flower	48.1–49.8 nm	Spherical	Cytotoxicity and antibacterial activity	(Rajakumar et al. 2017)
Nyctanthes arbortristis	Silver	Flower	20 nm	Spherical	Antioxidant and antibacterial activity	(Gogoi et al. 2015)
Leaf extract						
Cymbopogon citratus	Gold	Leaf	20–50 nm	Triangular, spherical, rod, and hexagonal	Mosquitocidal	(Murugan et al. 2015)
Mukia maderaspatana	Silver and Gold	Leaf	Silver: 20 nm, gold: 50 nm	Spherical	Antimicrobial	(Devi et al. 2017)
Eucalyptus	Silver	Leaf	4–60 nm	Spherical	ND	(Mo et al. 2015)
Eucalyptus	Iron	Leaf	20–80 nm	Spheroidal	Remediation of eutrophic wastewater	(Wang et al. 2014)
Azadirachta indica	Silver	Leaf	9–15 nm	Spherical	Decolorization of Rose Bengal and bactericidal potential	(Ramar et al. 2018)
Syzygium cumini	Silver	Leaf	30 nm	Spherical	ND	(Kumar et al. 2010)
Cinnamomum camphora	Silver and Gold	Leaf	Silver = 55–80 and gold = 10–40 nm	Triangular or spherical	ND	(Huang et al. 2007)
Bark extract						
Terminalia cuneata	Silver	Bark	20–50 nm	Disordered spherical	Reduction of direct yellow-12	(Edison et al. 2016)
Albizia lebbeck	Zinc oxide	Bark	Average 66.25 nm	Irregular spherical	Antimicrobial, antioxidant and cytotoxic activities on human breast cancer cell lines	(Umar et al. 2018)
Viable/whole plant						
Arabidopsis thaliana	Palladium	Viable plant	3 nm	Spherical	Catalytic activity in Suzuki coupling reaction	(Parker et al. 2014)
Lolium multiflorum	Silver	Aqueous extract of whole plant	20–100 nm	Irregular and spherical	Antibacterial against poultry pathogens	(Lee et al. 2018)
Sida cordifolia	Silver	Aqueous extract	3–4 nm	Cubic	Antibacterial against fish and human pathogenic bacteria	(Pallela et al. 2018)

Table 2 (continued)

Type of the plant	MNPs	Plant tissues used to prepare an extract	Size of the MNPs	Morphology of the MNPs	Applications of the MNPs	Reference
Root extract						
Panax ginseng	Silver, gold	Root	Silver = 10–30 nm, gold = 10–40 nm	Spherical	Antimicrobial	(Singh et al. 2016)
Berberis vulgaris	Silver	Root	30–70 nm	Spherical	Antibacterial	(Behravan et al. 2019)
Seed extract						
Coffea arabica	Silver	Seed	20–30 nm	Spherical	Antibacterial	(Dhand et al. 2016)
Pongamia pinnata	Zinc oxide	Seed	30.4–40.8 nm	Spherical	Anticancer, antimicrobial	(Malaikozhundan et al. 2017)
Syzygium cumini	Silver	Seed	90 nm	Spherical	ND	(Kumar et al. 2010)
Abelmoschus esculentus	Gold	Seed	45–75 nm	Spherical	Antifungal	(Jayaseelan et al. 2013)
Jatropha curcas	Silver	Seed	15–50 nm	Spherical, cubic	ND	(Bar et al. 2009b)

ND not determined

by washing the separated MNPs with water and repeated cycles of ultra-high centrifugation.

Although it is possible to utilize living plants as biofermenters for the synthesis of MNPs, however, this domain remains as less explored. To date, synthesis of silver and gold NPs was performed in vitro using legume mung bean (*Vigna radiata* L.), and alfalfa (*Medicago sativa*) plants respectively (Gardea-Torresdey et al. 2002; Kumari et al. 2017). Furthermore, Parker et al. successfully used *Arabidopsis thaliana* plants growing in medium containing potassium tetrachloropalladate (K_2PdCl_4) for the synthesis of palladium NPs (Parker et al. 2014). Briefly, reports about the plant-mediated synthesis of MNPs with their applications are shown in (Table 2) and applications are explained in the "Biomedical applications" section.

Phyto-synthesis of MNPs may occur by oxidation and reduction of metallic ions into their non-toxic, stable, and zero-valent form. However, the exact components and the mechanisms responsible for the phyto-mediated synthesis of MNPs yet remain unclear. It has been studied that amino acids, vitamins, proteins, organic acids, and also secondary metabolic products, such as polyphenols, flavonoids, terpenoids, alkaloids, polysaccharides, heterocyclic compounds, and lipids, have a vital role in the reduction of metallic ions to stabilize MNPs (Devi et al. 2017; Duan et al. 2015). Recently, Ovais et al. discussed the role of phytochemical and microbial enzymes in the synthesis of metallic nanoparticles. Authors emphasized on explaining the biosynthesis pathways of phenolics, flavonoids, terpenoids, mevalonate, and methylerythritol phosphate; however, less emphasis was given on how these biomolecules interact with different metals for the synthesis of their corresponding zero-valent nanoparticles (Ovais et al. 2018). Hence, there is room to investigate how these biomolecules play their role in the synthesis of MNPs. Therefore, the role of phytochemicals that takes part in the synthesis of MNPs is elaborated in the following sections.

Phytochemicals and synthesis of MNPs

Flavonoids

They are secondary water-soluble metabolites containing 15 carbons and comprising of six major subgroups including anthoxanthins, flavans, flavanones, anthocyanidins, flavanonols, and isoflavonoid. Flavonoids are considered to be the major reducing agent of plant extracts involved in the reduction of metallic ions to their corresponding zero-valent nanoparticles. The oxidation and reduction potential of flavonoids is attributed to the molecular oxygen of flavonoids (Zhou et al. 2010). Pietta (2000) has reported that the removal of hydrogen during keto-enol conversion in flavonoids results in the formation of rosmarinic acid and luteolin which are

responsible for the metal ion reduction to their MNPs (Ahmad et al. 2010). Ghoreishi et al. documented the reduction of hydroxyl groups of myricetin and quercetin into carbonyl groups during metallic (gold) ion reduction and the formation of AuNPs (Ghoreishi et al. 2011). In another study, microwave-assisted guava (*Psidium guajava*) leaf extract-mediated synthesis of AuNPs has been documented. Authors concluded that the flavonoids present in guava leaves are responsible for the synthesis of biogenic AuNPs (Raghunandan et al. 2009).

Phenolic acids

Phenolic acids are polyphenols containing a phenolic ring and a carboxylic functional group, and their metal reduction potential is attributed to their nucleophilic aromatic rings (Wang et al. 2007). The synthesis of *Terminalia chebula* fruit extract-mediated AgNPs is attributed to the phenolic hydroxyl group of gallic acid that undergoes oxidation during interaction with silver ions leading to the formation of AgNPs (Edison and Sethuraman 2012). In another study, AuNPs were synthesized using aqueous extract of *Macrotyloma uniflorum* and showed that the release of hydrogen during conversion of caffeic acid to ferulic acid is responsible for the reduction of gold ions to AuNPs (Aromal et al. 2012). Due to the presence of propanoic acid side chain, caffeic acid is acting as a strong reducing agent by delocalization of electron between the propanoic chain and aromatic ring. The metal reduction potential of lignin, tannin, and flavonoid glycosides has also been reported in the literature (Kasthuri et al. 2009a; Kasthuri et al. 2009b; Lopes et al. 2018).

Terpenoids

Also called isoprenoids are the abundant organic compounds responsible for color, taste, and aroma in various plant species. Recently, phytochemicals are reported for the synthesis of AuNPs using bark extract of *Pterocarpus santalinus* L. (Srinath and Rai 2018). Authors reported the involvement of terpenoids in the reduction of gold ions to synthesize biocompatible AuNPs. Similarly, *Cinnamon zeylanicum* bark extract harboring terpenoids such as eugenol, linalool, and methyl chavicol are also reported for the reduction of metallic ions for the synthesis of AgNPs (Sathishkumar et al. 2009). Sing et al. reported the synthesis of amine group functionalized gold and silver nanoparticles using eugenol of clove (*Syzygium aromaticum*) extract (Singh et al. 2010). The release of the electron from hydroxyl group of eugenol transforms eugenol to its anionic form, making it a reducing agent. Also, the reduction potential of eugenol further increased due to the inductive effect of electron withdrawing allyl and methoxy functional groups present at ortho and para positions of the OH group. The simultaneous release of electrons is

considered to be responsible for the reduction of metallic ions to for NPs.

Proteins

To date, proteins are considered to be the ultimate working force of the living system. Proteins play a vital role in the synthesis of metallic nanoparticles through their carboxylate and/or amino groups (Cuellar-Cruz 2017). Tan et al. studied the peptide-mediated synthesis of AuNPs and investigated the metal binding and reducing potential of 20 amino acids (Tan et al. 2010). AgNPs were synthesized using the latex of *Jatropha curcas*, and cyclic peptides present in the latex were proved to be responsible for the synthesis of AgNPs (Bar et al. 2009a). The silver ion-reducing potential of tyrosine has been described, through ionization of phenolic group of tyrosine. This ionization resulted in the conversion of tyrosine in the semi-quinones (Roy et al. 2014). Reports are also available showing the involvement of tryptophan in the reduction of metallic ions by transient transformation of tryptophan into tryptophol radical by releasing an electron (Tamuly et al. 2013; Veerakumar et al. 2013).

Organic acids

Plant secondary metabolites such as alkaloids and organic acids are reported for their metal reduction and synthesis of MNPs. Tamuly et al. reported the biosynthesis of AgNPs by using pedicellamide (A) isolated from *Piper pedicellatum* C.DC leaf (Tamuly et al. 2014). Mechanism involved in the pedicellamide-mediated synthesis of AgNPs is attributed to the release of reactive hydrogen from pedicellamide. The synthesis of AgNPs by ascorbic acid of orange peel extract has been reported (Konwarh et al. 2011). In another study, the tautomerization of benzoquinone derivatives obtained from mesophyte *Cyperus* sp. has been reported for the reduction of metals.

Similarly, phytochemicals of *Hydrilla* sp., including catechol, protocatecheuic acid, and ascorbic acid have been reported for the synthesis of AgNPs through the release of reactive hydrogen. Also, malic and pyruvic acid synthesized during redox reaction of glycolytic pathway in *Bryophyllum* sp., (a xerophyte) are reported for the reduction of silver ions to AgNPs (Jha et al. 2009). Gonzalez-Ballesteros et al. found that the carbonyl and hydroxyl groups of protein from plant extracts could help in the production of stable NPs (González-Ballesteros et al. 2017; M Joseph et al. 2016).

Parameters affecting biological synthesis of MNPs

Although biological synthesis of MNPs has numerous advantages, a polydispersity of the nanoparticles remains a

disadvantage. Therefore, the scientific community has focused on process optimization for enhanced production of monodispersed uniformly sized MNPs (Tables 1 and 2). Optimization of the growth medium composition and parameters such as temperature, pH, salt concentration, incubation period, mixing ratio, redox conditions, irradiation, and aeration are the necessary steps in almost every type of biological process (Rao and Paria 2015; Ahmad et al. 2018; Verma and Mehata 2016; El-Naggar and Abdelwahed 2014; Kammoun et al. 2008). Among others, the pH has reported as a critical parameter responsible for the variation in the size of synthesized MNPs. Kumari et al. found that the smallest gold NPs of 4 nm size were synthesized by *Trichoderma viride* when the pH of the reaction mixture was set at 9.5 (Kumari et al. 2017). However, optimum synthesis of AgNPs by *Microbacterium* sp. MV4 was observed at pH 7. The change in the pH of the reaction mixture alters the charged species of natural biomolecules both in microbial and phyto-extracts and affects their metal ion reduction capability. *Avena sativa* extract was used to develop small sized gold NPs by adjusting pH at 3.0, and 4.0, however, further decrease in the pH up to 2.0 resulted in the aggregation of synthesized NPs. Authors proposed that this effect may be because of nucleation and binding of metal ions to the numerous functional groups that become possible at 4.0 and 3.0 instead of pH 2.0 (Sankar et al. 2017). In another study, the extract of pears was exploited for the synthesis of gold NPs. Authors reported that the triangular and hexagonal gold NPs were observed at alkaline pH instead of acidic pH (Ghodake et al. 2010). Likewise, salt concentrations, incubation time and chances for NPs synthesis depend on the source and nature of extracts (Pereira et al. 2015).

Current understanding of the biological synthesis of MNPs

Potentially microorganisms can synthesize MNPs both intra- and extracellularly. Microbial extracellular formation of MNPs occurs when metallic ions come in contact with reduced sugars of cell wall/membrane. Previously, the use of *Fusarium oxysporum* and *Verticillium* sp. ruled out the possible involvement of reduced sugars present in the cell wall for the synthesis of gold NPs by reducing Au^{+3} ions. However, negatively charged $AuCl_4^-$ ions interact with positively charged amino acids of the enzymes localized on the cell wall (Kitching et al. 2015). Contrastingly, formation of intracellular Au^{3+} NPs, the ions diffused inside the cell through the cell membrane, is reduced by intracellular redox mediators. Though, it is not clear either the cross-membrane diffusion is active bioaccumulation or passive biosorption. The biosorption of gold ions could be due to their toxicity to the viable microbial cell that induces pores in the cell wall/membrane. Intracellularly, nicotinamide adenine dinucleotide phosphate (NADPH) or nicotinamide adenine dinucleotide (NADH) is usually involved in the reduction of metallic ions. X-ray diffraction analysis of various microorganisms revealed that the intracellular concentration of zero-valent metals increases and the concentration of charged ions decreases with increased incubation time. This observation suggested that the increased incubation allows more ions to move into the cell where they get reduced to their zero-valent state. Also, the formation of ethylated metallic ions suggested the possible defense mechanism of viable cells against metal toxicity (Gholami-Shabani et al. 2016; Otari et al. 2015).

The available reports showed that metal-induced toxicity trigger intracellular signaling pathway for the activation of stress response genes resulting in the production of reductases and oxygenases. The upregulation of such genes takes place at sub-toxic concentrations of metal ions; however, at higher concentrations metal toxicity hinders the expression of proteins and inhibits cellular growth (Demidchik 2015; Gupta et al. 2017). For example, results of SDS-PAGE showed upregulated proteins from *Rhizopus oryzae* when exposed to Au^{3+} ions. Further, investigation on the biosynthesis of gold NPs from extracts of fungi, bacteria, and plants demonstrated the involvement of NADH/NADPH-dependent reductase in metal bioreduction process (Prasad et al. 2016). Also, the possible involvement of aromatic amino acids, for example, tryptophan and tyrosine in the reduction of metal ions to produce MNPs was confirmed by Fourier transform infrared spectroscopy (FTIR).

Synthetic biology and MNPs

Recently, there is a growing interest among the scientific community to explore the potential use of synthetic biology (SynBiol) for the synthesis of tailored MNPs (Chessher et al. 2015; Kolinko et al. 2014) (Fig. 4). It is challenging to produce monodisperse single magnetic domain NPs at ambient temperatures. Magnetotactic bacteria have shown a huge potential for the mineralization of magnetosomes (membrane-bounded magnetic nano-crystalline particles depicting unprecedented magnetic features). Because of the difficult handling of magnetotactic bacteria, Kolinko et al. tried to express the underlying biosynthetic pathway from these fastidious bacteria into non-magnetic host using synthetic biology approaches. They successfully transferred a minimal set of genes from magnetotactic donor bacterium *Magnetospirillum gryphiswaldense* into a non-magnetic photosynthetic model bacterium *Rhodospirillum rubrum*. Authors concluded that this approach will enable the sustainable production of tailored biogenic nanoparticles in non-native biotechnologically important hosts. Also, they suggested that this is a step towards the endogenous magnetization of different organisms using synthetic biology (Kolinko et al. 2014).
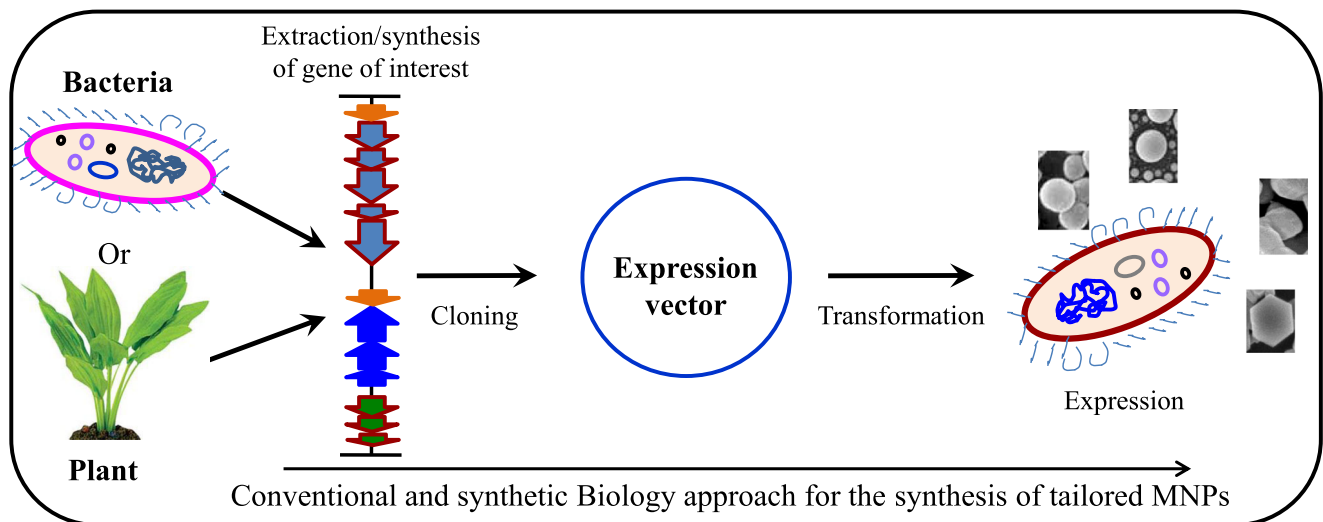
Fig. 4 Use of synthetic biology for biological synthesis of MNPs, a generalized approach

Chessher and co-workers discovered a gene controlling the synthesis of magnetosome and clustered in 115 kb large genomic island interspersed with many genes of unknown functions (Ullrich et al. 2005). Later functions of different genes of this island were determined (Lohbe et al. 2011). Afterward, authors stitched together many expression cassettes containing 29 genes (25 kb) of four operons in different combinations and deleted one gene (*ftsZm*) from *mamXY* operon because of its known interference function with cell division during cloning. Transformation of recombinant expression cassettes into non-magnetic strains of *M. gryphiswaldense* resulted in the formation of stable native type magnetosome biomineralization showing the success of cloning and functionality of transferred operons. Also, authors transferred expression cassettes into non-magnetic photosynthetic alphaproteobacterium *R. rubrum* foreign host bacterium. After transformation of the optimized expression cassette (Fig. 5a), the strain ABG6X of *R. rubrum* encompassed all 29 relevant genes of magnetosome island except *ftsZm*. The cell of recombinant ABG6X strain showed magnetic response within several hours, and a pellet of bacterial cells become visible near the magnet placed at the edge of culture flask showing that the strain ABG6X has attained magnetotactic features (Fig. 5b) (Kolinko et al. 2014).

Possible mechanisms for cellular uptake and cytotoxicity of MNPs

Possible mechanisms for cellular uptake of MNPs

Cell membranes are semipermeable allowing only small molecules/ions to pass through it while hindering others. Communication among or between the cells and their microenvironment and uptake of nutrients take place through the cell membrane by different mechanisms. Small nonpolar or hydrophobic molecules, water, carbon dioxide, and oxygen can diffuse through the cell membrane based on their concentration gradients. Molecules like amino acids and various ions move across the cell membrane through active transport mediated by membrane protein pumps (Jentsch 2016); however, hydrophilic biomacromolecules at the nano-scale conventionally entered the cell through endocytosis, a plasma membrane-driven process that encapsulates the cargo into transport vesicles (Conner and Schmid 2003).

How do MNPs apt in the cellular uptake system? Findings of various experiments showed how engineered MNPs could pass through the plasma membrane of diverse cell types, such as human alveolar epithelial (Park et al. 2007), human mesenchymal stem cells (Greulich et al. 2011), and human epidermal keratinocyte (HEK) cells (Monteiro-Riviere et al. 2013). Based on the experimental findings, the mechanisms involved in the cellular uptake of nanoparticles have been summarized in (Fig. 6). Nevertheless, the mechanisms of cellular uptake of nanoparticles proposed by different research groups are sometimes inconsistent or even contradicting with each other. A systematic understanding of the process of uptake and intracellular trafficking of NPs hence became a topic of great interest among the scientific community.

Different physicochemical properties such as size and shape, surface chemistry, and surface charges play a vital role in cellular uptake of metallic nanoparticles (Carnovale et al. 2019). Figure 6 summarizes the cellular uptake of MNPs through endocytosis that is a form of active transport where cells encapsulate objects with cytoplasmic membrane resulting in the formation of vesicles. Such endocytotic processes known for their involvement in the uptake and intracellular dissemination of MNPs are (1) phagocytosis, (2) pinocytosis, and (3) clathrin-mediated or caveolae-dependent endocytosis (Nel et al. 2009; Verma and Stellacci 2010; Ishimoto et al. 2008).
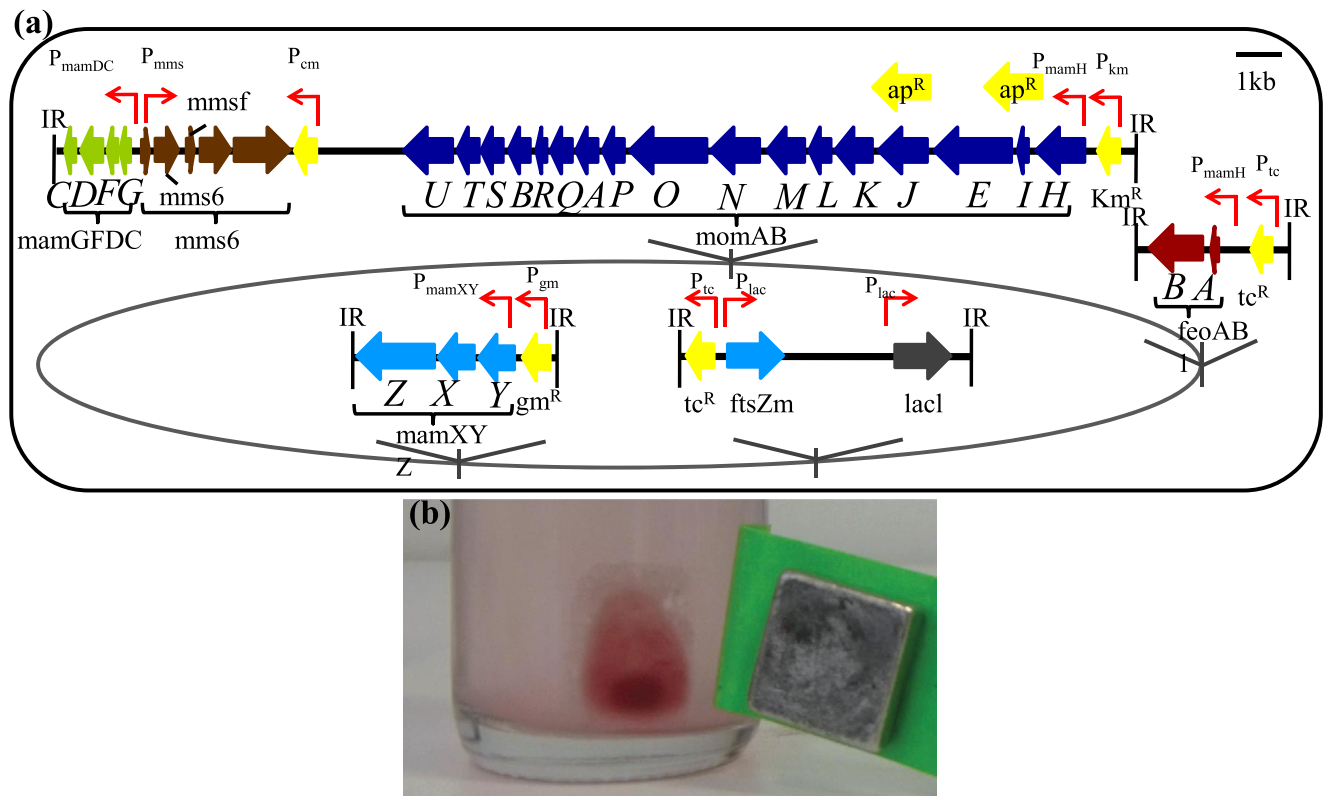
Fig. 5 **a** Schematic presentation of molecular arrangement of gene cassettes introduced into the chromosome of *R. rubrum* in a stepwise manner. Broad arrows indicate the extensions and transcriptional directions of individual genes. Different colors illustrate the cassettes inserted into the chromosome (oval shape, not to scale) as indicated by their gene names in the figure. Shown in yellow are antibiotic resistance genes (*km*R, kanamycin resistance; *tc*R, tetracycline resistance; *ap*R, ampicillin resistance; *gm*R, gentamicin resistance). Thin red arrows indicate different promoters (P) driving transcription of inserted genes (Pkm, Pgm, Ptc, promoters of antibiotic resistance cassettes; PlacI, promoter lac repressor; Pmms, PmamDC, PmamH, PmamXY, native promoters of the respective gene clusters from *M. gryphiswaldense*; Plac, lac promoter). Crossed lines indicate sites of gene deletions of *mamI* and *mamJ* in strains *R. rubrum_ABG6X_dI* and *R. rubrum_ ABG6X_dJ*, respectively. IR, inverted repeat defining the boundaries of the sequence inserted by the transposase (Kolinko et al. 2014). **b** Cells of *R. rubrum_*ABG6X accumulated as a visible red spot near the pole of a permanent magnet at the edge of a culture flask (Kolinko et al. 2014)

Phagocytosis is a process usually operated by particular mammalian cells such as macrophages, neutrophils, and monocytes. It plays a vital role to engulf solid particles with a diameter greater than 750 nm to form internal phagosomes (Ishimoto et al. 2008). Macropinocytosis or pinocytosis that occurs in almost every cell type is responsible for the uptake of particles varying in size from few to several hundred nanometers. Possibly, the primarily characterized pathway for the internalization of nanoparticles is active uptake through clathrin-mediated endocytosis, and the cargo is encapsulated into small vesicles with a diameter smaller than 100 nm (Harush-Frenkel et al. 2007; Li et al. 2008) that fuses with endosomes (Zhang et al. 2009). Also, clathrin-independent mechanisms rely on the cholesterol-dependent grouping of lipid-attached proteins into various domains at microscale (called lipid raft carriers) (Kirkham and Parton 2005). These lipid rafts/caveolae comprise of 50–80 nm invaginations of plasma membrane harboring sphingolipids, caveolins, and cholesterol (McIntosh et al. 2002). Caveolae-mediated endocytosis is a significant mechanism for the cellular uptake of MNPs in endothelial cells (Partlow et al. 2008; Wang et al. 2009).

Almost every type of nanoparticle adapted a specific mechanism for their entrance into the cell. For example, incubation of gold nanoparticles with HeLa cells in their growth medium results in the adsorption of serum proteins on the surface of gold nanoparticles leading the nanoparticles towards cells through receptor-mediated endocytosis (RME) (Khan et al. 2007). Clathrin-dependent endocytosis and RME are names of the same process where cells encapsulate molecules by inward growth of plasma membrane to make vesicles at the particular receptor site specific to the proteins attached with the nanoparticles being internalized. Internalization of Herceptin encapsulated gold nanoparticles is carried out through RME with the help of ErbB2 receptor of the plasma membrane. During this process binding of gold particles, activation of the ErbB2 receptor and expression of the protein is strictly dependent on the size of the nanoparticles (Jiang et al. 2008).

The encapsulation of gold nanoparticles with various organic/biological molecules usually alters their mode of
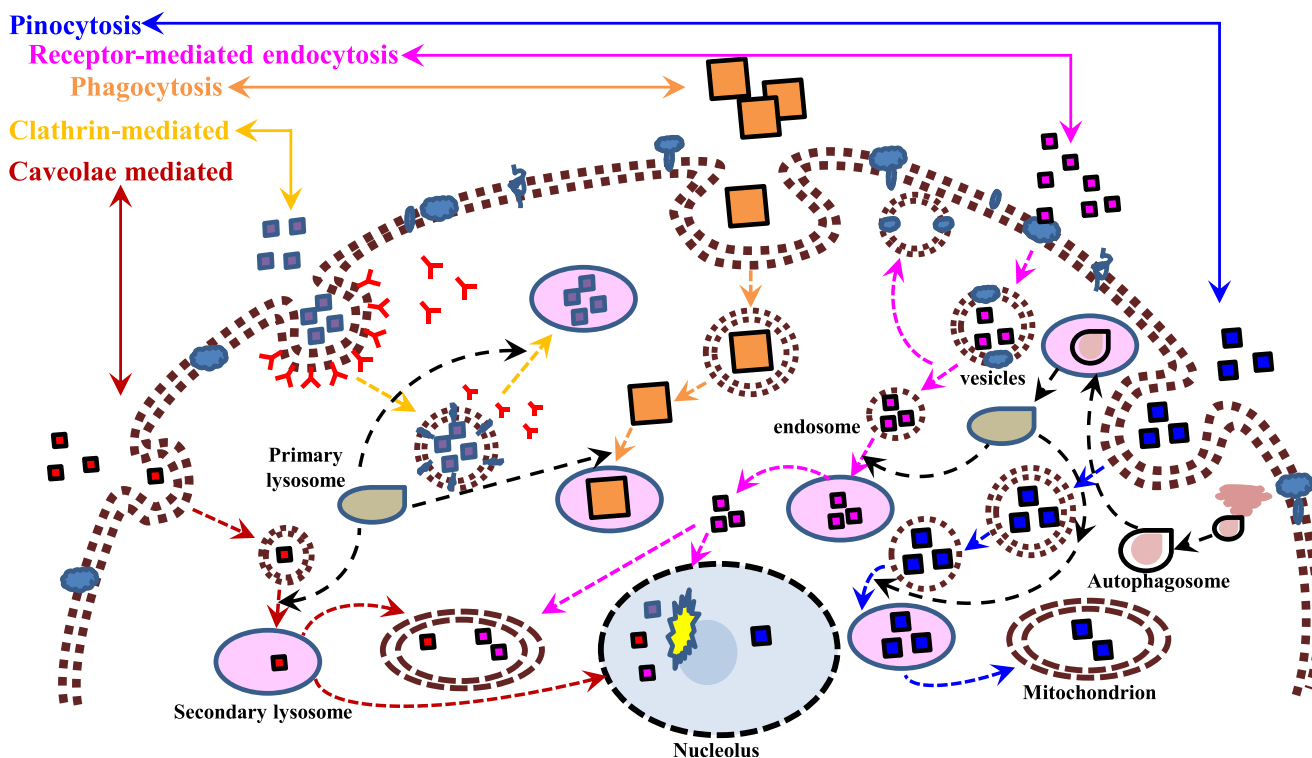
Fig. 6 The possible mechanisms involved in cellular uptake of MNPs

cellular internalization. Such internalization of particles with polymeric surfaces involves dynamin as well as F-action that is usually energy-dependent. For the uptake of nanoparticles with positive charges on their surfaces, micropinocytosis seems to be a significant pathway. However, clathrin or caveolae-independent endocytosis seems to be an important pathway for the uptake of MNPs with negative charge of their surfaces (Dausend et al. 2008; Van Haute et al. 2018). For example, positively charged gold nanoparticles with plain surface were internalized by clathrin and caveolin-dependent endocytosis as well as micropinocytosis, while negatively charged gold nanoparticles coated with polyethylene glycol (PEG) were internalized through caveolin or clathrin-dependent endocytosis without the involvement of micropinocytosis (Brandenberger et al. 2010).

Autophagy is a conserved process involved in the degradation of cytoplasmic organelles and cellular proteins by encapsulating them with phagophores to form autophagosomes. Recently, the idea of nanoparticle-induced autophagy has attracted the intention of many researchers (Klionsky 2007; Mishra et al. 2016). Various MNPs such as neodymium oxide, silver (Ag), and gold (Au) are reported for inducing autophagy in different cells (Chen et al. 2005; Li et al. 2010; Mishra et al. 2016). Reports are published showing the successful use of different metallic nanoparticles such as zinc oxide, iron oxide, and gold for the treatment of cancerous T cells, lung epithelial cells, and oral cancer cells respectively (Hanley et al. 2008; Khan et al. 2012; Wu et al. 2011). However, the actual process

of autophagy and mechanisms involved in the nanoparticles mediated treatment of cancer remains unknown which need to be addressed.

Possible mechanism of MNP-induced cytotoxicity

Different types of MNPs with diverse physical and chemical properties have been shown to induce reactive oxygen species (ROS)-mediated cytotoxicity. ROS constitute a pool of oxidative species containing hydroxyl radical ($OH^{\bullet}$), singlet oxygen ($^1O_2$), superoxide anion ($O_2^{\bullet-}$), hypochlorous acid (HOCL), and hydrogen peroxide (H_2O_2). These oxygen species are known to induce cytotoxicity through oxidative stress both in vivo and in vitro (Donaldson et al. 2001; Yang et al. 2009). Generation of primary ROS species ($O_2^{\bullet-}$) is intrinsically catalyzed by nicotinamide adenine dinucleotide phosphate (NADPH) via one-electron reduction from molecular oxygen. Subsequently, the reduction of oxygen may lead to the formation of $OH^{\bullet}$ or H_2O_2 via metal-induced Fenton reaction and dismutation respectively (Forrester et al. 2018; Thannickal and Fanburg 2000).

Several reports showed that ROS generation and oxidative stress are the events leading towards MNPs-induced cytotoxicity. Oxidative stress is correlated with the physicochemical properties of MNPs. The key factors involved in the NP-induced cytotoxicity are (1) activation of NADPH-dependent oxidation system, (2) mitochondrial respiration and apoptosis, (3) depletion of antioxidant enzymes, and (4)

alteration in cell homeostasis. MNP-mediated ROS generation triggers cell signaling pathways, expressions of chemokine and cytokines, and activation of transcription factors. Triggering of these pathways is linked with the transcription of genes responsible for inflammation, fibrosis, genotoxicity, and cancer. Thereafter, observed cytotoxicity during MNPs exposure could be endorsed to the generation of ROS. To access the toxic effects of MNPs, the inclusion of these cellular responses is an essential screening tool. For example, biological system undergoes mild oxidative stress when antioxidant enzymes show their overexpression, whereas severe oxidative stress results in mitochondrial apoptosis. ROS provides a scale to access the cytotoxic effects upon exposure to the MNPs. To access the cytotoxic effects of MNPs, a rigorous characterization of MNPs and in detail investigation of oxidative stress markers both in vivo and in vitro are vital.

Biocompatibility of biologically synthesized MNPs

The biocompatibility of biologically synthesized MNPs has been widely ascribed to molecules encapsulating the metallic core of the nanoparticles (Aditya et al. 2017). Knowledge about the biocompatibility of synthesized MNPs is vital before their applications. Generally, a range of biomolecules such as phenolics, carbohydrates, vitamins, flavonoids, tannins, terpenoids, proteins, and polycerids are responsible for different properties of MNPs. These biomolecules control the net charge on the surface of MNPs that is the key factor responsible for determining the mechanism of action of MNPs (Sendra et al. 2017). Various biomolecules are functionally divergent and may act as nonspecific reducing agents, legends, and free radical scavengers to bind with the metallic core of the MNPs (Fig. 2). Different cell types depict varying levels of tolerance against biomolecules derived from both plants and microbes.

However, the question is how a crust of biomolecules can eradicate the toxic effects of the metallic core of MNPs. To answer this question, the epigenetic effect of capped biomolecules on mammalian gene expression for disease prevention and protection has been investigated in cellular models. The involvement of plant-derived phenolic antioxidants in the prevention of human diseases such as Alzheimer's disease, cancer, and cardiovascular diseases through epigenetic modulation has been reported (Malireddy et al. 2012; Tang and Tsao 2017; Thakur et al. 2014). Cell viability assay of the cervical cancer cell line (SiHa) with biologically synthesized platinum NPs encapsulated with tea polyphenols (TPP@Pt) and bimetallic next-generation Pt@Cu synthesized using polyphenon 60 showed that the cell proliferation of SiHa cells was inhibited. Treatment with TPP@Pt and Pt@Cu nanoparticles significantly increased the percentage of cells in G_2/M phase, indicating cell cycle arrest in the G2/M phase and an increased

cell number in sub-G0 cell death phase (Alshatwi et al. 2015; Athinarayanan et al. 2016). In two separate studies, authors suggested that both TPP@Pt and Pt@Cu can be used for cervical cancer treatment. Separately, a study conducted on Parkinsonism in zebrafish model reported that green synthesized Pt-NPs had successfully inverted the neurotoxic impact of MPTP by optimizing levels of mitochondrial complex I, superoxide dismutase, dopamine, glutathione peroxidase, and glutathione (Ganaie et al. 2017; Nellore et al. 2013). Dedicated research is still required to be carried out to understand whether or not encapsulating biomolecules or metallic core of biologically synthesized MNPs has been involved in inducing epigenetic effects.

Panda et al. reported the use of aromatic spath of male inflorescence of screw pine (*Pandanus odorifer*) mediated biologically synthesized silver nanoparticles (24-55 nm), commercial silver nanoparticles (70 nm) procured from Sigma-Aldrich, USA, and other silver species including silver ions, colloidal silver chloride, to investigate their genotoxicity effects in their own established *Allium cepa* assay. Authors found no effect on genotoxicity when both types of AgNPs were applied at 10 μg/ml. Also, the evaluation of MNP-mediated cytotoxicity-associated biomarkers including the generation of ROS species, mitotic index, DNA damage (using comet assay at 20 to 80 μg/ml), mitotic aberrations, micronucleus, and cell death revealed that both biologically synthesized and commercial AgNPs showed lesser cytotoxicity and greater genotoxicity as compared with Ag^+ ions alone. Cell death induction potential of different species of silver in roots of *Allium cepa* were arranged as; Ag^+ > colloidal AgCl > commercial AgNPs > biologically synthesized AgNPs. DNA damage and cell death caused by biogenic AgNPs was prevented through dimethyl thiourea and Tiron by scavenging H_2O_2 and O_2^-. ROS was suggested as the potential source for inducing AgNPs mediated DNA damage and cell death (Panda et al. 2011).

Separately Sarkar et al. investigated toxicity induced by *Alternaria alternata*-mediated synthesized protein-capped biogenic AgNPs (25 to 45 nm) and evaluated the DNA damage in human lymphocytes. Non-significant changes in cell viability of cells treated with 400 μg/ml of AgNPs as compared with control (untreated cells) cells were observed through trypan blue dye exclusion method. DNA damage analysis of in vitro treatment of lymphocytes via comet assay showed no DNA damage up to 40 μg/ml of AgNPs, while an increase in DNA damage was observed in dose-dependent manner up to 300 μg/ml. This DNA damage was represented in terms of olive tail moment test and percentage of DNA in the tail of the comet assay tail. Comet assay revealed that the DNA damage was approximately five times higher in the positive control (cell treated with 100 μmol/l methyl methanesulphonate) as compared with the lowest treatment dose of biogenic AgNPs (Sarkar et al. 2011).

Available methods for biocompatibility analysis of MNPs

At present, different qualitative and quantitative assays have been utilized to study the biocompatibility of MNPs. For qualitative analysis, these assays include live or dead cell staining assays such as acridine orange and ethidium bromide cellular staining assays. However, for quantitative analysis of biocompatibility, 2,3-bis-(2-methoxy-4-nitro-5-sulfophenyl)-2H-tetrazolium-5-carboxanilide (XTT), 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), and lactate dehydrogenase (LDH) leakage tests are most widely used dye-conversion assays (Patil and Kim 2017; Sriranjani et al. 2016). The LDH leakage assay indicates the damage to the cell membrane, while the MTT assay is the sign of mitochondrial viability. Further, the protein content of a viable cell and lysosome activity can be measured by protein assay and neutral red assay respectively (Fotakis and Timbrell 2006; Lobner 2000). Type of metallic nanoparticles (gold, iron, silver, platinum, copper oxide), dose (concentration × time), selection of cell line, size, shape, and surface properties of MNPs have a significant role in overall biocompatibility of the MNPs (Kononenko et al. 2017; Muthiah et al. 2013; Shang et al. 2014).

Biomedical applications

Biologically synthesized metallic nanoparticles (MNPs) have many applications in the biomedical field with a vast potential for continued growth in this area. Various MNPs have been widely implemented for their antibacterial, optical, and anticancer properties in diagnostic, therapeutic, and hyperthermia applications. Further, applications of different MNPs are described with examples in the following sections.

Antimicrobial activity

Antibacterial activity

Exposure to AgNPs causes cytotoxicity in bacteria. Silver ions and AgNPs interact with plasma membrane resulting in disturbance of cell permeability, cellular respiration, and prevention of DNA replication by denaturing the ribosomes or by binding the DNA (Chaloupka et al. 2010). The mechanism of AuNPs induced antibacterial potential against *E. coli* is illustrated by Cui et al. (2012). Authors reported that AuNPs distorted membrane potential and inhibited activity of ATPase resulting in the significant decrease of cellular ATP. Also, Sadhasivam et al. reported that the exposure to AuNPs showed inhibition of rRNA binding with ribosomes. Antimicrobial potential of bacteria-mediated synthesized AgNPs and AuNPs was documented by Sadhasivam et al. (2012) and Sadhasivam et al. (2010). In these studies, *Streptomyces hygroscopicus*-mediated biologically synthesized NPs were used as an antimicrobial agent against *Enterococcus faecalis*, *Bacillus subtilis*, *Staphylococcus epidermidis*, *E. coli*, *S. aureus*, and *Salmonella typhimurium*. Recently, *Saraca asoca* plant leaf extract was used for the synthesis of AgNPs and antibacterial potential of synthesized NPs was investigated against *Staphylococcus aureus*, *Salmonella typhi*, and *Streptococcus pyogenes* (Fatema et al. 2019).

Antifungal activity

Biologically synthesized MNPs have been reported for the antifungal properties. *Alternaria alternata*-mediated extracellularly synthesized biological AgNPs showed increment in antifungal activity of fluconazole against *Phoma herbarum*, *Phoma glomerata*, *Candida albicans*, *Trichoderma* sp., and *Fusarium semitectum* (Gajbhiye et al. 2009). *Ocimum vasilicum* leaf extract-mediated synthesized AgNPs were applied as antibacterial as well as antifungal agent. Synthesized AgNPs showed higher antifungal activity against *Aspergillus flavus*, *Aspergillus niger*, *Aspergillus terreus*, and *Aspergillus fumigatus* (Elumalai et al. 2019).

Antiviral activity

Viruses are the causative agents of various diseases of plants and animals and a potential source of diverse problems in medicine. Relatively less number of reports on antiviral potential of biogenic metallic nanoparticles has been reported. *Aspergillus ochraceus*-mediated synthesized intracellular AgNPs have been reported for potential antiviral agent (Vijayakumar and Prasad 2009). In this report, authors isolated the biogenic AgNPs by heat treatment and applied against M13 phage and antiviral potential was determined through plaque count method. Gaikwad et al. reported the feasibility for mycosynthesis of AgNPs, and their antiviral activity varies with the production system used. Authors demonstrated the interaction of AgNPs with human parainfluenza virus type 3 and herpes simplex virus types 1 and 2 are dependent on the size of AgNPs. In this study, the reduction of viral infectivity has attributed the potential of AgNPs to hinder the interaction between virus and cell, which might be dependent on zeta potential and size of the AgNPs (Gaikwad et al. 2013).

MNPs as anticancer agents

Cytotoxicity of biologically synthesized MNPs in various cancer cell lines has been well documented. Amarnath et al. reported the facile synthesis of AuNPs using phytochemicals

present in grapes (*Vitis vinifera*) acting as reducing and stabilizing agents. AuNPs showed a strong affinity towards human breast cancer cells (HBL-100) and induced apoptosis in exposed cells (Amarnath et al. 2011). Joseph et al. synthesized medicinal plant *Indigofera tinctoria* leaf extract induced biogenic AgNPs and AuNPs (Joseph and Mathew 2018). Both silver and gold NPs exhibited dose-dependent cytotoxicity to lung cancer cell line A549, where NPs showed more toxic effect on cancer cell lines as compared to the control (pure plant leaf extract). In another study, cytotoxic properties of fungus (*Penicillium brevicompactum*)-mediated synthesized biogenic AuNPs were analyzed in mouse myoblast cancer (C2C12) cells (Mishra et al. 2011). Recently, Pugazhendhi et al. reported the biogenic synthesis of magnesium oxide nanoparticles (MgONPs) by using brown algae *Sargassum wightii* as reducing and capping agent. Cytotoxicity of biogenic MgONPs in exposed lung cancer cell line A549 was dose-dependent with IC_{50} value of 77.5 ± 0.34 μg/ml. Safety evaluation using peripheral blood mononuclear cells (PBMCs) were used for safety evaluation of synthesized MgONPs, and results illustrated that MgONPs to be non-toxic (Pugazhendhi et al. 2019).

MNPs as drug carriers

Naturally crystalline magnetic greigite Fe_3S_4 and/or magnetite Fe_3O_4 are biomineralized by magnetotactic bacteria (MTB) in a phospholipid bilayer membrane encapsulated structure called magnetosomes. It is documented that researchers isolated and purified the magnetosomes from a magnetotactic bacterium (*Magnetospirillum gryphiswaldense*) and encapsulated/loaded with a chemotherapy drug doxorubicin (DOX) (Sun et al. 2008). Anticancer potential of DOX-loaded bacterial magnetosomes was checked by performing cytotoxicity assay in EMT-6 and HL60 cancer cells. In this study, authors concluded that DOX-loaded magnetosomes have successfully inhibited the proliferation of carcinoma cells and suppressed the level of mRNA of the *c-myc* gene, suggesting that DOX-loaded magnetosomes are important for cancer treatment. In another study, Li et al. revealed in vitro biocompatibility of phospholipid bilayer membrane encapsulated purified and sterilized bacterial magnetosomes in mouse fibroblast cells (Xiang et al. 2007). Recently, magnetosomes derived from *Magnetospirillum gryphiswaldense* are investigated in anti-tumor immunotherapy (Tang et al. 2019). In this study, authors selected syngeneic TC-1 mouse models of cancer to investigate whether anti-4-1BB agonistic antibody-loaded bacterial magnetosomes could enhance the therapeutic effects of anti-4-1BB in localized disease settings. Intravenous injection of antibody-coupled bacterial magnetosomes along with magnetic treatment showed significantly ($p < 0.05$) higher tumor protection than other treatment approaches.

Anti-4-1BB antibody-loaded bacterial magnetosomes may have potential for their clinical application to anti-tumor antibody therapy.

MNPs in medical diagnostics and biosensors

The combined use of biogenic MNPs and chemical sensors has been documented for the detection of medically relevant compounds such as glucose and peroxides. For example, Zheng et al. reported the synthesis of AuNPs using eggshell membrane (ESM) (AuNPs/ESM) at ambient temperature and immobilized glucose oxidase (GO_x) on AuNPs/ESM to investigate glucose biosensing. Range of glucose biosensor was 20 μM to 0.80 mM with detection limit 17 μM, indicating that biosynthesized AuNPs on ESM can be used in the biosensing field (Zheng et al. 2010). Subsequently, the same material was used as glucose biosensor to determine the level of glucose in blood serum, and results obtained showed an agreement with standard spectrophotometric tests (Zheng et al. 2011). An environmental isolate *Bacillus pumilus* sp. BAB-3706-mediated extracellularly synthesized biogenic selenium nanoparticle (SeNPs) was reported as low-cost H_2O_2 biosensor (Prasad et al. 2015). Wang et al. utilized *Bacillus subtilis*-mediated synthesized SeNPs for the preparation of H_2O_2 sensor. Based on bacterial extracellular proteins, spherical SeNPs could be converted into trigonal wires. An electrode (glassy carbon) was dipped in a drop of SeNPs suspension and horseradish peroxidase. Subsequently, voltammetry analysis showed that SeNPs increased the detection of H_2O_2 with 80 nM detection limit (Wang et al. 2010).

MNPs and medical imaging

Due to the diverse optical properties, MNPs have been attracting the attention of the scientific community for centuries. Various optical features linked with MNPs are low- and high-refractive index, photoluminescence properties, surface plasmon resonance, and photonic crystals. In nanophotonics where light interacts with nanoparticles, localized surface plasmon resonances and size-dependent semiconductor band gap are the significantly important properties.

Microalgae *Klebsormidium flaccidum* encapsulated with silica-mediated synthesis of AuNPs resulted in the construction of biohybrid material. In this work, in situ images of silica-encapsulated cells were obtained through Raman spectroscopy to study the effect of AuNPs on the photosynthetic potential of algae. Photosynthesis-based biosensors might be developed by coupling the sol-gel encapsulation and Raman imaging (Sicard et al. 2010). Iron oxide and superparamagnetic iron oxide NPs have dual

capacity to act as photothermal and magnetic agents that can be used for hyperthermia, cancer therapy, tissue repair, targeted drug delivery, and immunoassays such as cell labeling, detoxification of biological fluids, and magnetic resonance imaging (Espinosa et al. 2016; Hajba and Guttman 2016; Laurent et al. 2017; Mou et al. 2015; Wu et al. 2015). Biogenic AgNPs synthesized by *Trichoderma viride* extracellular filtrate are reported for blue and orange light emission. These NPs showed photoluminescence in the range of 320 to 520 nm after laser excitation making them a promising candidate for imaging and labeling purposes (Fayaz et al. 2010).

Conclusion and future prospects

Synthesis of MNPs by microbes and plants has emerged with many advantages such as lack of toxic chemicals, monodispersity, and efficient eco-friendly and rapid approach. The factors such as temperature, incubation time, and pH play an essential role in the synthesis of MNPs. Biologically synthesized MNPs showed higher biocompatibility as compared with the MNPs synthesized through various physicochemical methods. The available knowledge to understand the mechanism of interaction between biomolecules (phytochemicals) and metal ions during synthesis of MNPs has been summarized to bridge the gap in this domain. Recently, the use of synthetic biology (SynBiol), which is a step forward in the synthesis of tailored biological MNPs, has been explained. Biologically synthesized MNPs have been extensively used to solve the problems or to enhance the process efficiency in industries and biomedical sciences. During in vivo application of MNPs, the problems like excretion, clearance, and non-targeted distribution of MNPs are required to be solved. Also, the availability of insufficient knowledge of signaling pathways and biochemical agents responsible for the synthesis of MNPs remains an open challenge to explore the potential of microbe and plants for the efficient synthesis of MNPs. The knowledge of biocompatibility of MNPs is still at the juvenile stage and dedicated research is required in this domain.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The article does not contain any studies with human participants or animals performed by any of the authors.

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