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Development of micro/nanostructured-based biomaterials with biomedical applications

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Abstract: Natural biomaterials are now frequently used to build biocarrier systems, which can carry medications and biomolecules to a target region and achieve a desired therapeutic effect. Biomaterials and polymers are of great importance in the synthesis of nanomaterials. The recent studies have tended to use these materials because they are easily obtained from natural sources such as fungi, algae, bacteria, and medicinal plants. They are also biodegradable, compatible with neighborhoods, and non-toxic. Natural biomaterials and polymers are chemically changed when they are linked by cross linking agents with other polymers to create scaffolds, matrices, composites, and interpenetrating polymer networks employing microtechnology and nanotechnology. This review highlights how microengineered and nanoengineered biomaterials are utilized to produce efficient drug-delivery systems and biomedical and biological therapies and how innovative sources of biomaterials have been identified.

Introduction

Synthesized microdevices and nanodevices have proved invaluable in biotechnology and biomedicine. Since 2012, biocompatible and biodegradable microparticles, of 0.1 to 1 μm size, have gained much attention as ideal drug carriers. Formulations using microparticles have a wide range of applications, such as oral vehicles for drug delivery, subcutaneous injections, intramuscular injections, and site-specific delivery vehicles. Furthermore, polymeric particulate-based materials have been widely used in the delivery of medications. Some of the critical factors for choosing a suitable polymer are the physicochemical properties, thermosensitivity, and pH-responsivity to the surrounding environment (Bao *et al.*, 2016; Onck *et al.*, 2005; Yilmaz *et al.*, 2016).

Nanobiotechnology is a multidisciplinary field that combines chemistry, biology, engineering, and medicine and has been the foundation of efforts for developing drug-delivery devices and methods. Site-specific targeting and the controlled release of conventional medicines, recombinant proteins, vaccines, and nucleic acids have been made possible with novel materials and formulations (Anderson *et al.*, 2004). Nanoscale drug-delivery devices can be developed to manage the biodistribution of drugs, optimize release kinetics, and reduce toxic side effects, thus increasing the therapeutic index of a drug (Kayser *et al.*, 2005).

Although current drug-delivery systems are efficient at producing high local concentrations of medications through controlled drug release, they are only able to target tissues rather than specific cells (Qiu and Bae, 2006). Since the mid-twentieth century, various metallic nanoparticles (NPs) have been biosynthesized by microorganisms through genetic modification, and extracts of these microorganisms could form metallic NPs. These biometallic NPs exhibit higher catalytic activity, are more stable and are less toxic than chemically produced metallic NPs. Furthermore, biometallic NPs can be generated by culturing microorganisms or cell-free extracts with dissolved metal ions for hours or days utilizing green and environmentally acceptable methods. Some of the metals that have been used in this type of synthesis to form NPs are silver, gold, cadmium sulfide, cadmium selenide, copper, copper oxide, gadolinium oxide, ferrimagnetic magnetite, lead sulfide, palladium, antimony trioxide, titanium dioxide, and zirconium dioxide (Kato and Suzuki, 2020; Sharaf *et al.*, 2022).

Numerous characteristics of nanoscale drug-delivery systems can be modified for particular uses in terms of their capabilities of drug release (physical interaction between drug and carrier, chemical cleavage of covalent spacer), drug encapsulation (physical interaction between drug and

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carrier), biodistribution (molecular weight, addition of targeting group), biocompatibility (electrical charge, addition of bioinert functionality), and biodegradability (backbone, spacer), as well as their shape (materials and chemistry employed) (Qiu and Bae, 2006; Rozan *et al.*, 2022). Their unique size-dependent properties make these materials superior to other delivery systems and indispensable in many areas of human activity (Salata, 2004). This brief review attempts to summarize the most recent developments in the field of applied nanomaterials, particularly, their applications in biology and medicine, and discussed their prospects for commercialization.

Microtechnology and nanotechnology: A preamble

Microtechnology and nanotechnology are used for the fabrication of materials of micron and submicron scales, respectively. When utilizing materials in a nanoform, the field of nanotechnology blends science and technology. It focuses on the synthesis of materials at scales ranging from 1 to 100 nm with applications in various industries, including agriculture, medicine, and the pharmaceutical industry; environmental applications; and uses in other fields (Elegbede and Lateef, 2020; Lateef *et al.*, 2018). This technology is developing rapidly, and scientists and researchers are working hard to incorporate new ideas that involve synthesis or new applications (Lateef *et al.*, 2021). Ongoing studies are focusing on the composition, structure, morphology, and other aspects of nanoscale formulations, and further development of such characterizations is required (Bai *et al.*, 2022). Nanomaterials' physical, chemical, and biological characteristics are fundamentally distinct from those of individual atoms, molecules, and bulk materials at the nanoscale (Khan *et al.*, 2022). Their greater surface area and quantum effects set them apart from other materials in a significant way. Their larger surface area often results in more chemically reactive qualities and also impacts the mechanical or electrical properties of the materials (Findik, 2021).

A recent subfield of nanotechnology, nanobiotechnology, has created particles with specific forms and functions by integrating biological methods with physical and chemical processes. Nowadays, metal and metal oxide NPs formed using silver, platinum, selenium, iron, and gold, as well as copper oxide, zinc oxide, and titanium dioxide, are quite popular because of their numerous beneficial features in a variety of application domains (Aygün *et al.*, 2020; El-Batal *et al.*, 2020; Elfeky *et al.*, 2020). Many of the damaging impacts of physical and chemical methods, such as a long processing time and the use of toxic ethylene glycol and organic reagents, can be avoided by green procedures employing diverse biological entities. Nanomaterial-based green assemblies are widely used for synthesis; they mostly rely on plants, bacteria, algae, fungi, actinomycetes, and arthropod metabolites to produce nanomaterials free of contaminants (Fouda *et al.*, 2020; Lotha *et al.*, 2019). These living things, notably fungal cells, are capable of producing molecules and active substances that stabilize and reduce the formation of nanomaterials with a variety of forms, physiochemical properties, and compositional features (Feroze *et al.*, 2020; Salem *et al.*, 2021).

Microbial synthesis of nanomaterials

Microbial nanotechnology, which combines microbiology with nanotechnology, uses microbes as nanostructures. Microorganisms are regarded as the perfect sources of nanostructures for microbial nanotechnology (Rehman *et al.*, 2020a; Shobha *et al.*, 2020) because of their extensive physiological variety, tiny size, and genetic malleability. Fig. 1 shows the relationship between microbiology and nanotechnology for the development of

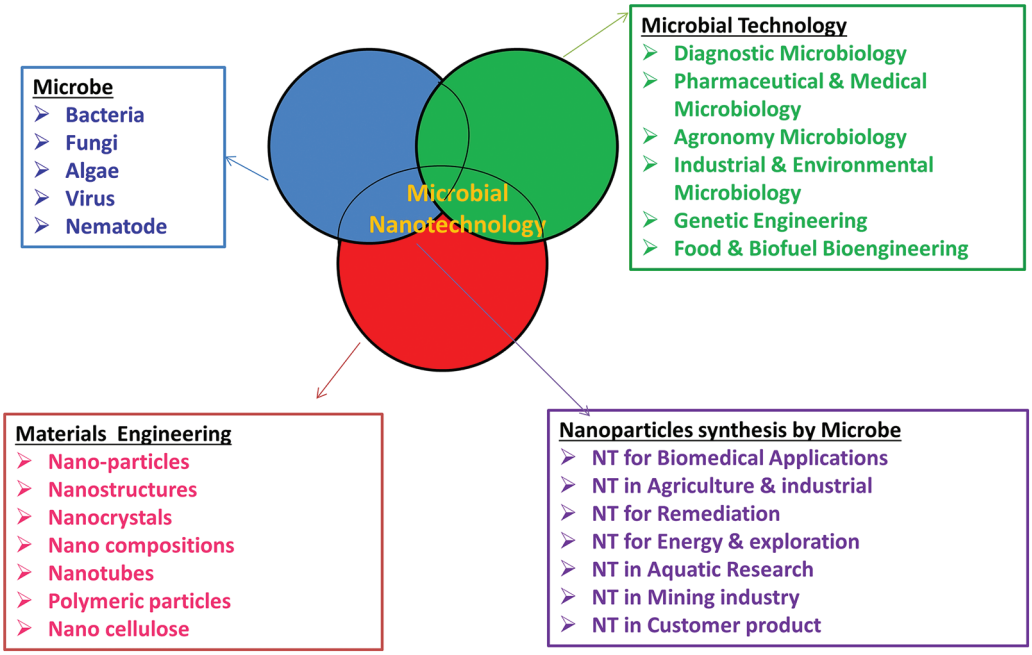

FIGURE 1. Relationship between microbiology and nanotechnology for the development of nanobiotechnology-based microbial (Ter-Zakaryan and Zhukov, 2021).

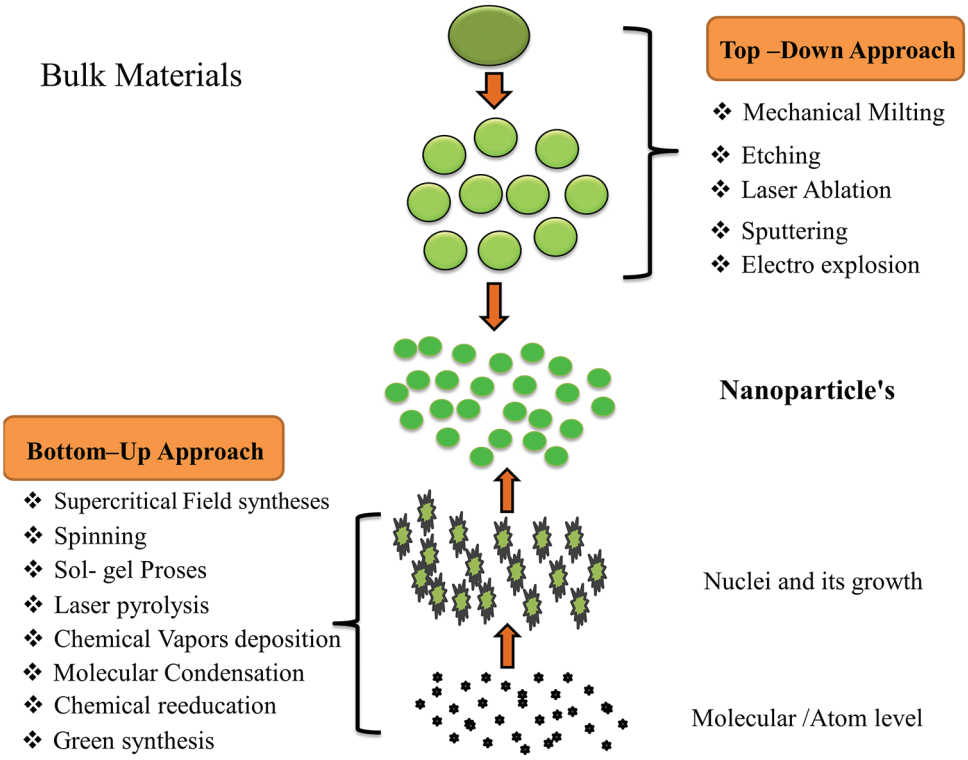

FIGURE 2. Synthesis of NPs either top-down or down-top approach.

nanobiotechnology-based microbial structures. It refers to a wide world encompassing bacterial, mycobacterial, viral, immunological, parasitological, protozoological, phycological, and nematological efforts (Saba *et al.*, 2021).

Green synthesis of nanoparticles by microorganisms

Various techniques have been employed for NP synthesis, including physical, chemical, and biological ones. Physicochemical approaches for NP synthesis have several drawbacks, including the use of costly machinery, the high generation of heat from the use of organic solutions that can be toxic, the limited capacity for solubility of substances with high melting points (Modan and Plăiașu, 2020), and the high energy consumption, as well as the limited yield of NPs (Gahlawat and Choudhury, 2019; Soni *et al.*, 2018).

The usage of hazardous chemicals, which can lead to environmental issues, is the fundamental disadvantage of these techniques (Pal *et al.*, 2019). There is now a demand for an ecologically benign method of producing NPs, with the current focus being on green synthesis methods using biological resources, such as plants, microbes, enzymes, polysaccharides, and degradable polymers (Roychoudhury, 2020). Due to its simplicity and cost-effectiveness and the fact that it does not require the use of hazardous or ecologically harmful substances, green synthesis is more advantageous than conventional physical and chemical procedures. Thus, it has become increasingly important in recent years (Pal *et al.*, 2019).

One of two approaches, generally referred to as the top-down and bottom-up approaches, is used to synthesize NPs. In the top-down approach, bulk materials are broken down into nanosized particles by various physical and chemical processes (Gahlawat and Choudhury, 2019; Prasad, 2019). The primary flaw of this method is that the NPs created have an irregular surface texture. This method is not ideal for large-scale manufacturing processes because it is a costly and time-consuming approach (Prasad, 2019). Bottom-up methods develop NPs by allowing atomic and molecular structures to self-assemble, giving them a more exact size, shape, and molecular makeup (Gahlawat and Choudhury, 2019). Fig. 2 illustrates how this technique uses both chemical and biological manufacturing methods.

Approaches and mechanisms of biosynthesis of nanoparticles by microorganisms

Most microorganisms have the potential to act as biofactories for the synthesis of eco-friendly and inexpensive NPs. Of these, the metals gold, silver, copper, zinc, and titanium, palladium, and nickel, are widely used. They can produce NPs with a predetermined form, size, content, and particle monodispersity (Fouda *et al.*, 2018; Kato and Suzuki, 2020; Khan *et al.*, 2018). The biosynthesis of NPs with microorganisms can be achieved by capturing target metal ions from their surroundings and converting them enzymatically into an elemental form via a reduction mechanism (Fouda *et al.*, 2018).

NPs are formed along metabolic or biosynthetic pathways and/or by cellular enzymes not present in all species; each microbe has a different metabolic process and enzymatic activity (Ramos *et al.*, 2020). Microorganisms must be able to tolerate heavy metals to produce NPs. High metal stress and several other parameters are important in determining the rate of production, yield, and morphologic features of NPs, including their temperature, pH, the concentration of metal precursor, and reaction time (Saxena *et al.*, 2016). These parameters also affect a variety of microbial processes. Certain bacteria are capable of reducing metal ions to a suitable metallic material while under stress

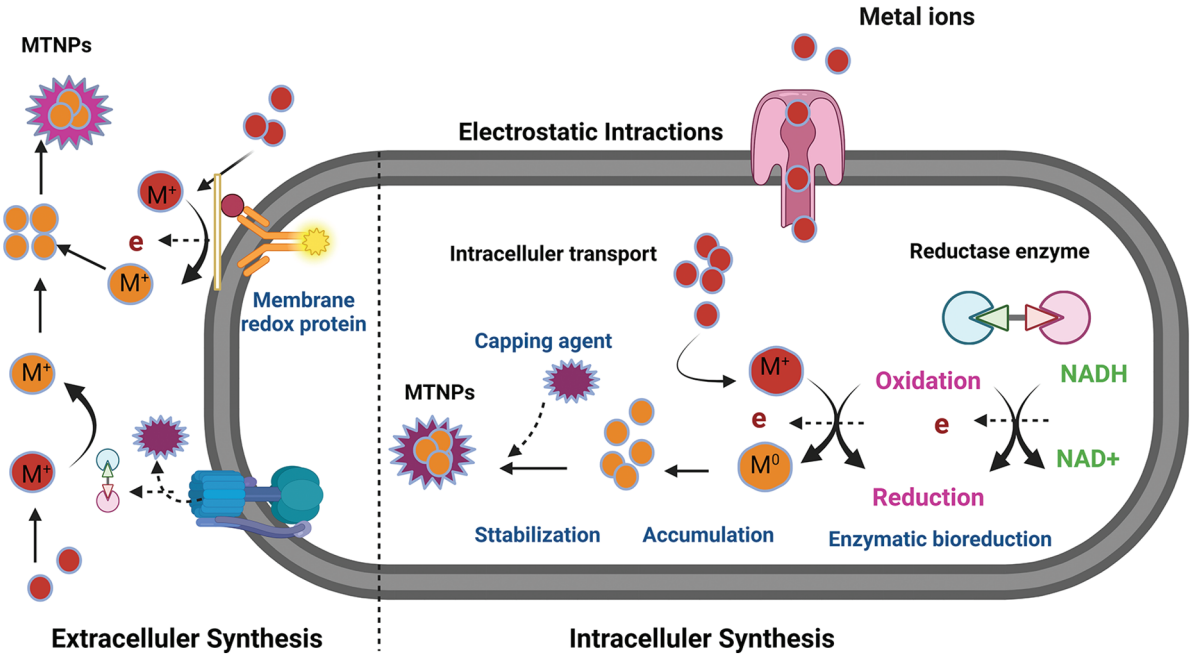

FIGURE 3. Mechanism of biosynthesis of nanoparticles by microorganisms.

(Husseiny *et al.*, 2015). In most cases, microorganisms that live in metal-rich ecosystems are extremely resistant to those metals because of the absorption and chelation of those metals by intracellular and extracellular proteins. Therefore, techniques based on imitating the natural biomineralization process may be advantageous for the synthesis of NPs (Rabeea *et al.*, 2020).

Fig. 3 is a schematic representation of the intracellular and extracellular pathways involved in the production of NPs. Through electrostatic interactions, metallic ions (positively charged) are deposited in cell walls (negatively charged). Ions are reduced through metabolic processes after being transported into the microorganism's cells to produce NPs, controlled by enzymes such as nitrate reductase. Subsequently, the NPs gathered in the periplasmic region might pass through the cell wall (Khan *et al.*, 2018).

Nitrate reductase is involved in the extracellular production of NPs. Reductase enzymes are found in the cell wall or released from the cell into the growth medium, and they create the NPs. The nitrate reductase converts metal ions to their metallic forms during this process. Microorganisms have various components critical to the reduction of NPs, including proteins, enzymes, and other biological molecules (Mohd Yusof *et al.*, 2019).

Studies have demonstrated that the synthesis of Mt NP is carried out by NADH-dependent enzymes. By using NADH-dependent reductases as the electron carriers, the reduction pathways appear to start by transferring an electron from NADH (Jain *et al.*, 2011). Additionally, microbes can release proteins that function largely as stabilizing agents, ensuring colloidal stability and inhibiting Mt NP clumping (Mohd Yusof *et al.*, 2019).

Effects of microbiologic synthesis factors of nanoparticles

There are some factors that can impact NP production, including the pH and temperature and the presence of specific enzymes; and the microbial biomass, precursor concentrations, and time of contact (Fig. 4). In order to maximize the production of silver NPs, zinc oxide NPs, and gold NPs from *Trichoderma* spp., *Sclerotinia sclerotiorum*, *Aspergillus terreus*, *Aspergillus niger*, and *Cladosporium cladosporioides*, researchers have looked at the temperature, inoculum of the fungal biomass, pH, and precursor concentration (Fouda *et al.*, 2018; Ramos *et al.*, 2020; Saxena *et al.*, 2016). They demonstrated how improving the aforementioned variables could considerably boost the production of these three NPs, and their mycosynthesis. Additionally, the size of the silver NPs produced by *Fusarium oxysporum* during mycosynthesis was significantly affected by the optimization of both the physical and cultural circumstances (Husseiny *et al.*, 2015).

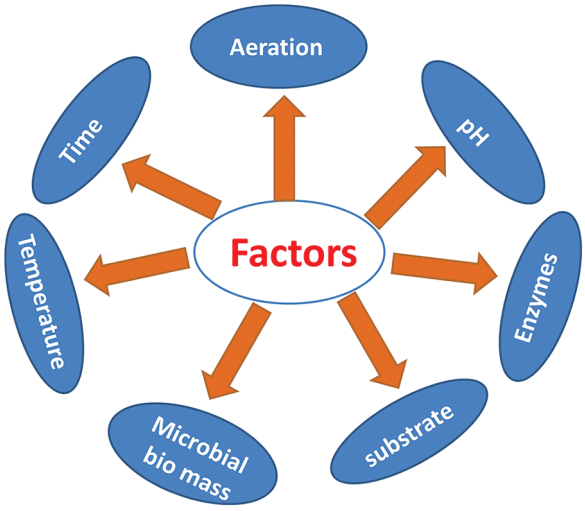

FIGURE 4. Factors affecting biosynthesizing of nanoparticles by microbiology.

TABLE 1

Fungi used for the synthesis of nanoparticles and their medical applications

NPs	Fungi	Size	Application in medicine	MIC	Ref.
Gold (Au) NPs	*Aspergillus niger* and *Trichoderma longibrachiatum*	4.88–22.27 nm 102.9–123.9 nm	Antimicrobial, antioxidant, anticoagulant, and thrombolytic activities	Antibacterial activity at 100 μg/mL^{-1} Antifungal activity at 150 μg/mL^{-1}	Elegbede *et al.* (2020)
	Fusarium solani	40–45 nm	Anticancer activities	0.8 ± 0.5 μg/mL^{-1} to 1.3 ± 0.5 μg/mL^{-1}	/
	Saccharomyces cerevisiae	18–15 nm	Controllable mycosynthesis	NI	/
	Cladosporium cladosporioides	60 nm	Antimicrobial and antioxidant activity	NI	/
	Pleurotus ostreatus	10–30 nm	Antimicrobial	NI	/
	Rhizopus oryzae	16–43 nm	Hemocompatibility	NI	/
	Penicillium aurantiogriseum	153.3 nm	Mycosynthesis NPs	NI	/
	Penicillium citrinum	172 nm			
	Penicillium waksmanii	160.1 nm			
Silver (Ag) NPs	*Penicillium chrysogenum*	5.2–9.7 nm	Biomedical application	0.172 mM	/
	Lentinus tuberregium	5–35 nm	Antibacterial and α-amylase inhibitory activity	12 μg/mL^{-1} to 15 μg/mL^{-1}	/
	Penicillium chrysogenum	26.38–61.75 nm	Biodeterioration	NI	Fouda *et al.* (2019)
	Alternaria tenuissima	9.8 nm	Antimicrobial and antioxidant properties	100 μg/mL^{-1}	/
	Phomopsis liquidambaris	18.7 nm	Antimicrobial and larvicidal activity	NI	/
	Ganoderma sessiliforme	45 nm	Antibacterial, antioxidant, and anticancer activities	NI	/
	Penicillium chrysogenum	18–60 nm	Anti-candida activity	62.5 μg/mL^{-1}	/
	Rhodotorula sp	8–21 nm	Antibacterial activity	0.25 μg/mL^{-1}	/
ZnO NPs	*Periconium* sp	16–78 nm	Antibacterial and antioxidant activity	40 to 50 μg/mL^{-1}	/
	Alternaria tenuissima	15.45 nm	Antioxidant, antibacterial, anticancer, and photo-catalytic activities	16.87 μg/mL^{-1} to 102.13 μg/mL^{-1}	Abdelhakim *et al.* (2020)
	Aspergillus niger	80–130 nm	Antioxidant activity, antibacterial, anticancer	NI	/
	Aspergillus niger	8–38 nm	Medical textile	NI	Mohamed *et al.* (2019)
	Aspergillus terreus	10–45 nm	Medical textile and UV protection	20 ppm	Fouda *et al.* (2018)
Platinum (Pt) NPs	*Penicillium chrysogenum*	5–40 nm	Cytotoxicity	40 μg/mL^{-1} to 80 μg/mL^{-1}	Subramaniyan *et al.* (2018)
Ag–Au NPs	*Aspergillus niger*	10.12–52.51 nm	Biomedical and catalytic activities	NI	Elegbede and Lateef (2020)
	Trichoderma longibrachiatum	6.98–25.20 nm			
	Neurospora crassa	3–90, 3–110 4–45 nm	Mycosynthesis	NI	/

(Continued)

Table 1 (continued)

NPs	Fungi	Size	Application in medicine	MIC	Ref.
Al_2O_3 NPs	*Colletotrichum* sp.	30–50 nm	Antibacterial activity	NI	/
Te NPs	*Aspergillus welwitschiae*	60 nm	Antibacterial property against MRSA	25 $\mu g/mL^{-1}$	/
Cobalt ferrite	*Monascus purpureus*	6.50 nm	Anticancer, antioxidant, and antimicrobial activities	250 $\mu g/mL^{-1}$ to 500 $\mu g/mL^{-1}$	/
Fe_3O_4 NPs	*Alternaria alternata*	5.4–12.1 nm	Antimicrobial activities	NI	/
	Aspergillus oryzae	10–24.6 nm	Mycosynthesis NPs	NI	/
Se NPs	*Penicillium corylophilum*	29.1–48.9 nm	Larvicidal, antibacterial and Cytotoxicity activities	171.8 and 104.3 ppm	Salem *et al.* (2021)
	Fusarium semitectum	32.80–103.82 nm	Anticancer and antimicrobial agents	NI	/
	Saccharomyces cerevisiae	75–709 nm	Antioxidant activity	5 $\mu g/mL^{-1}$	/
	Magnusiomyces ingens	70–90 nm	Anti-bacterial	NI	/
	Penicillium chrysogenum	33.84 nm	Biomedical and therapeutic applications	25.0 $\mu g/mL^{-1}$	/
CuO NPs	*Pleurotus ostreatus*	35 nm	Wound pathogens	NI	El-Batal *et al.* (2020)
	Stereum hirsutum	5–20 nm	Mycosynthesis	NI	/
CuO NPs	*Trichoderma asperellum*	10–190 nm	Development of anticancer nano-therapeutics	NI	/
	Stereum hirsutum	5–20 nm	Mycosynthesis	NI	/
TiO_2 NPs	*Aspergillus flavus*	–	Immunogenic and hematologic effects	20 $\mu g/mL^{-1}$	/
	Aspergillus niger	73.58–106.9 nm	UV protection and bacterial resistance, fabrication and larvicidal activity	6.7 ppm to 8.4 ppm	/

Myconanotechnology

Myconanotechnology is a field of science that combines mycology and nanotechnology (Rabeea *et al.*, 2020). In this developing field, fungi may be used to synthesize NPs or nanostructures with desired shapes and sizes (Fouda *et al.*, 2018; Subramaniyan *et al.*, 2018). A simple technique for rapidly generating stable biological NPs is mycosynthesis or mycofabrication. The effective and inexpensive synthesis of NPs can be done by simply cultivating fungi because they contain substantial metabolites (carbohydrates, proteins, and lipids) with better bioaccumulation capabilities and simple downstream handling (Fouda *et al.*, 2019).

Advantages of using fungi in nanoparticle synthesis

Fungi-mediated green NP generation has several advantages, such as simple and straightforward scaling up, simple processing, economic viability, good biomass processing, and good recovery of significant surface distances with the optimal outgrowth of mycelia (Abdelhakim *et al.*, 2020; Salem *et al.*, 2021). From an economic standpoint, the utilization of a fungal biomass filtrate containing various metabolites as a green way of producing metallic NPs was superior to previous biological techniques (Mohamed *et al.*, 2019). Additionally, different kinds of fungi grow swiftly and produce vast masses of fungal cells, and they can easily be kept safe in a laboratory (Elegbede *et al.*, 2020). As a result, extracellular synthesis of NPs is preferable to intracellular synthesis and is suitable for large-scale production. Research on intracellular manufacturing is possible for theoretical academic research. The employment of basidiomycetes for the creation of NPs has yet to be substantially researched, whereas syntheses utilizing lesser fungi and bacteria have been studied. The fungal biological system has environmentally benign and energy-saving regeneration characteristics. The most well-known species of mushrooms are found in the division Basidiomycota, order Polyporales. Over 1800 species of fungi are found in this division. Academic theoretic investigations on intracellular manufacturing are possible (Rehman *et al.*, 2020b).

Basidiomycetes are advantageous for the green production of nanoscale particles because they are nonpathogenic and non-toxic and can be grown in pure cultures (Rehman *et al.*, 2019). Due to their abilities to produce large amounts of protein and high yields of particles, their low residual toxicity, and ease of handling, fungi are appealing as reducing and stabilizing agents in the biogenic manufacture of silver NPs (Rehman *et al.*, 2019). Due to its many advantages, including its low cost, ease of

TABLE 2

Bacteria used for the synthesis of nanoparticles and their medical applications

NPs	Algae	Size	Application in medicine	MIC
Ag NPs	*Neochloris oleoabundans*	40 nm	Antibacterial	NI
	Amphiroa rigida	25 nm	Antibacterial, cytotoxicity, and larvicidal efficiency	NI
	Chaetomorpha linum	70–80 nm	Efficient anticancer agent	NI
	Leptolyngbya	5–50 nm	Antibacterial, anticancer	100 µL (1 mg/mL^{-1})
	Ulva armoricana sp.	33 nm	Bactericidal	10 µg/mL
ZrO_2 NPs	*Sargassum wightii*	18 nm	Antibacterial	NI
CdSe QD NPs	*Chlorella pyrenoidosa*	4–5 nm	Imatinib sensing	0.014 µg/mL^{-1}
Pd NPs	*Spirulina platensis*	10–20 nm	Adsorbent	0.5 g/L
Au NPs	*Spirulina platensis*	15.60–77.13 nm	Antiviral	NI
	Galaxaura elongate	3.85–77 nm	Antibacterial	NI
	Cystoseira baccata	8.4 nm	Anticancer	NI

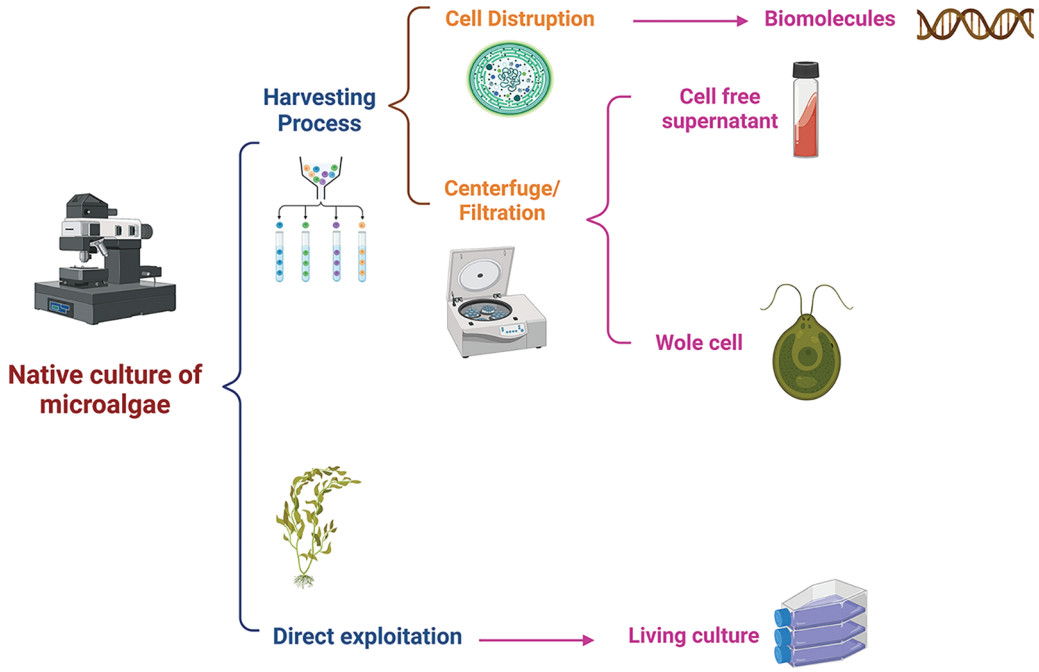

FIGURE 5. Method of nanoparticles biosynthesized by algae.

use and control, and exceptional qualities, *F. oxysporum* is used to manufacture NPs. It should receive greater publicity because it might be a practical solution for the industrial production of NPs (Zielonka and Klimek-Ochab, 2017). As shown in Table 1, several fungal species can be potentially used for preparations.

Advantages of using bacteria in nanoparticle synthesis

Due to their high yield and ease of handling, bacteria are desirable for use in biotechnological applications such as the manufacture of NPs. Bacteria have a built-in defense mechanism called CRISPR Cas, which enables them to deal with challenges such as changes in pH and hazardous environments brought on by concentrations of metal ions, among other things (Dauthal and Mukhopadhyay, 2016). There are certain disadvantages, too, such as a sluggish rate of synthesis, the difficulty of controlling the size and form of the NPs, and sterile conditions. As a result, employing plants and their components as an alternative for producing NPs is an option. Because plants are non-toxic, are naturally capable of capping ends, contain reducing metal ions, and have the capacity to collect heavy metals in their cells, they have attracted the interest of scientists all over the world (Marooufpour *et al.*, 2019).

As bionanofactories, several metallic NPs, including those of silver, gold, copper, selenium, and iron, as well as metal oxide NPs, including silver oxide, copper oxide, zinc oxide, and titanium dioxide, have been produced. It is important to control the conditions of the production process since the pH, the material utilized, the presence of light, the concentration of metal ions, and the temperature all have the potential to impact the shape and size of

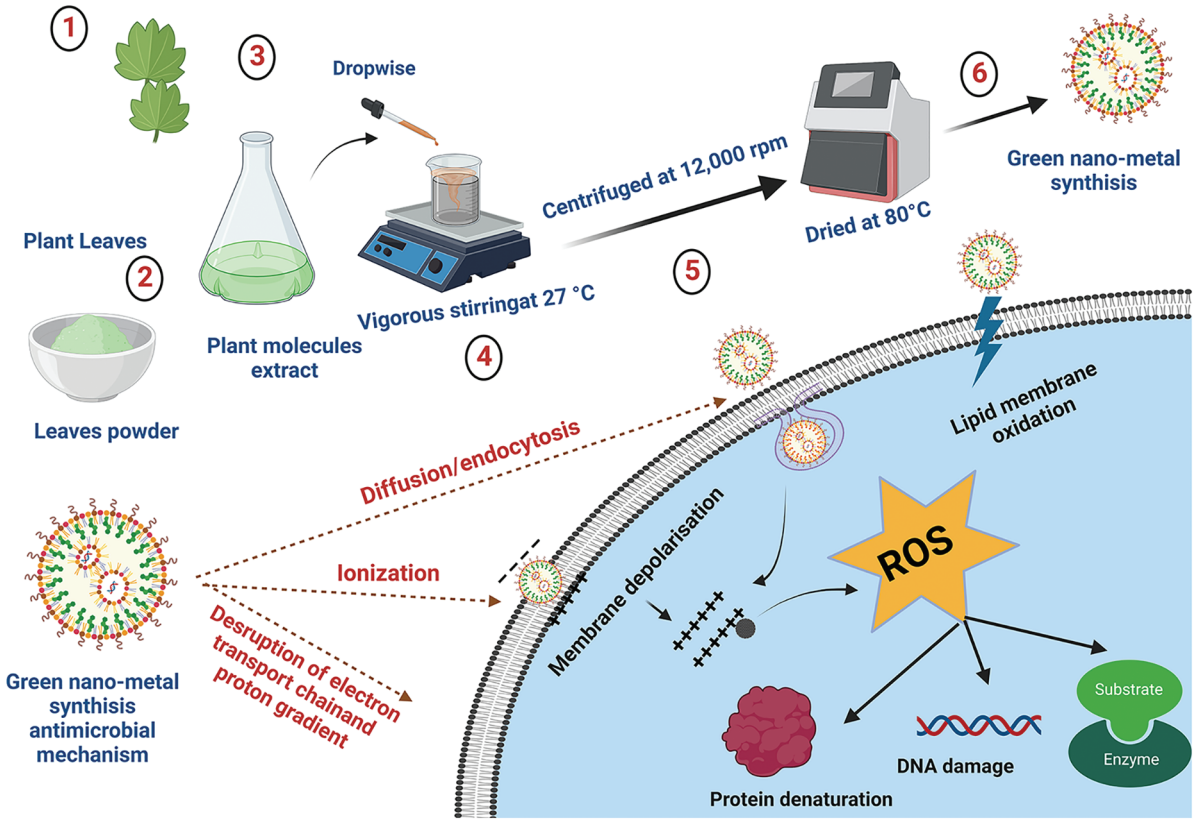

FIGURE 6. Techniques are used for the synthesis of nanoparticles via plant extracts and its antibacterial mechanism.

metallic NPs, as well as the efficiency of manufacturing them. Therefore, metallic NP biosynthesis is particularly significant when extremophilic bacteria are used that have naturally evolved to survive under severe environmental circumstances (e.g., high concentrations of metals, high and low temperatures, an acidic or alkaline pH, high pressure, high levels of salt, and high levels of radiation) (Atalah *et al.*, 2022).

Similar characteristics of other bacteria enable the control of the NPs' sizes. For instance, the thermophilic strain GWE1 of *Geobacillus wiegelii*, isolated from a drying oven, could create nonmetallic NPs. The microorganism could make elemental tellurium NPs when exposed to the sodium tellurite salt, and it could convert the selenium ion Se^{4+} to elemental selenium (SeO) and produce selenium NPs both within and outside of cells when exposed to sodium selenite. The pH and temperature have been demonstrated to affect the size and shape of selenium NPs generated by this microorganism (Atalah *et al.*, 2022). Adding 5% polyvinylpyrrolidone to the culture medium caused the NPs to shrink by 52% (da Silva *et al.*, 2019).

Advantages of using algae in nanoparticle synthesis

Using algae for the biosynthesis of NPs is becoming increasingly popular (Table 2). Phyconanotechnology is a very young area of nanoscience that deals with the use of algae to create NPs. Algae are employed to make NPs because they can grow at low temperatures, have a high capacity to absorb metal, are simple to handle and maintain, and are less harmful to the environment than some other entities (Negi and Singh, 2018).

Algae are frequently used these days for the production of NPs because of their remarkable ability to absorb metals and decrease metal ions, relatively inexpensive cost when used in manufacturing, and, most importantly, their ability to be used for the large-scale synthesis of NPs (Rajkumar *et al.*, 2021; Singh and Singh, 2019).

Their greater capacity to withstand extreme climatic conditions than other microbes is an additional intriguing characteristic (Khan *et al.*, 2019). An algal biomass may be utilized to create both alive and dead NPs, which is why these organisms are referred to as bionanofactories (Omar *et al.*, 2017). An additional benefit of employing algae is the duration of time necessary for the manufacture of silver NPs. Compared with other microorganisms, algae-mediated synthesis is faster. Synthesis of silver NPs from *Escherichia coli* takes around 60 h (Baltazar-Encarnación *et al.*, 2019).

Typically, an algal species produces an NP by first accumulating and then decreasing cations. The extracellular or intracellular processes can be used to produce them from the algal biomass (Fig. 5). In contrast to the intracellular process, which involves enzyme activity inside the cell wall and cell membrane, the bioreduction of a metal ion to its NP occurs on the surface of the algal cell in the extracellular pathway (Negi and Singh, 2018). Algae play an important role in the production of silver NPs under a variety of physical, chemical, and environmental circumstances. The extract or biomass content, pH, incubation period, lighting,

TABLE 3

Different methods of algal nanoparticle synthesis

Nanoparticles	Bacteria	Size	Medical application	MIC
Ag NPs	*Bacillus cereus*	20–40 nm	Antibacterial	NI
	Escherichia coli	5–50 nm	Antimicrobial	NI
	Exiguobacterium aurantiacumm			
	Brevundimonas diminuta			
	Thermophilic Bacillus sp. *AZ1*	9–32 nm	Antimicrobial	NI
	Gordonia amicalis	5–25 nm	Antioxidant scavenging activity	NI
	Lactobacillus gasseri	58.5 nm	Antimicrobial	NI
TiO_2 NPs	*Lactobacillus* sp.	50–100 nm	Antibacterial	62.5 μg/mL
Au NPs	*Micrococcus yunnanensis*	53.8 nm	Antibacterial and Anticancer	73.6 ± 1.9–105.3 ± 1.7 μg/mL
ZnO NPs	*Mycobacterium* sp.	5–55 nm	Anticancer	3500 μg/mL
	Aeromonas hydrophila	57.7 nm	Antimicrobial	25 μg/mL
Cu NPs	*Lactobacillus sporogenes*	145.70 nm	Antimicrobial	–
	Shewanella loihica	10–16 nm	Antibacterial	100 μg/mL
Cadmium sulfide NPs	*Bacillus licheniformis*	20–40 nm	Antibacterial	40 mg/mL
Zinc sulfide NPs	*Serratia nematodiphila*	80 nm	Antibacterial	50 mg/mL
Lead (IV) sulfide NPs	*Idiomarina* sp. *strain PR58-8*	6–10 nm	Bioimaging	NI
Selenium NPs	*Bacillus* sp.	80–220 nm	Antioxidant and cytotoxic effects	NI
	Pantoea agglomerans	90–110 nm	Antioxidant	41.5 ± 0.9 μg/mL

precursor concentration, and temperature are a few of the crucial variables.

Advantages of using medicinal plants in nanoparticle synthesis

Reports of microbe-based synthesis procedures date back to at least 1989. In contrast, the biological creation of NPs from plants did not start until 2002 (Singh *et al.*, 2020). The primary limitations of aseptic conditions and complex procedures, such as microbial isolation, growth optimization, and maintenance, which demand trained personnel and slow reaction times, increase the scaling-up cost (Herlekar *et al.*, 2014). They are the major drawbacks of microbe-mediated NP synthesis. On the other hand, depending on the kinds of plants employed and the concentration of phytochemicals, plant-mediated NP production can be finished in a few minutes or hours (Ameta *et al.*, 2018). Plant-mediated synthesis of metallic NPs is gaining in popularity due to its ease of use, the speed of producing NPs with a variety of morphologic characteristics, lack of need for labor-intensive cell culture maintenance, and environmental friendliness (Velmurugan *et al.*, 2016). Plant extracts are employed in various ways to manufacture NPs, as shown in Fig. 6, and different types of NPs are produced by biosynthesis, as shown in Table 3. These methods save money, are environmentally beneficial, and do not require complicated procedures (Celik *et al.*, 2020; Koca *et al.*, 2020).

However, the green synthesis of NPs using plant materials has more advantages, such as environmentally friendly behavior, less toxicity, lower cost, more biocompatibility, better profile for controlling the size, and biocompatibility (Bhardwaj *et al.*, 2020). The metal NPs

TABLE 4

Different nanoparticles produced by different parts of plants

NPs	Plants	Size	Medicinal application	MIC	Ref.
Ag NPs	*Nigella sativa*	25.2 nm	Anti-inflammatory and antioxidant effects	NI	/
	Vitis vinifera's tannin fruit	40–60 nm	Antimicrobial activity	NI	/
	Allium rotundum, *Falcaria vulgaris Bernh Ferulago angulate* Boiss	20 nm	Antimicrobial activity	MIC of tetracycline to *Pseudomonas aeruginosa* and *Staphylococcus aureus* was 32 and 33 μg/mL, respectively. The MIC of kanamycin to *P.*	/

(Continued)

Table 4 (continued)

NPs	Plants	Size	Medicinal application	MIC	Ref.
				aeruginosa was 30 μg/mL, and the MIC of cefpirome against *S. aureus* was 35 μg/mL.	
	Brillantaisiapatula, *Crossopteryxfebrifuga* and *Senna siamea*	45–110 nm	Antimicrobial activity	NI	/
	Andrographis paniculata	410 nm	Antimicrobial and cytotoxic Activity	The NPs cause hemolysis (4% hemolysis) to human RBCs at 12.5 μg/mL. *In vitro* MTT assay of Ag NPs exhibited that half of the cells were killed at 10 μg/mL. Moreover, the wound healing assay revealed an effective inhibition of cello proliferation.	/
	Gomphrena lobose (Globe amaranth) leaf extract	15–25 nm	Antibacterial	NI	/
	Parkiaspeciosa leaf extract	20 nm	Antioxidant and antibacterial	NI	/
Se NPs	*Urtica dioica*	633 nm	Antibacterial activity against Gram-positive and Gram-negative bacteria, as well as unicellular and multi-cellular fungi	SeNPs against *Escherichia coli*, *P. aeruginosa*, *Bacillus subtilis*, and *S. aureus* were 250, 31.25, and 500 μg mL^{-1}, respectively, and 62.5, 15.62, 31.25, and 7.81 μg mL^{-1} against *Candida albicans*, *Aspergillus fumigatus*, *Aspergillus niger*, and *Aspergillus flavus*, respectively. The cytotoxicity of SeNPs was performed on Vero normal-cell line CCL-81, where IC_{50} was 173.2 μg mL^{-1}.	/
Ag-Se NPs	*Nepeta* and *Berberine* plant extract	120 nm	*Anti–A. fumigatus*: TIMML-025, *C. parapsilosis*: ATCC-2201, *C. albicans*: TIMML-491 and *A. flavus*: TIMML-050	0.125 μg/mL	Salem *et al.* (2021)
ZnO NPs	Leaf of *Becium grandiflorum*	20 nm	Anti-bacterial	NI	/
	Leaf of *Cassia fistula* and *Melia azadarach*	3–68 nm	Anti-bacterial	10 μL to 200 μL	/
TiO_2 NPs	Leaf of *Mentha arvensis*	20–70 nm	Anti-bacterial	10 μg/mL	/
	Leaf of *Ochradenusarabicusis*	20–40 nm	Anti-bacterial	*S. aureus* (31.25 μg/mL) *P. aeruginosa* (128 μg/mL)	/
	Seed of *Nephelium lappaceum* L.	70–90 nm	Anticancer	73.65 μg/mL	/
CuO NPs	Leaf of *Terminalia chebula*	100 nm	Applications on diesel engine	NI	/
	Leaf of *Cedrus deodara*	100 nm	Antimicrobial	*S. aureus* (MIC = 25 lg/mL) and *E. coli* (MIC = 150 lg/mL)	/
	Leaf of *Olea europaea*	75 nm	Antimacriobial and anticancer	NI	/
αFe_2O_3	Leaf of *Stevia rebaudiana*	18.34 nm	Antimicrobial and anticancer	NI	/

derived from plant extracts have been shown to be biocompatible and also nontoxic, and have therefore, recently received much attention. These NPs have antiviral, antibacterial, and anticancer properties (Mittal *et al*., 2013; Rajan *et al*., 2015), offering a great potential for targeted drug delivery (Table 4).

Conclusions

NPs and microparticles derived from molecular substrates such as algae, fungi, bacteria, and medicinal plants have been widely employed for several biological applications. The primary goal of nanotechnology is to develop reliable stream-lined production methods that regulate the chemical composition, morphologic features, and monodispersing systems in the large-scale production of nanomaterials. NPs offer good possibilities for the delivery of medications, imaging, and biosensing because of their tiny size, which allows them to permeate tissues and be ingested by cells. The most recent developments in the use of NPs for diverse therapeutic purposes have been highlighted in a number of studies cited in this review. Numerous eco-friendly designs for the synthesis of NPs from plants, bacteria, and fungi (green synthesis) have been mentioned and recommended because of their environmentally friendly attributes, low toxicity, low cost, good biocompatibility, good profile for controlling the size of NPs, and biocompatibility. The use of NPs for antimicrobial and cancer therapies is one area that has attracted much interest. The designs show significant promise for delivering medicines directly to tumors while limiting side effects related to hazardous chemotherapies. The benefits are due to the tiny size of these particles, their tendency to collect in tumors, and their ability to attach to the outer membranes of bacteria. The use of NPs and microparticles for immunological therapies has also garnered significant interest.

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