Chapter 2
Medical and Cosmetic Applications of Fungal Nanotechnology: Production, Characterization, and Bioactivity

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Abstract Nowadays, nanotechnology is widely applied for the development of highly efficient products in the pharmaceutical and cosmetic industries. Converting bioactive materials to nanoscale not only increases their biocompatibility but also increases their effectiveness, even when lower doses are used. Metal nanoparticles can be synthesized by fungal cells both intra- and extracellularly. Stabilization of the physical and chemical properties of various noble metal nanoparticles produced by fungi can be achieved through controlling the size, surface morphology, and surface chemistry of the nanoparticles. Intracellular synthesis provides smaller nanoparticles with well defined dimensions, but contributes to difficulty in downstream processing activity as compared with synthesis by extracellular methods. Recently, the production of nanoparticles from fungi has received extensive attention, owing to the capacity of fungi to produce nanoparticles extracellularly, a process that is more reliable and

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ecofriendly than intracellular methods, with relatively simple downstream processing. Fungi secrete extracellular enzymes for their survival and they control metal cation transportation to maintain intracellular homeostasis; when more protein is excreted nanoparticle synthesis is increased. To maximize nanoparticle synthesis, the rate of their synthesis can be increased through optimization of the total fungal cell mass and bioprocessing parameters, such as time of exposure, temperature, and pH. This will facilitate increased productivity in the fungal synthesis of nanoparticles for applications in the pharmaceutical and cosmetic industries.

Keywords Cosmetics · Nanotechnology · Antibacterial · Antiviral · Fungi · Algae · Mushroom · Drug delivery · Cancer therapy · Wound healing

2.1 Introduction

Nanotechnology presents a new trend for the creation and control of nanometer-sized features in materials and devices, leading to the development of new products in the food, cosmetic, personal care, pharmaceutical, medical device, agricultural, and environmental industries (Prasad et al. 2014, 2017b). However, a great emergent issue in nanotechnology is the applicability of the technology for the production of reliable and cost-effective synthesized nanoparticles (NPs) or nanocomposites of less than 100 nm (Thakkar et al. 2010). Naturally, bulk materials have consistent physical properties regardless of their size (Husein and Siddiqi 2014). However, when in the form of nanoscale particles they undergo some changes in their electric, magnetic, optical, and chemical properties (Castro et al. 2014; Chan and Mat Don 2013), owing to changes in the shape and size of the particles (Chan and Mat Don 2013). Silver and gold are among the most studied metals because of their potential use in medical and cosmeceutical products (Schröfel et al. 2014). Although regarded as inert materials, silver nanoparticles (Ag-NPs) function well with antimicrobial compounds by inducing the production of reactive oxygen species, such as hydrogen peroxide, to enhance antimicrobial activity (Deepek et al. 2011). Thus, they can act as antimicrobial agents to reduce infections with pathogens during surgery and to combat the problem of microbial resistance to antibiotics. Recent research has shown that Ag-NPs also exhibit anti-inflammatory, anti-angiogenic, and anti-permeability activities, and thus they have become useful for health-care industries (Zare et al. 2012; Schröfel et al. 2014; Park et al. 2016). Gold nanoparticles (Au-NPs) exhibit potential anticancer and antimicrobial properties, as well usefulness in the treatment of a wide range of skin diseases (Schröfel et al. 2014; Zare et al. 2012; Li et al. 2011; Srivastava and Constanti 2012). Advances in this technology have led to the development of Au-NPs with unique optical, electrical, and photothermal properties with high stability that support their application in health care and medical diagnostics (Shedbalkar et al. 2014; Yadav et al. 2015). Apart from Ag-NPs and Au-NPs, other metal nanoparticles, such as those of platinum, magnetite (Fe_3O_4), Zinc oxide (ZnO), and cadmium salts (Cd salts) have been synthesized using different green technologies (Ding et al. 2015; Mirzaei and Darroudi 2017; Bharde et al. 2006; Velusamy et al. 2016).
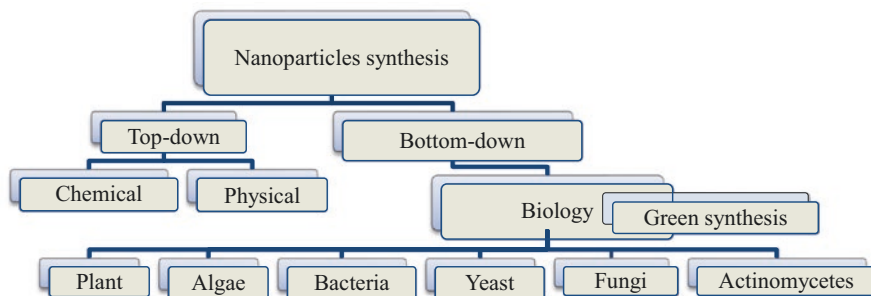
Fig. 2.1 Synthesis of metallic nanoparticles

The production of NPs was previously done by conventional physicochemical methods. However, these methods have several negative impacts, in that they release residues that are highly toxic for humans and cause severe environmental problems for the disposal of this dangerous waste. In addition, these methods involved the use of high tech instruments and high energy consumption, limiting the use of this technology on a commercial scale (Kitching et al. 2014; Pantidos and Horsfall 2014). Recently, novel approaches have been developed for the production of NPs based on using biological systems such as plants and microorganisms; this is known as wet technology. This method has many advantages, such as its low cost, energy-efficiency, and production of nontoxic products, when compared with the physico-chemical approach. The most important aspect of this wet technology is that the characteristics of NPs are well defined and their properties can be customized through controlling their particle size, shape, composition, and morphology; this governs their chemical stability and optical properties, such as plasmon resonance (Mock et al. 2002); their antimicrobial activities (Wani and Ahmad 2013); and their catalytic properties (Zhou et al. 2010).

2.2   Green Synthesis of Metal Nanoparticles

Currently, since noble metal nanoparticles are widely applied in areas related to human health, there is a growing need to develop the sustainable production of NPs that avoids the use of harmful organic chemical substances (Shams et al. 2013). The disadvantages of physicochemical NP synthesis are mainly the low production rate, structural particle deformation, and inhibition of particle growth. The diversity and importance of nanotechnology for us has led to the development of versatile methods to synthesize Ag-NPs with well defined and controlled properties. Generally, there are two main approaches to the synthesis of nanomaterials: "top-down" and "bottom-up" (Fig. 2.1). The "bottom-up" approach involves a homogeneous system wherein catalytic activity to synthesize nanoscale materials can be controlled by catalytic agents such as reducing agents and enzymes, with bioprocessing conditions involving stabilizers and appropriate temperatures, exposure times, and pH

with the relevant metal ion (Oza et al. 2012; Iravani 2014; Das et al. 2014). The physicochemical properties, surface structure, and morphological characteristics of the produced NPs depend on the precursor concentrations and reaction conditions (Mason et al. 2012). In contrast, the synthesis of NPs by the "top-down" approach basically works with the material in bulk form, and size reduction to the nanoscale is achieved by specialized physical or chemical, or both, treatments. However, the application of physical treatments such as lithography, thermal decomposition, laser ablation, mechanical milling, etching, and sputtering thermal decomposition of silver compounds; as well as radiation-assisted, electrochemical, sonochemical, and microwave-assisted processes is not preferred because of the high energy consumption involved (Varshney et al. 2009; Abou El-Nour et al. 2010; Elzatahry et al. 2012). Therefore, chemical reduction is the most common synthetic pathway for metal NP synthesis (Pal et al. 2011; El-Faham et al. 2014). In this way, negatively charged Ag-NPs can be obtained from a process using sodium citrate acting as a reducing agent, while positively charged Ag-NPs can be produced from reactions with branched polyethyleneimine, formaldehyde, alkali metals in ammonia, inorganic and organic borohydrides, ascorbic acid, free radicals, monoalcohols, polyols, acetonitrile, hydrazine, citrate, or ethylene diamine tetra acetic acid (Varshney et al. 2009). As reported by Thakkar et al. (2010), the major drawback of chemical and physical synthesis is an imperfect surface structure that can contribute to the physical properties and surface chemistry of the nanoscale materials in terms of the surface area-to-volume ratio.

In general, many of the reducing agents, solvents, and additives used in the reduction process when NPs are synthesized by "top-down" approaches often pose severe environmental and biological risks and the NPs are not suitable for human application. Therefore, it is important to develop ecofriendly non-toxic precipitation processes, especially for the large-scale production of NPs. The physicochemical approaches are also characterized by a low production rate, structural particle deformation, and inhibition of particle growth (Varshney et al. 2009). Considering the rather limited choices of water-soluble precursor compounds in the "bottom-up" approach, most attempts to produce NPs through green synthesis by microorganisms focus on selecting capping and reducing agents which is the metabolites synthesis by the microbes and the cell mass itself. The main reason for this focus is to be able to synthesize homogeneous NPs with uniform shapes and sizes, a feature that contributes to the optical properties of the NPs. This is important for applications in biological and chemical fields, as well as for optical, medical, and electronic devices (Suresh et al. 2010; Gurunathan et al. 2014; Prasad 2014).

2.3   Microorganism-Mediated Synthesis of Nanoparticles

Much research has been published on the production of metallic NPs by microbial cells by wet synthesis. In general, microorganisms have the capacity to detoxify heavy metals, which they do mainly with metal-binding proteins and peptides, as a bioremediation process for survival in areas contaminated with heavy metals. This mechanism provides several advantages for the biosynthesis of NPs compared with the traditional chemical synthesis methods (Pantidos and Horsfall 2014). Thus, microorganisms are considered as potential biofactories for the synthesis of NPs of different metals such as gold, silver, platinum, palladium, and titanium. Microorganisms are known as efficient NP biofactories because of their capacity to produce large amounts of proteins, enzymes, amino acids, polysaccharides, and vitamins, which act as reducing and capping agents for reducing metal ions (Prasad et al. 2016). The biosynthesis of metallic NPs by various microbes, such as bacteria, yeasts, algae, and lower fungi, as well as edible mushrooms, has been studied (Prasad et al. 2016). First, the microorganism chosen for the synthesis of the NPs should be of the generally-regarded-as-safe (GRAS) category according to the United States Food and Drug Administration (FDA) and should belong to Risk group level 1 as defined by the World Health Organization (WHO) (Fernández et al. 2016). Therefore, it is recommended that the synthesis of NPs should be performed with GRAS microorganisms to avoid any toxic metabolites. Thus, research has focused on microbes classified as GRAS, such as lactic acid bacteria, as well as edible mushrooms, for application in the nutraceutical and food industries (Sen et al. 2013a, b; Al-Bahrani et al. 2017; Visha et al. 2015; Markus et al. 2016). The extracellular synthesis of NPs using biomass or cell-free filtrate, owing to its simpler and cheaper downstream processing, seems to be preferable to intracellular synthesis (Abo-State and Partila 2015). The intracellular synthesis of NPs requires additional steps, such as ultrasound treatment or reactions with suitable detergents to optimize the biosynthesis and release of the NPs (Kalimuthu et al. 2008; Das et al. 2014). Castro et al. (2014) reported the extracellular synthesis of Au-NPs of different shapes, including spherical, triangular, hexagonal, decahedral, and pyramidal, by *Botrytis cinerea*. *Aspergillus oryzae* var. *viridis* has been reported to synthesize spherical Au-NPs both extracellularly and intracellularly with particle sizes between 10 and 60 nm (Binupriya et al. 2010; Siddiqi and Husen 2016). However, the greatest advantages of biosynthesis by fungae are that the synthesis of stable NPs is done in a single step and the NP sizes and shapes are controlled; there is also a lack of complex chemicals, and a lack of toxic contaminants (Singh et al. 2016).

The biosynthesis of metal NPs by microbes can be controlled in terms of shape, size, particle dispersity, and stability (Sarangadharan and Nallusamy 2015). The smaller the size of the NPs the better, in terms of conductivity, chemical stability, and catalytic and antibacterial activity. Therefore, the main features of NPs that are good antimicrobial agents are small size and uniform shape. The advantage of the synthesis of small particles with uniform dispersion is that this improves the effective surface area of of the NPs, reducing their stability in solution and their surface

reactivity (Klaine et al. 2008; Wigginton et al. 2010; Sarangadharan and Nallusamy 2015). Several approaches can be used to control NP size during the production process; namely, optimizing the concentration of the metal solution and the pH at the beginning of the process. Some studies have also reported the influence of the microbe growth phase and the role of light during the synthesis of NPs. Sarangadharan and Nallusamy (2015) reported on the production of smaller size Ag-NPs, ranging from 3 to 130 nm, when *Bacillus licheniformis* was exposed to 1 mM $AgNO_3$ solution, and the size of the NPs increased with increased concentrations of $AgNO_3$ solution. The size distribution and dispersal of the NPs contribute to the stability of the Ag-NP surface plasmon band, which avoids aggregation of particles in aqueous solution, was also affected by the concentration of the $AgNO_3$ solution. However, the size and stability of metal NPs also depends on the species and strain of microbe and the biosynthesis capacity of the capping agents used (Ahmad et al. 2003a, b).

2.3.1 Bacteria

The biosynthesis of NPs by microbes provides uniformity in both size and morphology of the NPs when compared with physicochemical methods. It has been reported that, with the extracellular production of Ag-NPs, when Ag+ ions were added to the supernatant the color changed to brown and the color intensity increased with the period of incubation, owing to the reduction of Ag+ to Ag^0 (Kushwaha et al. 2015). Several bacterial strains, such as *Bacillus* sp., *Lactobacillus* sp*., Pseudomonas* sp., *Escherichia coli*, *Geobacillus ferrireducens, Klebsiella aeruginosa, Actinomycetes,* and *Aeromonas* sp. were employed successfully for the synthesis of metal NPs. As studied by Zhang et al. (2011a, b), under controlled conditions at 28 °C and ambient pressure, *Pseudomonas alkaliphila* synthesized monoclinic selenium NPs with a well defined shape.

The advantages of using bacteria for the production of NPs, compared with other biological routes, are their ease of handling, short cultivation period, and the ease of high cell density production with an optimized cultivation strategy. Therefore it is important to study the optimum bioprocessing conditions for the biosynthesis of NPs. He et al. (2007) showed the critical effect of the initial pH of the bioprocessing process on Au-NP size and morphology during biosynthesis by *Rhodopseudomonas capsulata*. They also reported that the non-pathogenic *E. coli* MC4100 and *Desulfovibrio desulfuricans* ATCC 29577, isolated from jewelry waste, showed gold bioremediation capacity when added to 2 mM $HAuCl_4$ solution. At acidic pH, single spherical Au-NPs (less than 10-nm diameter) were produced, but for pH values between 7.0 and 9.0, a mixture of smaller (∼10 nm) and bigger (∼50 nm) well defined triangles, hexagons, and rods was formed (Iravani 2014).

Much research has also shown the capacity of *Bacillus* sp. to produce Au-NPs and Ag-NPs of different sizes and shapes (Gopinath and Velusamy 2013). The study of Das et al. (2014) demonstrated that *Bacillus* sp. isolated from soil heavily contaminated with metal synthesized NPs both intracellularly and extracellularly, with

the size of the Ag-NPs ranging from 42 to 92 nm. Pugazhenthiran et al. (2009) reported the isolation of a silver-resistant airborne *Bacillus sp.* that could synthesize small Ag-NPs of 10–15 nm in size in the periplasmic space of the bacterial cells (i.e., between the outer and inner cell membranes). Other research showed that *Bacillus subtilis* synthesized Au-NPs both intracellularly and extracellularly after 1-day addition of chloroaurate ion, while Ag-NPs were biosynthesized only extracellularly after 7-day exposure to silver ions, with the NPs being smaller than 10 nm (Reddy et al. 2010). The supernatant from *Bacillus licheniformis* may act as both reducing and capping agents in Ag-NP synthesis. This supernatant, which is rich in enzymes, proteins, and amino acids, plays an active role in the reduction of silver ions (Sarangadharan and Nallusamy 2015). The widely accepted mechanism for the synthesis of Ag-NPs is via reduction mediated by the nitrate reductase enzyme (Park et al. 2016; Sawle et al. 2008). Nicotinamide adenine dinucleotide (NADH) and NADH-dependent nitrate reductase enzyme are known as cofactors in the bioreduction of Ag^+ to Ag^0 in metal NPs (Sarangadharan and Nallusamy 2015). Fourier transform infrared spectroscopy (FTIR) analysis has been used to determine the functional chemical groups in dried AgNPs samples (Gopinath and Velusamy 2013; Sarangadharan and Nallusamy 2015). FTIR analysis has shown the reducing/capping protein that accounts for both the bioreduction and stabilization of AgNPs by *Bacillus* sp. FTIR spectral analysis of protein in the cell-free supernatant of *Bacillus megaterium* (NCIM 2326) revealed the presence of stretching vibration of Ag-NPs at 3392, 2142, 1642, and 718 in the region of 450–4000 cm^{-1}. The bond stretching were identified as C–H, C=O, C–C and O=C; this arises owing to carbonyl stretch in the amide linkage of the protein, which strongly binds silver to form a coat that covers and stabilizes the Ag-NPs (Saravanan et al. 2011).

2.3.2 Yeasts

Yeasts such as *Candida glabrata* (Velusamy et al. 2016), *Saccharomyces cerevisiae* (Sen et al. 2011), *Cryptococcus laurentii*, and *Rhodotorula glutinis* (Fernández et al. 2016), and *Magnusiomyces ingens* (Zhang et al. 2016a, b) have been reported to produce metallic NPs. The NPs produced by yeasts have good potential for the bulk production of NPs by a simple and ecofriendly method (Yadav et al. 2015). Synthesized Ag^0 and Au^0 nanoparticles exhibited excellent catalytic activities for the reduction of nitrophenols (4-NP) (i.e., 4-nitrophenol, 3-nitrophenol, and 2-nitrophenol) to aminophenol (4-AP) in the presence of $NaBH_4$ (Zhang et al. 2016a, b; Fernández et al. 2016); this was related to the particle size and the functional groups on the surfaces of the NPs that were responsible for the catalytic activity (Mishra and Singh 2015). Cell-free supernatant of *Magnusiomyces ingens* LH-F1 showed capacity for the rapid synthesis of Au-NPs within 4–6 h when incubated with Au^{3+}. The produced Au-NPs had various shapes, including spherical, triangular, and hexagonal structures (Zhang et al. 2016a, b). FTIR analyses and sodium dodecyl sulfate-polyacrylamide gel electrophoresis suggested that

protein-containing amide and carboxyl groups could be adsorbed on the surfaces of Au-NPs, and these groups could be involved in the reduction of Au^{3+} and the stabilization of Au-NPs. Similar observations were made in the synthesis of NPs with the cell-free supernatants of *Cryptococcus laurentii* and *Rhodotorula glutinis* (Fernández et al. 2016). The production of Ag-NPs was evidenced by the appearance of a color change from pale yellow to dark brown in the reaction flasks. In this study, the larger nitrate NPs had an important role in catalytic reduction, and the smaller particles generally exhibited higher activities (Zhou et al. 2010).

Zhang et al. (2016a, b) observed that different cell concentrations, as well as initial gold ion concentrations, controlled the sizes and shapes of the synthesized NPs. No synthesis of Au-NPs was observed when the concentration of $HAuCl_4$ at the beginning of the activation was over the threshold limit for the synthesis of NPs (Zhang et al. 2016a, b). On the other hand, with the same accepted concentration of the gold salt for maximum reduction to Au^0 and increasing cell numbers, the particle size was decreased and this contributed to a difference in the average size of the NPs. Cell numbers and gold salt concentrations were also used as critical variables to control NP size (Pimprikar et al. 2009). To conclude, optimization of the processing conditions, such as the incubation period, the ratio of metal ions and cell mass, temperature, pH, and aeration may influence the size, distribution, and shape of NPs, as well as the overall productivity of NP synthesis (Singh et al. 2016).

2.3.3 Algae

The synthesis of pure metallic Ag-NPs and Au-NPs by the reduction of Ag^+ and Au^+ ions was reported using powder or extracts of the seaweed *Sargassum longifolium* (Rajeshkumar et al. 2014), and powder or extracts of *Enteromorpha flexuosa* (Abdel-Raouf et al. 2013), *Padina pavonica* (Isaac and Renitta 2015), *Scenedesmus abundans* (Aziz et al. 2014), *Chlorella pyrenoidusa* (Oza et al. 2012), *Sargassum tenerrimum*, and *Turbinaria conoides* (Ramakrishna et al. 2016). The production of extracellular Au-NPs using *P. pavonica* was achieved within 24-h exposure to the metal ion solution. The resulting NPs were spherical, with size ranging from 30- to 100-nm diameter, and they exhibited high antibacterial activity against *Bacillus subtilis*, but less bactericidal activity when tested against *E. coli* (Isaac and Renitta 2015).

Abdel-Raouf et al. (2013) showed the synthesis of highly stable Au-NPs by *Galaxaura elongata* using the cell powder and ethanolic algal extract. The NPs produced were spherical, along with a few rods and triangular, truncated triangular, and hexagonal-shaped NPs with a size range of 3.85–77.13 nm and very smooth edges. Interestingly, in this study, Abdel-Raouf et al. (2013) observed that chemical constituents of the algal extract, such as andrographolide, alloaromadendrene oxide, glutamic acid, hexadecanoic acid, oleic acid, 11-eicosenoic acid, stearic acid, gallic acid, epigallocatechin, catechin, and epicatechin gallate acted as reducing, stabiliz-

ing, and capping agents. Furthermore, the NPs synthesized by *G. elongata* powder were found to be highly effective as antimicrobial agents against *E. coli* and *Klebsiella pneumoniae*. Recently, the biophysical synthesis of Ag-NPs was successfully achieved by a combination of Calothrix algae with ultrasound irradiation, which process was also efficient for the rapid synthesis of Au-NPs with a truncated conical shape, with sizes in the range of 30–120 nm (Kumar et al. 2016). This synthetic protocol was low cost, ecofriendly, and active for catalytic conversion in reducing 4-NP to 4-AP via a one-step reduction process.

Brown seaweed mediated a single-step process for the synthesis of Ag-NPs when an extract of *Sargassum longifolium* was used (Rajeshkumar et al. 2014). The production of Ag-NPs was improved when the biosynthesis processing conditions, such as incubation time and pH, were further optimized. These authors reported that the increased ultraviolet-visible (UV-vis) absorbance they observed, as a function of increased NP synthesis, was owing to an increase in the pH level. The synthesized Ag-NPs were characterized by scanning electron microscope (SEM), showing that their shape was spherical. FTIR analysis confirmed the presence of biomolecules responsible for the reduction of Ag ions and capping of the particles. The algal-mediated Ag-NPs showed high activity against pathogenic fungi, such as *Aspergillus fumigatus*, *Candida albicans*, and *Fusarium* sp., as well as *S. longifolium* (Rajeshkumar et al. 2014).

2.3.4 Fungi

The biosynthesis of metal NPs using filamentous fungi has been extensively studied and recognized as a green and efficient method for NP production. Fungal cells are highly efficient in the extracellular synthesis of NPs, based on their high capacity to excrete reducing agents that are used in this synthesis (Sawle et al. 2008; Prasad et al. 2016). Fungi are characterized by their high capacity to excrete a wide range of metabolites; this maintains their internal hemostasis and enables their survival under harsh environmental conditions with limited nutrients and in the presence of toxic materials (Vahabi et al. 2011). In the biosynthesis of NPs the metal ions are reduced to inorganic solid metal NPs through the catalytic effect of extracellular enzymes and the release of large amounts of proteins into solution (Vahabi et al. 2011; Ahmad et al. 2005). This phenomenon has been proven to contribute to the biosynthesis of stable NPs without the need to add external capping agents (Gupta and Bector 2013). Therefore, fungal cells are widely used in NP synthesis since they are tolerant to high metal concentrations during the process and produce good NP dispersion (Vahabi et al. 2011). In addition, for the large-scale production of NPs, fungal cells are recommended as first-choice biofactories owing to their high productivity and low energy consumption. Compared with bacterial cells, fungal cells can be easily separated from the broth through a simple filtration process, thus saving considerable cost in the downstream process (Vahabi et al. 2011; Prasad 2016, 2017).

After the reaction of *Fusarium oxysporum* cell-free supernatant with silver ions following 72-h catalytic activity, the intense yellow color of the aqueous solution showed that the reduction of the metal ions had taken place extracellularly (Ahmad et al. 2003a). The color change was caused by the excitation of surface plasmon vibrations in the NPs. However, the production of metal NPs with a uniform particle size distribution was made possible by using cell-free extract of *Trichoderma asperellum* (Mukherjee et al. 2012). Ahmad et al. (2005) reported that the cell mass of *Trichothecium* sp. synthesized Au-NPs extracellularly under static conditions. Recently, Balakumaran et al. (2015) found that *Guignardia mangiferae*, an endophytic fungus isolated from the leaves of medicinal plants, extracellularly synthesized well dispersed and extremely stable spherical AgNPs, 5–30 nm in size, under optimized reaction conditions within 12 h of the beginning of the process. In this study, the optimum antibacterial activity was achieved when the Ag-NPs were synthesized at pH 7. Other research has shown that the extracellular broth of *A. oryzae* var. viridis could be used for the extra- and intracellular synthesis of spherical Au-NPs with a size range of 10–60 nm (Patra et al. 2015). Castro Longoria et al. (2011) and Zhang et al. (2011a, b) also reported the potential synthesis of Au-NPs using *Neurospora crassa* and *Aureobasidium pullulans.* However, the NPs were produced inside the cells and needed additional purification steps to release the intracellular NPs, unlike the NPs produced by *Penicillium* sp., which could be produced in extra- and intracellular forms (Du et al. 2011). Recently, white rot fungi have been used extensively in the remediation of toxic metal damage, based on their capacity to reduce a wide range of environmentally hazardous compounds to metal ions, by oxidative enzymatic mechanisms. Chan and Mat Don (2013) isolated five species of white rot fungi and studied their potential application in NP biosynthesis. It was interesting that the synthesis of Ag-NPs by *Pycnoporus sanguineus* produced a yield of about 98.9%. The bioreduction of Ag-NPs involved the absorption of metal ions onto the cell surface of *P. sanguineus* by functional groups on the cell wall, and the NPs were indirectly reduced to metal ions by reducing sugars from the polysaccharide hydrolysates of the biomass. In that study, the Ag-NPs produced were spherical, with an average diameter of 52.8–103.3 nm (Vigneshwaran et al. 2006; Chan and Mat Don 2013).

In conclusion, the possibility of developing a rational, fungal-based method for the synthesis of Ag-NPs and Au-NPs has been reported using a wide range of fungal strains, including *Botrytis cinerea, Trichoderma reesei, Aspergillus clavatus, A. fumigatus, A. oryzae* var. viridis*, A. sydowii, A. terreus, Hormoconis resinae, Fusarium semitectum, Alternaria alternata*, and *Penicillium brevicompactum* (Table 2.1). These fungi were simply exposed to solutions of different types of metal or inorganic ions for the single-step synthesis of various types of metal NPs (Park et al. 2016). Ag-NPs and Au-NPs have drawn much attention because of their extensive application in the medical and cosmetic industries.

Table 2.1 Synthesis of nanoparticles (NPs) by microorganisms

Microorganisms	Localization	NPs	Shapes	Size (nm)	References
Lower fungi					
Botrytis cinerea	Extracellular	Au	Spherical	1–100	Castro et al. (2014)
			Triangular Hexagonal		
			Decahedral Pyramidal		
Trichoderma reesei		Ag	Spherical	5–50	Vahabi et al. (2011)
Hormoconis resinae		Ag	Cubic	20–80	Varshney et al. (2009)
Fusarium semitectum		Au	Spherical	18–50	Sawle et al. (2008)
		Au-Ag		10–35	
Aspergillus clavatus		Au	Triangular	24.4 ± 11	Verma et al. (2011)
			Spherical		
			Hexagonal		
A. fumigatus		ZnO	Spherical	1.2–6.8	Raliya and Tarafdar (2013)
			Hexagonal		
A. oryzae var. viridis		Au	Spherical	10–60	Binupriya et al. 2010
A. sydowii		Au	Spherical	8.7–15.6	Vala (2015)
A. terreus		Ag	Spherical	1–20	Li et al. (2012)
A. tubingensis		$Ca_3P_2O_8$	Spherical	28.2	Tarafdar et al. (2012)
Aureobasidium pullulans		Au	Spherical	29 ± 6	Zhang et al. (2011a, b)
Cylindrocladium floridanum		Au	Spherical	19.05	Sanghi and Verma (2009)
		Au	Spherical	5–35	
Hormoconis resinae		Au	Spherical	3–20	Mishra et al. (2010)
Penicillium brevicompactum		Au	Spherical	10–60	Mishra et al. (2011)
			Triangular Hexagonal		
P. fellutanum		Ag	Spherical	5–25	Kathiresan et al. (2009)
P. nagiovense		Ag	Spherical	25 ± 2.8	Maliszewska et al. (2014)
Penicillium sp.		Au	Spherical	30–50	Du et al. (2011)
Phanerochaete chrysosporium		Au	Spherical	10–100	Sanghi et al. (2011)
Rhizopus oryzae		Au	Spherical	16–25	Das et al. (2012a, b)
T. koningii		Au	Spherical	10–14	Maliszewska (2013)
T. viride		Ag	Spherical	5–40	Fayaz et al. (2010)
Neurospora crassa	Intracellular	Au	Spherical	3–100	Castro-Longoria et al. (2011)
Hormoconis resinae		Ag	Spherical	20–80	Varshney et al. (2009)

Table 2.1 (continued)

Microorganisms	Localization	NPs	Shapes	Size (nm)	References
Fusarium semitectum		Au	Spherical	10–35	Sawle et al. (2008)
		Au-Ag			
Mushrooms					
Pleurotus florida	Aqueous extract	Ag	Face-centered cubic	2.445 ± 1.08	Sen et al. (2013a)
P. florida		Au	Spherical	8	Sen et al. (2013b)
P. ostreatus		Ag	Spherical	10–40	Al-Bahrani et al. (2017)
Agaricus bisporus		Ag	Spherical	5–50	Manzoor-ul-Haq et al. (2015)
Ganoderma sp.		Au	Spherical	20	Gurunathan et al. (2014)
Tricholoma matsutake		Ag	Spherical	10–50	Anthony et al. (2014)
Ganoderma sp.		Ag	Spherical	2	Ekar et al. (2015)
Tricholoma matsutake		Ag	Spherical	20–50	Manzoor-ul-Haq et al. (2015)
Cordyceps militaris		Ag	Spherical	15	Wang et al. (2016)
Schizophyllum commune	Extracellular	Ag	Spherical	54–99	Arun et al. (2014)
	Intracellular				
Flammulina velutipes	Intracellular	Au	Cylindrical tubes	20	Narayanan et al. (2015)
Yeasts					
Candida glabrata	Extracellular	Cd	Hexagonal	20–29 Å	Velusamy et al. (2016)
	Intracellular				
Saccharomyces cerevisiae		Au	Spherical	15–20	Sen et al. (2011)
Cryptococcus laurentii	Extracellular	Ag	Spherical	–	Fernández et al. (2016)
Rhodotorula glutinis		Ag	Spherical	–	Fernández et al. (2016)
Magnusiomyces ingens		Au	Spherical	80	Zhang et al. (2016a)
			Triangular		
			Hexagonal		
Yarrowia lipolytica	Intracellular	Au	Spherical	9–27	Pimprikar et al. (2009)
			Triangular		
			Hexagonal		
Bacteria					
Rhodopseudomonas capsulata	Extracellular	Au	Spherical	10–20	He et al. (2007)
Escherichia coli		Ag	Spherical	20–50	Kushwaha et al. (2015)

(continued)

Table 2.1 (continued)

Microorganisms	Localization	NPs	Shapes	Size (nm)	References
Pseudomonas aeruginosa		Ag	Spherical	50–100	Abo-State and Partila (2015)
Bacillus licheniformis		Ag	Spherical	10–120	Sarangadharan and Nallusamy (2015)
Bacillus strain CS 11		Ag	Spherical	42–92	Das et al. (2014)
Bacillus megaterium		Ag	Spherical	80–99	Saravanan et al. 2011
Bacillus marisflavi		Ag	Spherical	40	Anthony et al. 2014
Actinomycetes	Intracellular	Au	Spherical	18–20	Balagurunathan et al. 2011
Streptomyces virodogens			Rod		
Streptomyces naganishii (MA7)		Ag	Spherical	5–10	Shanmugasundaram et al. 2013
Streptomyces sp.		Ag	Spherical	70	Udaya Prakash et al. 2014
Streptoverticillium sp.		Ag	Spherical	8	Udaya Prakash et al. 2014
Streptomyces griseus	Extracellular	Au	Spherical	50	Derakhshan et al. 2012
Streptomyces glaucus		Ag	Spherical	4–25	Zinicovscaia et al. (2011)
Streptomyces hygroscopicus		Au	Spherical	10–20	Sadhasivam et al. (2012)
Streptomyces albogriseolus		Ag	Spherical	16.25	Samundeeswari et al. (2012)
Streptomyces albidoflavus		Ag	Spherical	10–40	Shetty and Kumar (2012)
Streptomyces rochei		Ag	Spherical	22–85	Abd-Elnaby et al. (2016)
Lactobacillus sp.	Extracellular	Gd$_2$O3	Spherical	10–20	Jha et al. (2010)
Lactobacillus sp.		Ti	Spherical	40–60	Prasad et al. 2007
Lactobacillus fermentum		Ag	Spherical	13.75	Omidi et al. (2014)
Lactobacillus sp.		Ag	Spherical	2–20	Ranganath et al. (2012)
Lactobacillus casei sub sp. *Casei*		Ag	Spherical	25–100	Korbekandi et al. (2012)
Lactobacillus acidophilus		Ag	Spherical	4–50	Rajesh et al. (2014)
Lactobacillus kimchicus	Intracellular	Au	Spherical	5–30	Markus et al. (2016)
Lactobacillus mindenis		Ag$_2$O	Spherical	2–20	Dhoondia and Chakraborty (2012)

(continued)

Table 2.1 (continued)

Microorganisms	Localization	NPs	Shapes	Size (nm)	References
Lactobacillus acidophilus	Extracellular	Se	Spherical	15–50	Visha et al. (2015)
	Intracellular				
Algae					
Enteromorpha flexuosa (Wulfen) J. Agardh.	Aqueous extracts	Ag	Circular	2–32	Yousefzadi et al. (2014)
Padina pavonica		Au	Spherical	30–100	Isaac and Renitta (2015)
Chlorella pyrenoidusa		Au	Spherical	25–30	Oza et al. (2012)
Calothrix algae		Au	Truncated conical	30–120	Kumar et al. (2016)
Stoechospermum marginatum		Au	Spherical	40–85	Rajathi et al. (2012)
Sargassum longifolium		Ag	Spherical	40–85	Rajeshkumar et al. (2014)
Turbinaria conoides		Au	Spherical	5–45	Ramakrishna et al. (2016)
Sargassum tenerrimum		Au	Spherical	27–35	Ramakrishna et al. (2016)

2.3.4.1 Edible and Medicinal Mushrooms

The preparation of metal NPs by edible medicinal mushrooms has been widely applied as a clean alternative approach for NP biosynthesis. Manzoor-ul-Haq et al. (2015) reported on the potential use of *Agaricus bisporus*, *Helvella lacunosa*, *Ganoderma applanatum*, *Pleurotus florida*, and *Fomes fomentarius* as biofactories for AgNPs. They showed that, among different types studied, *Agaricus bisporus* was considered as the most potent mushroom for the synthesis of Ag-NPs. Bioactive compounds, such as enzymes, proteins, polysaccharides, and nucleic acids, are extracted from the basidiocarps of mushrooms, which are a potential source of many essential nutrients, as well as therapeutic bioactive compounds that are considered to have immune-modulator, anti-tumor, antidiabetic, and antioxidant properties (Maftoun et al. 2015). Mushroom extracts also contains highly diverse bioactive molecules such as amino acids, fatty acids, vitamins, minerals, and polysaccharides. It is also known that almost 75% of mushroom extracts are rich in proteins that are necessary for the NP biosynthesis process (Anthony et al. 2014). It was also reported that mushroom extracts contain large numbers of volatile organic compounds, such as octanones, octanols, and benzaldehyde, which can act as reducing agents for the reduction of metal ions to the corresponding metal NPs (Philip 2009). The study of Antony et al. (2014) has shown that protein and enzymes extracted from *Tricholoma matsutake* play an important role in the reduction of metal ions by the oxidation of benzaldehyde (aldehyde groups) to carboxylic acids, as FITR analysis detected a band shift of the hydroxyl and carbonyl groups and the loss of existing carbonyls, and the appearance of a new carbonyl peak. The FTIR spectrum of Ag-NPs

synthesized using *T. matsutake* extract showed the broad spectrum of the IR peak at 3400 cm^{-1}, suggesting the binding of silver ions with hydroxyl groups. In addition, detection of the band spectrum at 1640 and 1550 cm^{-1} as the stretching vibrations of the primary and secondary amines, respectively, confirmed the presence of proteins for the synthesis and stabilization of Ag-NPs (Anthony et al. 2014).

Many selected mushroom strains show the capacity to synthesize metal NPs by both extracellular and intracellular synthesis mechanisms. The employment of *Pleurotus* sp. can contribute to the non-toxic production of NPs, since *Pleurotus* sp. is well known as an edible mushroom with GRAS status according to the FDA. Recent research by Al-Bahrani et al. (2017) showed that an aqueous extract of the edible mushroom *P. ostreatus* acted as a reducing and stabilizing agent for the biosynthesis of spherical Ag-NPs and this was an efficient and ecofriendly system for NP synthesis; the size and morphology of NPs, analyzed by transmission electron microscopy (TEM), demonstrated only spherical Ag-NPs, with a size of 10–50 nm. Other research reported that *P. florida* exhibited high capacity for the synthesis of Au-NPs by reducing chloroauric acid (HAuCl$_4$) with a glucan that acts as both a reducing and a stabilizing agent (Sen et al. 2013b). *P. florida* showed size-controlled synthesis with well distributed Au-NPs in a process that depended on the concentration of HAuCl$_4$ in the solution. The resulting Au NP-glucan bioconjugates function as efficient heterogeneous catalysts in the catalytic conversion of reducing 4-NP to 4-AP, in the presence of sodium borohydride, via a one-step reduction process (Sen et al. 2013b).

In addition, the intracellular synthesis of Au-NPs has been reported by using the mushroom *Flammulina velutipes* (Narayanan et al. 2015). The incubation of this mushroom in chloroaurate solution resulted in the synthesis and immobilization of stable Au NPs inside the mushroom mycelia; these AuNPs exhibited heterologous catalytic potential to reduce the organic pollutants methylene blue and 4-NP. Other recent research, by Wang et al. (2016), reported on the high capacity of *Cordyceps militaris* to produce spherical Ag-NPs, using mushroom cell filtration. The resulting NPs were highly crystalline and had a diameter of about 15 nm. The Ag-NPs were relatively stable and exhibited antibacterial activities against clinically pathogenic bacteria (Wang et al. 2016). The synthesis of Ag-NPs of uniform size and typical dispersal by *Ganoderma* sp. was reported by Ekar et al. (2015). The morphology of the spherical particles with an average size of 2 nm was visualized in micrographs of TEM images, showing that *Ganoderma* sp. extract also contains capping and catalytic/reducing agents that have high capacity to biosynthesize highly stable Ag-NPs. NPs of small size are needed, as a small NP is efficient and reliable for improving NP efficiency and biocompatibility (Kim et al. 2008).

2.4 Mechanism of Metal Nanoparticle Biosynthesis by Fungi

Fungi produce NPs as a cellular defense mechanism against the chemical pollutants found in their habitats. Toxic ions are reduced to their metal NPs by various chemical reactions, e.g., precipitation and co-precipitation, complexation, biosorption,

ion-form modification, immobilization, or bio-coupling (Das et al. 2012a, b; Dorcheh and Vahabi 2016). Fungi use their cellular enzymes, proteinaceous molecules, or cell membrane-bound molecules as electron donors during the reduction process. Once reduced, the toxic ions are easily precipitated as metal NPs, either intracellularly or extracellularly, depending on the mechanism of biosynthesis (Vigneshwaran et al. 2007).

2.4.1 Extracellular Fungal Biosynthesis of Metal Nanoparticles

Fungal cell membranes play an important role in the extracellular biosynthesis of metal NPs. They contain large amounts of differently bound molecules, e.g., peptides, proteins, polysaccharides, oxidoreductases, and quinones, which participate in the process of metal ion reduction and precipitation (Sharma and Dietz 2006; Keat et al. 2015; Moghaddam et al. 2015).

Extracellular reductases are the key enzymes responsible for the biosynthesis and growth of metal NPs (Vahabi and Dorcheh 2014). *F. oxysporum* cells have been reported to produce nicotinamide adenine dinucleotide phosphate (NADPH)-dependent nitrate and sulfite reductases and use them for the biosynthesis of Ag-NPs and Au-NPs, respectively (Ahmad et al. 2003a, b; Kumar et al. 2007). Additionally, hydrogenases (Gilbert et al. 2003), flavin adenine dinucleotide (FAD)-dependent glutathione reductase (Scott et al. 2008), and nitrate reductases (Vahabi et al. 2011) have been found to participate in the fungal biosynthesis of metal NPs. However, reports have confirmed that the reductase enzyme system requires an electron shuttle for metal reduction (Durán et al. 2011). Quinones (anthraquinones and naphthopquinones) and their quinine derivatives have been found to participate in the reduction process. Moreover, metalloproteins, i.e., phytochelatin and metallothionein, were found to be overexpressed when fungal cells were subjected to heavy metal ion toxicity, and these metalloproteins helped in the reduction process by complexing the metal ions through their reducing and binding properties (Cobbett and Goldsbrough 2002; Park et al. 2016).

The extracellular fungal biosynthesis of NPs can be mediated through protein molecules embedded in mycelial membranes. It has been proposed that surface-bound proteins present in the mycelial cells of *R. oryzae* and *Coriolus versicolor* bind with gold and silver ions, leading to the reduction and stabilization, respectively, of Au-NPs and Ag-NPs (Das et al. 2012a, b; Sanghi and Verma 2009). The formation of these bonds (i.e., protein-metal bonds) has been attributed to the electrostatic reactions between protein-free amine or cysteine residues and enzyme carboxylate groups in the fungal cells. Accordingly, a redox state is created, leading to the precipitation and formation of metal NPs (Park et al. 2016).

A wide range of extracellular fungal products have also been found to contribute to the biosynthesis of metal NPs, in which these NPs were produced to overcome

the toxic effects of the metal ions, and these ions were precipitated in the form of NPs. *Curvularia lunata* was reported to produce extracellular mucilage materials in response to Cu(II), Pb(II), and Zn(II) toxicity (Paraszkiewicz and Dlugonski 2009). Further, Ni(II) and Cd(II) toxicity was found to trigger pullulan production by *Aureobasidium pullulans*, and glomalin glycoprotein was reported to sequester Cu(II) in cultures of *Glomus* (Cornejo et al. 2008).

2.4.2 Intracellular Fungal Biosynthesis of Metal Nanoparticles

The intracellular fungal biosynthesis of metal NPs is mainly attributed to cellular ATPases and hydrogenases. *F. oxysporum* was found to produce Au-NPs intracellularly in cytoplasmic vacuoles, and the reaction was modulated by plasma membrane-ATPase, 3-glucan binding protein, and glyceraldehyde-3-phosphate dehydrogenase (Vahabi and Dorcheh 2014). Hydrogenases function to produce cytoplasmic hydrogen, which is required to precipitate metal NPs (Riddin et al. 2009).

Yeast cells have been found to use their intracellular glutathione, and the two metal-binding proteins (phytochelatin and metallothionein) in their detoxification mechanism (Breierová et al. 2002). This finding was attributed to the fact that these compounds have important redox and nucleophilic characteristics, and thus participate in the bioreduction of metal ions. Additionally, fungal cells have been reported to use their antioxidative systems to detoxify metal ions, to protect the cells from being injured by the oxidative power of these metal ions (Jha and Prasad 2016). Oxygen can be reduced intracellularly upon cell exposure to heavy metals, leading to the formation of reactive oxygen species (ROS), e.g., hydrogen peroxide, which can then produce highly active and toxic free hydrogen radicals. The fungal cellular machinery uses different enzyme systems, such as antioxidative systems, to stop these reactions (Morano et al. 2012). Fungal antioxidative systems include catalases and superoxide dismutases (Culotta et al. 2006), methionine sulfoxide reductase (Le et al. 2009), thioredoxins (Trotter and Grant 2005), peroxiredoxins (Park et al. 2000), glutathione (Grant et al. 1996), and glutathione peroxidases and transferases (Michiels et al. 1994; Sheehan et al. 2001).

Fungal cells use different membrane channels and transporter proteins to transport required substrates (C- and N-sources), micronutrients, and ions inside the cells. However, toxic metals can take advantage of these channel systems and enter the cytoplasmic space. Primarily, cells can block or even eliminate such transport systems to avoid the entrance of the toxic metal ions into the cytoplasm (Támas et al. 2005). However, this can affect the cellular machinery, and some metal ions will enter the cells by using multiple transport systems. In such cases, the cellular enzymes will react with the metal ions and precipitate nanomaterials.

With changing growth conditions, the intracellular fungal biosynthesis of metal NPs is mediated by the same enzymes and proteins as those responsible for the extracellular biosynthesis of NPs. *Trichothecium* sp. was found to produce extracellular NPs when cells were grown in static cultures. On the other hand, on growth in submerged culture, the biosynthesis was switched to intracellular mechanisms. This switch was obtained by applying different intracellular mechanisms to biosynthesize metal NPs (Ahmad et al. 2005). This change in biosynthesis was attributed to the finding that static cultures promote fungal cells to excrete their enzymes and proteins extracellularly, while these enzymes were not released from the cells in a submerged culture system (Mohanpuria et al. 2008).

2.5   Characterization of Metal Nanoparticles

Researchers usually use different techniques to characterize biosynthesized NPs. These techniques are generally employed to give useful information about the size, composition, crystalline type, and chemical state, as well as the optical and magnetic properties, of the biosynthesized NPs (Kulkarni 2015). The techniques employed are classified into different categories, such as microscopy-, diffraction-, spectroscopy-, magnetic properties-, and mechanical properties-dependent techniques. Table 2.2 summarizes the different techniques used to characterize biosynthesized NPs.

Table 2.2   Different techniques used to characterize biosynthesized nanoparticles

Category	Techniques	Properties determined
Microscopy	Optical microscope, confocal microscope, scanning electron microscope (SEM), transmission electron microscope (TEM), atomic force microscope (AFM), scanning near-field optical microscope (SNOM)	Morphology, structure, size, composition
Spectroscopy	UV-vis-IR, Fourier transform infra-red (FTIR), atomic absorption, electron spin (paramagnetic) resonance (ER or EPR), nuclear magnetic resonance (NMR), Raman spectroscopy, electron spectroscopy for chemical analysis (ESCA), luminescence techniques, X-ray photoelectron spectroscopy (XPS), Auger electron spectroscopy (AES)	Chemical analysis (bonding, charge transfer), energy gaps, level of impurities, band formation, transition probabilities
Diffraction	X-ray diffraction, electron diffraction, neutron diffraction, small angle X-ray scattering (SAXS), small angle neutron scattering (SANS), dynamic light scattering (DLS)	Particle shape, average particle size, structure
Magnetic properties	Magneto resistivity, superconducting quantum interference device (SQUID), vibrating sample magnetometer (VSM)	Behavior of synthesized material in external magnetic fields
Mechanical properties	Hardness, elasticity	Material properties

2.5.1 Electron Microscopy (TEM and SEM)

TEM microscopy is normally employed to investigate the morphological characteristics of biosynthesized NPs (Gupta and Bector 2013). These characteristics include nanoparticle shape and size, the formation of aggregates, and symmetrical properties. As the fungal biosynthesis of NPs proceeds via protein capping to provide stability and protection for the formed NPs, TEM can be combined with elemental spectroscopy imaging (ESI) to characterize the capping procedure (Maliszewska et al. 2014). Mukherjee et al. (2001a) used TEM scanning to determine the location of Ag-NPs produced within fungal cells.

The elemental characterization of produced NPs was investigated with the help of SEM, accompanied by energy dispersive X-ray spectroscopy (EDS) (Durán et al. 2005). The presence of nanomaterials within fungal mycelia has been confirmed using SEM combined with energy diffraction analysis (Vigneshwaran et al. 2007).

2.5.2 Spectroscopic Techniques

2.5.2.1 UV-Visible Spectroscopy

The application of the UV-visible spectroscopy technique depends on the development of surface plasmon resonance, which produces strong absorption and scattering of light when the biosynthesized NPs have sizes smaller than or similar to the penetration depth of the electromagnetic field in the metal (Durán et al. 2010). Plasmon resonance is used to validate the biosynthesis of AgNPs (Netala et al. 2016), and its development can be affected by various parameters, i.e., particle shape and size and the medium dielectric constant. UV-visible spectroscopy is also used to differentiate nanoparticles having aggregate structures from those not forming aggregates, depending on the separation between UV bands (Basavaraja et al. 2008). Moreover, the fact that protein is absorbed at 270 nm, owing to the presence of tryptophan and tyrosine residues, makes it possible to detect protein capping for the synthesized NPs.

2.5.2.2 Fluorescence and FTIR

Fluorescence and FTIR are generally employed to evaluate the binding properties of the cellular proteins with the biosynthesized NPs (Durán et al. 2005). Ag-NPs have been excited at 260 nm and found to emit another band at 340 nm. This was attributed to the fact that fungal cellular proteins are attached to the peripheral areas of the NPs, while unbound proteins in the solution remain in their original form.

FTIR spectroscopic analysis is also widely employed to investigate protein-NP interactions in terms of the formation of secondary structures. This analysis has also

been used to detect protein conformational changes that occur upon binding to the newly synthesized nanomaterials, as well as to confirm the presence of functional groups and thiol derivatives in the excreted proteins (Srivastava and Mukhopadhyay 2015). Such investigations are useful for establishing the mechanism of the reduction process and, hence, the stabilization of the formed nanomaterial.

2.5.2.3 Photoluminescence

The capacity of biosynthesized nanoparticles to enhance fluorescence emission has made it possible to use photoluminescence as a powerful tool to investigate the optical characteristics of produced NPs. For example, AgNPs synthesized by *Phanerochaete chrysosporium* were found to emit at 423 nm, while the original silver nitrate solution did not emit at this wavelength (Vigneshwaran et al. 2006).

2.5.2.4 X-Ray Diffraction (XRD)

X-ray diffraction has been widely used to determine the particle size, and the particle size distribution, of biosynthesized NPs (Magdi and Bhushan 2015). The crystalline nature of the formed nanomaterials can also be examined by XRD (Khatami et al. 2016). The technique uses the Debye-Scherrer equation to calculate particle size. Particle size determined by XRD is closely correlated with measurements obtained from TEM calculations (Basavaraja et al. 2008).

2.6   Advantages of Fungal Biosynthesis Compared with Bacterial Biosynthesis

Generally, in terms of procedures, capacities, and costs, biological production processes for metal NPs are more efficient than chemical processes (Durán et al. 2011). Also, chemical processes require toxic solvents and further treatment steps (Dorcheh and Vahabi 2016). Moreover, biologically synthesized NPs have great potential owing to their unique optical, chemical, and electronic characteristics (Mohanpuria et al. 2008).

Fungi have potential characteristics that favor this group of microbes over bacteria and plants in the biosynthesis of NPs. Fungi are more developed than bacteria in terms of cellular organization and metabolic activities (Jha and Prasad 2016), and, compared with bacteria, fungi have fewer cultivation requirements, higher growth rates, and higher maximal yields in terms of the initial raw material ratio (Castro-Longoria et al. 2011). Fungi mostly produce extracellular NPs; therefore, the recovery of the synthesized NPs is much easier and cheaper than the recovery of the NPs synthesized from bacteria (Bäuerlein 2000). Additionally, the waste from the pro-

duction medium and the fungal biomass can be degraded biologically and can serve as organic fertilizers (Mansoori 2010). Concerning metal NPs, fungi have been used to produce NPs that have well defined dimensions and a very good degree of monodispersion (Mukherjee et al. 2001b).

In the large-scale production of metal NPs, fungi are characterized by their fast growth rates, easy downstream processes, easy biomass handling, and their production of large amounts of the enzymes and extracellular proteins required for NP biosynthesis (Vahabi and Dorcheh 2014; Narayanan and Sakthivel 2010; Prasad et al. 2016, Prasad 2016, 2017). On the other hand, although there is much research on the use of safe edible mushrooms, most of the studied fungi are human or plant pathogens, which renders them unsuitable for use in large-scale processes (Vahabi and Dorcheh 2014).

2.7 Applications of Metal Nanoparticles

All biogenic NPs synthesized by edible mushrooms and lower fungi are of special interest, based on their high biocompatibility (Kitching et al. 2015; Gurunathan et al. 2014). Nowadays, researchers involved in this field explore the applications of metal NPs in targeted drug delivery, such as in the delivery of proteins, peptides, DNA, and plasmids; metal NPs are also being investigated for alternative cancer treatments and for gene therapy; for use as biosensors; and for their antibacterial and antifungal activity (Siddiqi and Husen 2016; Wanigasekara and Witharana 2016; Prasad et al. 2016). Therefore, metal NPs synthesized by fungi are finding many applications in the medical and cosmeceutical industries.

2.7.1 Applications of Metal Nanoparticles in Medical Fields

2.7.1.1 Drug Delivery

Over the past decade, NPs have been explored and identified as carriers for drug delivery (Gref et al. 1994; Prasad et al. 2017a). New drug delivery systems based on nanotechnology have been applied in the treatment of human diseases, such as cancer, diabetes, microbial infections, and in gene therapy (Surendiran et al. 2009). The benefits of these treatments are that the drug is targeted to diseased cells, and its safety profile is enhanced by the reduced toxic side effects to normal cells (Wanigasekara and Witharana 2016). In general, NPs can be conjugated with different types of drugs to deliver bioactive compounds to the target site by various methods, such as the use of nanotubes, liposomes, quantum dots, nanopores, and dendrimers (Surendiran et al. 2009). For example, because of their safety in terms of toxicity and immunocompatibility, Au-NPs are suitable for the preparation of drug delivery scaffolds. Nanomaterials synthesized by a biological approach can be employed as alternative drugs for the treatment of diabetes mellitus. Au-NPs showed

good therapeutic effects by reducing the levels of liver enzymes such as alanine transaminase and alkaline phosphatase, and reducing uric acid in a diabetic mouse model (Daisy and Saipriya 2012). Au-NPs synthesized by *Trichoderma viride* with vancomycin were bound to the microbial surface by ionic interaction, and effectively suppressed the growth of vancomycin-resistant *Staphylococcus aureus* at a low concentration, of 8 μg/mL. The cell death of *S. aureus* was proven by TEM analysis, showing that the vancomycin-bound Au-NP had penetrated the bacterial membrane (Fayaz et al. 2011). In another study, Sun et al. (2012) loaded doxorubicin into bacterial magnetosomes by using covalent attachment, and these magnetosomes supressed tumor growth by 86.8%. Brown et al. (2010) reported that Au-NPs functionalized with a thiolated polyethylene glycol monolayer capped with a carboxylate group successfully enhanced the delivery of the anticancer drug oxaliplatin.

2.7.1.2 Cancer Therapy

Cancer is the leading cause of death worldwide. Chemotherapy has led to good results, but in many cases cells developed resistance to the chemotherapy agents. Therefore, scientists have made many attempts to develop methods that are biocompatible and cost-effective for the treatment of cancer patients and that reduce the side effects of the chemicals used. Studies have shown that biogenic Ag-NPs can induce apoptotic pathways in vitro through the generation of free oxygen radicals (Ortega et al. 2015). Accordingly, increased interest has been shown in regard to Ag-NPs for the diagnosis and treatment of human cancer (Zhang et al. 2016a, b; Ortega et al. 2015), and thus these molecules are considered as potential antitumor and anti-proliferative agents; they are also considered to be antiangiogenic. Biosynthesized Ag-NPs produced by the yeast *Cryptococcus laurentii* (BNM 0525) showed significant antitumor activity in the breast cancer cell lines MCF7 and T47D (Ortega et al. 2015). The cyototoxicity of Ag-NPs against breast cancer cells was investigated by Gurunathan and co-workers (2013), who obtained the Ag-NPs from an extract of *G. Neo-japonicum* mycelia. Their study revealed that after 24-h exposure to solutions of Ag-NPs at concentrations of 1 to 10 μg/mL, breast cancer cell growth was inhibited and membrane leakage was induced. Arun et al. (2014) investigated the anticancer activity of Ag-NPs produced in shaken broth cultures; an MTT cytotoxicity assay showed cell deaths of 27.2% to 64% in human laryngeal carcinoma cells (HEP-2) at Ag-NP concentrations of 10 to 100 μg/mL.

2.7.1.3 Wound Healing

Robert Burrell was the first person to develop a commercial nano silver particle product to be used clinically; it was used in the treatment of various wounds, such as burns, ulcers, and epidermal necrolysis (Chaloupka et al. 2010). This approach to wound healing treatment was also taken by Huang et al. (2007), who used a wound

dressing loaded with NPs that reduced healing time and inhibited bacterial growth to a greater extent than standard silver sulfadiazine, without harmful effects on the treated patients. Sundaramoorthi et al. (2009) found that Ag-NPs synthesized using *Aspergillus niger* were promising agents for wound healing, acting against pathogenic bacteria, and modulating the cytokines involved in wound healing. In an in-vivo study of Ag-NPs produced by *Fusarium oxysporum*, this biogenic silver formulation, together with enoxaparin, enhanced wound healing without adverse effects (Marcato et al. 2015). The benefits gained were reduced time required for the differentiation of fibroblasts into hyperactive cells (myofibroblasts) involved in the generation of contraction forces in the wound, and a shorter time for the inflammatory process compared with that seen with standard wound dressings (Marcato et al. 2015)

2.7.1.4 Antibacterial Activity

In recent years, with epidemics and the increasing resistance of microorganisms to many generally used antibiotics, NPs have been considered as potential alternatives to commonly used dosage forms. Ag-NPs synthesized from the fungus *Aspergillus niger*showed good inhibitory activity against Gram-positive bacteria such as *S. aureus* and Gram-negative bacteria such as *E. coli.* Sudhakar et al. (2014) produced Ag-NPs by using the edible mushroom, *Agaricus bisporus*, as a bioreductant. The produced nanometal particle exhibited antimicrobial activity against human pathogens such as *E. coli*, *Proteus vulgaris*, and *Klebsiella* spp. Durán and co-workers (2007) reported that extracellular Ag-NPs secreted by *Fusarium* sp. killed *S. aureus* and thus were of use in the treatment of textile fabrics. Fayaz et al. (2009) reported that Ag-NPs synthesized by *T. viride* had potential to inhibit *E. coli* growth, with a minimal inhibitory concentration (MIC) of 30 μg/mL. *Aspergillus clavatus* has been used as a biofactory for the production of Ag-NPs, with antimicrobial activity shown against *C. albicans*, *P. fluorescens*, and *E. coli* (Verma et al. 2010). Ottoni et al. (2017) reported that, among 20 fungal strains screened, two types of each of *Rhizopus* sp., *Trichoderma* sp., and *Aspergillus* sp. could be used as potential Ag-NP biofactories. The produced Ag-NPs acted as antibacterial agents, with the capacity to inhibit the growth of microbes such as *E. coli*, *S. aureus*, and *P. aeruginosa*. In another study, Govindappa et al. (2016) reported that the Ag-NPs produced by *Penicillium* strongly inhibited the growth of *E. coli* and *P. aeruginosa*, confirmed by the use of SEM. This study also found that the Ag-NPs showed strong antioxidant, anti-inflammatory, and anti-lipoxygenase activity, as well as tyrokinase inhibitory activity, when applied at high concentrations. Another study, by Singh et al. (2017), reported the development of a cheap, rapid, one-step technique for Ag-NP synthesis using endophytic fungal supernatant from *Alternaria* sp. and *Raphanus sativus*. Transmission electron microscope and atomic force microscope results established that the synthesized Ag-NPs were of particle size between 4 and 30 nm, and XRD, EDS, and SAED (selected area diffraction) analysis confirmed the crystalline nature and composition of the synthesized Ag-NPs. These Ag-NPs showed antibacterial activity against *E. coli*, *Bacillus subtilis*, *S. aureus*, and *Serratia marcescens* (Singh et al. 2017).

2.7.1.5 Antifungal Activity

In medicine, scientists have made many efforts to develop antimicrobial agents through the discovery of new bioactive agents and new formulations of products that can be used for the clinical treatment of diseases caused by pathogenic bacteria and fungi. Consequently, Ag-NPs have been shown to have great potential as anti-microbial agents, and they are of proven use in the formulation of clinical products for preventing secondary hospital infections (Rodrigues et al. 2013; Duran et al. 2010; Gade et al. 2008; Aziz et al. 2016). It has been shown that *Aspergillus tubingensis* and *Bionectria ochroleuca* synthesized Ag-NPs that had antifungal activity and these Ag-NPs could be used in hospital infections caused by *Candida* sp., when applied at concentrations of 0.11–1.75 μg/mL (Rodrigues et al. 2013); this study also reported that *A. tubingensis* synthesized Ag-NPs extracellularly, with a high yield. Another study, by Ishida et al. (2013), reported a green chemistry approach (integrated microbial and nanotechnology) to obtain NPs produced by *Fusarium oxysporum.* The produced particles showed high antifungal activity and inhibited the growth of human fungal pathogens such as *Candida* spp. and *Cryptococcus neoformans*. These NPs showed ability to damage the cell walls and cytoplasmic membranes of fungal cells (Ishida et al. 2013). Further, Ag-NPs produced by *Schizophyllum commune* exhibited excellent antifungal activity against dermatophytic fungal pathogens such as *Trichophyton simii*, *Trichophyton mentagrophytes*, and *Trichophyton rubrum* (Arun et al. 2014). Xue et al. (2016) studied the antifungal activity of Ag-NPs produced by *Arthroderma fulvum* against ten fungal pathogens, involving *Candida* spp., *Aspergillus* spp., and *Fusarium* spp. The results clearly demonstrated that the Ag-NPs exhibited significant antifungal activities against all tested pathogenic fungi when applied at concentrations ranging from 0.125 to 4.00 μg/mL.

2.7.1.6 Antiviral Activity

As well as the effects exhibited by nano metals as antifungal and antibacterial agents, they also exhibit antiviral properties. It has been reported that Ag-NPs synthesized by *Aspergillus fumigatus* showed antiviral activity against HIV-1. Other research, done by Narasimha et al. (2012), reported the antiviral properties of Ag-NPs synthesized from *Aspergillus* sp., noting that at concentrations of 30 to 180 ppm, the Ag-NPs reduced the number of viral plaques, whereas at higher concentrations, of 210 to 240 ppm, the Ag-NPs showed total inhibition of the viral particles in the bacterial host, leading to complete inactivation of viral replication. Narasimha et al. (2011) and Elechiguerra et al. (2005) reported that Ag-NPs of 1–10 nm in size could bind to HIV-1 and prevent viral attachment to the host cell surface.

2.7.2 Applications of Metal Nanoparticles in Cosmetics

Cosmetics have been defined by United States Federal Food, Drug, and Cosmetic Act as "articles intended to be applied to human body by being rubbed, poured, sprinkled, or sprayed for cleansing, beautifying, promoting attractiveness, or altering the appearance" (U.S. Food and Drug Administration 2016). The term 'cosmeceutical' is used to descibe a cosmetic product for which there are specific therapeutic claims. Cosmeceutical products have shown strong growth on the global market in recent years, with up to approximately $US42.4 billion forecast for 2018, up from $US31.84 billion in 2016 (GBI Research; RNCOS E-Sevices 2016). In cosmeceutical technologies, nanotechnology has been the most effective approach in the cosmetic arena by introducing smaller particles (<100 nm) that can penetrate the skin and be easily absorbed, reaching the targeted tissue easily (Lohani et al. 2014). Thus, nanoparticles are commonly used in the cosmetics industry, being employed in different products and formulations.

Nanotechnology is now widely used in cosmetics and dermatological products, such as soaps, anti-wrinkle creams, perfumes, toothpastes, lipsticks, moisturizers, sunscreens, hair care products, skin cleansers, and nail care products (Lohani et al. 2014). According to Lohani et al. (2014), NPs are generally classified into eight product classes in terms of their size and functionality; these are liposomes, nanocapsules, solid lipid nanoparticles, nanocrystals, dendrimers, cubosomes, niosomes, and nanogold and nanosilver. Recently, considerable attention has focused on ecofriendly new technologies for the production of metal nanoparticles such as gold, silver, and platinum (Rai et al. 2010). The technology is called ecofriendly because the agents used, such as bacteria, fungi, yeasts, and plants, are the biofactories for the NPs (Rai et al. 2008).

2.7.2.1 Silver Nanoparticles as Preservatives in Cosmetics

In the formulation and production of cosmetics, preservatives are essential components to prevent primary microbial contamination, and they are also important to prevent secondary microbial contamination after manufacture, when the consumer opens and closes the containers during daily use (Kokura et al. 2010). Phenoxyethanol and parabens are commonly used in cosmetics; however, these antibacterial compounds not only temporarily irritate the skin but they can also increase skin sensitivity to UV light (Handa et al. 2006; Ishiwatari et al. 2007). Therefore, for many years researchers have been looking to replace these chemicals with safe alternatives. Ag-NPs are now commonly used as preservatives, based on their antimicrobial properties (Gajbhiye and Sakharwade 2016). These NPs are extensively used in cosmetics such as deodorants, face packs, and anti-aging creams. (Lohani et al. 2014). Gajbhiye and Sakharwade (2016) also reported that, owing to the antibacterial activity of Ag-NPs, these agents are now incorporated as preservatives in toothpastes and shampoos.

Penicillium is an endophytic fungal genus that is used to synthesize Ag-NPs. Phytochemicals identified in *Penicillium* extracts include tannins, saponins, terpenoids, and flavonoids. These substances can act as reducing and capping agents in the conversion of silver particles into NPs (Govindappa et al. 2016). It has also been reported that capping agents, such as the amide and carbonyl groups detected in Ag-NPs of 10–60 nm biosynthesized from *Fusarium semitectum*, are stable for 6–8 weeks. Capping agents are important to avoid the agglomeration of NPs and they can also give stability to the product (Rai et al. 2009). These stable properties can contribute to the appearance of cosmetic products and they can also improve the sensory properties of the product, because they support the product's homogeneous appearance and prevent sedimentation of the product for more than 1 year (Kokura et al. 2010). In cosmetic products, nano zinc oxide and titanium dioxide can give better feel and spreadability to cosmetic formulations. Other than that, they can also exhibit better sun protection than their non-nano equivalents. Similarly, nano silver can increase the antimicrobial properties of the molecule compared with the application of silver in the original state (Raj et al. 2012).

2.7.2.2 Antimicrobials in Cosmetics

Penicillium spp. silver NPs (PAg-NPs) have strong antibacterial properties with a high capacity to inhibit *E. coli* and *P. aeruginosa* growth at 100-μl culture filtrate/1 ml pathogen broth (Govindappa et al. 2016). Other studies of Ag-NPs have reported that these NPs also showed potential antimicrobial effects against *E. coli, B. subtilis, V. cholera, P. aeruginosa,* and *S. aureus* (Cho et al. 2005; Morones et al. 2005). When applied to fungal cells, Ag-NPs can disturb the fungal envelope structure and lead to significant damage to fungal cells, including many strains of Candida spp., such as *C. albicans, C. tropicalis, C. glabrata, C. parapsilosis*, and *C. krusei* (Kim et al. 2008; Mehnert and Mader 2001).

Antimicrobial activity was also reported by Kokura et al. (2010), where Ag-NPs, at the low concentration of 1.0 ppm, exhibited antimicrobial properties in mixed bacterial (*E. coli, P. aeruginosa, S. aureus*) and fungal (*C. albicans, A. niger, P. citrium, A. pullulans*) extracts present in filtered kitchen and drainage wastewater . Ttitanium oxide (TiO$_2$) NPs have been used in sunscreen cosmetics (Rai et al. 2010), as well as in whitening creams, morning and night creams, and skin milks (AzoNano 2013). It was reported that TiO$_2$ NPs produced by *Aspergillus flavus* inhibited *E. coli* growth when applied at a concentration of 40 μg ml^{-1} (Rajakumar et al. 2012).

2.7.2.3 Antioxidants and Anti-inflammatory Agents in Cosmetics

Recently, nanoparticles have been included in many of the cosmetic products due to their advantages. They improve sensory properties and stability of products, give better feeling, and enhance better sun protection (Gajbhiye and Sakharwade 2016). PAg-NPs exhibited strong antioxidant activity, proven by DDPH

(1,1-diphenyl-2-picrylhydrazyl) and FRAP (Ferric Reducing Ability of Plasma) tests. They also showed anti-inflammatory activities, and therefore, they have been considered as additives in cosmetic products in order to benefit from their expected functions. Furthermore, the Ag-NPs proved to significantly increase wound healing properties of some cosmetic products. The anti-inflammatory effect of PAg-NPs is exhibited by their role in increasing membrane stabilization. There are only few reports available regarding the anti-inflammatory activities of endophytic fungal Ag-NPs (Joel and Bhimba 2012; Ruma et al. 2013; Pretsch et al. 2014; Naz et al. 2014). However, the main concern was the risk of NPs toxicity owing to their nano-size and expected penetration through the skin. Recently, it has been reported that about 0.002-0.02 ppm of AgNPs could penetrate the skin, which did not show any toxicity at these levels (Gajbhiye and Sakharwade 2016). It has been claimed that at these levels, AgNPs are flushed away from the blood stream, showing no toxicity.

2.7.3   Other Applications

Metal nanoparticles synthesized by fungi have great potential to be used as sensors for optical and electronic devices. Fayaz et al. (2010) found that *Trichoderma viride* synthesized Ag-NPs that were successfully used in biosensor and bio-imaging applications. These Ag-NPs were used for blue orange light emission at wavelengths of 320–520 nm and full characterizations were carried out by EDX (Energy Dispersive X-ray) and XRD analyses. Zheng et al. (2010) described the synthesis of Au-Ag alloy nanoparticles by yeast; the application of these Ag-NPs as a novel vanillin sensor showed that they were five times more sensitive than other methods. This study revealed the high potential of Ag-NPs as sensors in the quantitative determination of vanillin production from the vanilla bean and vanilla tea. Thibault et al. (2008) showed that Au-NPs enhanced the enzyme activity of glucose oxidase (GOx) as an indicator for the determination of glucose content in commercial glucose injections. The action of this Au-NP-GOx-based biosensor is based on the highly sensitive detection exhibited by Au-NPs (Thibault et al. 2008).

2.8   Potential Hazards of Metal Nanoparticles

Generally, all NPs are potentially hazardous to humans because of their small size and the nature of the particles. Nanoparticles have the potential to cause a wide range of respiratory, gastrointestinal, and cardiovascular system pathologies. Nanoparticles can enter the central nervous system by two routes: first, through axons of the olfactory pathway and, second, through the systemic circulation. Ag-NPs can cause in-vivo cytotoxicity to human peripheral blood mononuclear cells (Shin et al. 2007) and human alveolar epithelial cells (Soto et al. 2007) and they have also shown cytotoxicity in a macrophage cell line (Hussain et al. 2006).

In regard to in-vivo toxicity, Kim et al. (2008) reported that Ag-NPs have the potential to accumulate inside human organs such as the liver, lungs, kidneys, stomach, testes, and brain. When human mesenchymal stem cells were exposed to Ag-NPs at a concentration of 10 μg/ml for 1, 3 and 24 h, cytotoxic and genotoxic effects were shown in these cells (Hackenberg et al. 2011). The biological effects included DNA damage, functional impairment, and cell death. Lee et al. (2007) reported that Ag-NPs at a size less than 12 nm disturbed the early development of fish embryos, damaged DNA, caused chromosomal abnormalities, and induced proliferation in zebrafish cell lines. Coradeghini et al. (2013) showed that Au-NPs penetrated the blood brain barrier and accumulated in neural tissue fibroblasts, these authors also showed that Au-NPs of 5 nm in size exhibited cytotoxic effects in Balb/3T3 mouse fibroblasts (Coradeghini et al. 2013). Zinc oxide NPs are widely used in cosmetics and in antimicrobial coatings for food containers; humans are exposed to these NPs daily through dermal, inhalation, and oral routes. Exposure to zinc oxide NPs after the oral consumption of up to 300 mg/kg for 14 days caused liver cellular injury, apoptosis, and DNA damage in a rat model (Sharma et al. 2012). Therefore, safety assessments should be considered before products containing NPs are submitted for approval

2.9 Global Market for Nanoparticle Products

Nanoparticles generally consist of nanometer-scale materials, in the range of 1–100 nm, which can be produced through biosynthesis or physicochemical processes. More than 1000 nanoparticle technology-based products are now available on the market. Some of the leading manufacturers who market products involving nanoparticle technology include Nanophase Technologies Corporation, Romeoville, IL, USA, Altair Nanotechnologies, Reno, NV, USA, Unidym, Sunnyvale, CA, USA, Nanosys, Milpitas, CA, USA, PEN, Miami, FL, USA, Advanced Diamond Technologies, Romeoville, IL, USA, and Bruker Nano GmbH, Karlsruhe, Germany. Nanotechnology plays a significant role in various industries, such as the healthcare, biomedical diagnostics, food and beverage, textile, and agriculture industries. A BBC Research Report noted that the global market for nanotechnology products was valued at $US22.9 billion in 2013 and had increased to about $US26 billion in 2014. This market is expected to reach about $US64.2 billion by 2019, a compound annual growth rate (CAGR) of 19.8% from 2014 to 2019. According to a new study by Grand View Research 2015, the global market trend for Ag-NPs is expected to reach $US2.54 billion by 2022, and the market trend for Au-NPs was more than $US1.30 billion for 2014, with a CAGR of over 25% forecast by 2022. In 2014, the largest application of NP technologies was in the health-care industry, accounting for more than 30% of the Ag-NP global market. As reported by Grand View Research, the global NP technology market is dominated by North America and the European region, with their increasing demand for the technology and its products, in line with the fast growth of research and development in those countries. The

United States is the world leader in the NP market and in research innovation. Recently there has been an increase in research and development spending in biotechnology industries by Asian companies, particularly in India and China, and this is expected to strengthen the growth of the global NP technology market in Asia. Asian manufacturers are expected to increase their research and development expenses in order to gain a competitive edge in the global NP technology market over the coming few years. More research and development spending by companies is expected to increase the development of new NP production approaches using safe microorganisms. In addition, more research will underpin the development of novel NP-based products, especially in the medical and cosmeceutical industries.

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