

RECENT ADVANCES IN BIOORGANISM-MEDIATED GREEN SYNTHESIS OF SILVER NANOPARTICLES: A WAY AHEAD FOR NANOMEDICINE

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ABSTRACT

Nanotechnology is an emerging branch of science utilizing technological advances of nanomaterials of size 1–100 nm. The nanotechnology in biomedical research and clinical practices emerged as nanomedicine that makes a major impact on human health. Nowadays, nanomaterials are increasingly used in therapeutics, diagnostics, theranostics, and targeted drug delivery due to their unique and specific function at the cellular, atomic, and molecular levels. Silver and silver containing compounds have been used as therapeutic agents since ages. With the pace of time, silver nanoparticles (AgNPs) have gained utmost position due to the wide range of pharmacological activities such as anticancer, anti-inflammatory, antiplatelet, antimicrobial, antiparasitic, and antiviral, etc. AgNPs have traditionally been synthesized using wet chemical techniques, where the chemicals used are often toxic, produces by-products, expensive, and flammable. In this

book chapter, ecofriendly, simple, and size/shape-controlled biosynthesis of silver nanoparticles using seaweeds, algae, bacteria, and fungi has been described along with the plausible mechanism of AgNPs formation.

18.1 INTRODUCTION

Nanotechnology has revolutionized all fields across the globe and opened up several frontiers in nanobiotechnology,¹ nanopharmacotherapeutics,² material and applied sciences.³ Recently, silver nanoparticles (AgNPs) gained key importance in biomedical sciences,⁴ drug delivery,⁵ catalysis,⁶ optics,⁷ and photoelectrochemistry.⁸ These silver nanomaterials have advantages due to their extremely small size and a very high surface-to-volume ratio which contributes chemical and physical attributes in their mechanical, steric and biological properties, catalytic activity, thermal and electrical conductivity, optical absorption, and melting point when compared with the bulk of the same material.⁹⁻¹⁰ This enables designing and production of the same materials with novel characteristics by simply controlling of shape and size at the nanometer scale, which ultimately influences their applications ranging from tumor therapy imaging,¹¹ biosensing,¹² electronics,¹³ bactericidal activity,¹⁴ and many more. The nanotechnology in biomedical research and clinical practice emerged as nanomedicine that could potentially make a major impact on human health. AgNPs are increasingly used in therapy, diagnostics, imaging, and targeted drug delivery due to their specific function at the cellular, atomic, and molecular levels. Nanomedicine has potential to integrate diagnostics/imaging with therapeutics and facilitates the development of theranostics for personalized medicine.¹⁵

In recent years, synthesis of AgNPs is a dynamic field in academics and applied research. Generally, the processes employed for the synthesis of nanoparticles are broadly classified into two types: the “top-down” process and “bottom-up” process. In “top-down” approach, the bulk material breaks down into particles at the nanoscale with various lithographic procedures like grinding, milling, etc., whereas in “bottom-up” approach, the atoms bring together to form a nucleus which grows eventually into a particle of nanosize.¹⁶ A variety of chemical and physical processes have been reported for the synthesis of metallic nanoparticles. However, various methods exist, but many problems are associated with these processes like utilizing toxic solvents, production of harmful by-products, expensive, etc.¹⁷ The chemicals hydrazine hydrate, hydrogen peroxide, sodium borohydride,

polyvinylpyrrolidone, dimethylformamide, and ethylene glycol are generally used for the reduction of metal salts, but it gets absorbed on the surface of nanoparticles formed, thereby producing toxicity. Thus, there is a need to explore ecofriendly green synthetic protocols for the synthesis of AgNPs.

Nature has provided abundant biological resources to synthesize AgNPs ecofriendly.¹⁸ With the advancement in technologies, a new way for research and development in the field of biology toward nanomedicine has been established.¹⁹ The use of biological resources in the synthesis of nanomaterials is rapidly developing due to their growing success, ease of formation of nanoparticles, economic, and ecofriendly in nature.²⁰ Over the past few years, purified extracts of bacteria, fungi, algae, seaweeds, and viruses have received adequate attention for the development of energy proficient, nontoxic, economic AgNPs.²¹

Typically, a bioorganism-mediated metallic salt reduction process occurs when the aqueous extract of bioorganism reacts with an aqueous solution of the metal salt (here, AgNO_3). The complete reaction occurs at room temperature within a few minutes. Due to the presence of a wide variety of chemicals, the bioreduction process is relatively complex. Biological synthesis of nanoparticles using plant extracts is relatively scalable and less expensive compared with microbial processes.²² The nature of plant extract, its concentration, the concentration of metal salt, pH, temperature, and contact time affect the rate of production, quantity, and characteristics of the nanoparticles. The source of the plant extract also influences the characteristics of nanoparticles because of varying concentrations and combinations of organic reducing agents.²³ For the green synthesis of nanoparticles, the following points must be considered for (1) selecting of appropriate bioresources for the reduction of metal salts and (2) providing optimal reaction conditions for nanoparticle formation.²⁴

This book chapter focuses primarily on bioorganism-mediated synthesis of AgNPs and their probable mechanism(s) of the formation.

18.2 BIOORGANISM-MEDIATED SYNTHESIS OF AgNPs

18.2.1 BACTERIUM-MEDIATED SYNTHESIS OF AgNPs

Synthesis of AgNPs employing bacteria as reducing principle is an exciting approach. A number of prokaryotic bacteria have been utilized to synthesize AgNPs intracellularly or extracellularly by enzymatic processes.²⁵ In

the former, the formation of AgNPs is due to their chemical detoxification as well as due to energy-dependent ion efflux from the cell by membrane proteins that function either as ATPase or as the chemiosmotic cation or proton antitransporters. In case of intracellular production, the accumulated particles are of the particular dimension and with less polydispersity. In order to release the intracellularly synthesized nanoparticles, additional processing steps such as ultrasound treatment or reaction with suitable detergents are required. In extracellular synthesis, the cell wall reductive enzymes or soluble secreted enzymes are involved in the reductive process of metal ions, and then it is obvious to find the metal nanoparticles extracellularly. The microbial-mediated synthesis of metal nanoparticles depends upon the localization of the reducing components of the cell.²⁶

Slawson et al. (1992) discovered few silver-resistant bacteria strain *Pseudomonas stutzeri* AG259 from silver mines which accumulated AgNPs of size 35–46 nm within the periplasmic space. When this bacterium was placed in a concentrated aqueous solution, particles of larger size (200 nm) were formed. In order to survive in environments containing high levels of metals, some microbes (esp. bacteria) have adapted mechanisms to cope with them.²⁷

These mechanisms involve altering the chemical nature of the toxic metal so that it no longer causes toxicity, resulting in the formation of nanoparticles of the metal concerned. Thus, nanoparticle formation is the “by-product” of a resistance mechanism against a specific metal, and this can be used as an alternative way of producing nanoparticles.²⁸

The rapid formation of AgNPs from Ag^+ by culture supernatants of *Klebsiella pneumonia*, *Escherichia coli*, and *Enterobacter cloacae* is of considerable interest.²⁹ The reduction of aqueous Ag^+ ions with the cell filtrate of *Rhodobacter sphaeroides* has been reported.³⁰ The size of AgNPs was controlled by the specific activity of nitrate reductase in the cell filtrate. Juibari et al. (2011) isolated thermophilus bacteria from geothermal hot springs and identified as *Ureibacillus thermosphaericus*, which showed high potential for AgNP biosynthesis with the extracellular mechanism. Biosynthesis reactions were conducted using the culture supernatant at different temperatures (60–80°C) and silver ion concentrations (0.001–0.1 M). The experimentation showed that pure spherical nanoparticles in the range of 10–100 nm was produced, and the maximum nanoparticle production was achieved using 0.01 M AgNO_3 at 80°C.³¹ Kalimuthu et al. (2008) synthesized silver nanocrystals of size 50 nm from bacterium

Bacillus licheniformis, which reduced silver ions into AgNPs as indicated by the change in color from whitish–yellow to brown.³² Ali et al. (2011) reported the extracellular biosynthesis of AgNPs of size 100–200 nm using marine cyanobacterium, *Oscillatoria willei* NTDM01, which reduces silver ions and stabilizes the AgNPs by a secreted protein.³³ The biosynthesis of AgNPs has been successfully conducted using *Plectonema boryanum* UTEX 485, a filamentous cyanobacterium, reacted with aqueous AgNO₃ solutions (560 mg/L Ag) at 25–100°C for upto 28 days have been reported.³⁴ Saifuddin et al. (2009) described a novel combinatorial synthesis approach for the synthesis of metallic nanostructures of silver (Ag) of size 5–60 nm, by using a combination of culture supernatant of *Bacillus subtilis* and microwave irradiation in water in the absence of a surfactant or soft template. Similarly, few bacterial species like *Morganella*, *Bacillus*, etc., have been utilized explicitly for the synthesis of AgNPs³⁵ (Table 18.1).

TABLE 18.1 Bacterium-Mediated Production of AgNPs.

S. no.	Bacteria	Size (in nm)	Application
1.	<i>Acetobacter xylinum</i>	NA	NA
2.	<i>Aeromonas</i> sp. SH10	6.4	NA
3.	<i>Bacillus licheniformis</i>	50	NA
4.	<i>Bacillus</i> sp.	5–15	NA
5.	<i>Bacillus subtilis</i>	5–60	NA
6.	<i>Bacillus thuringiensis</i> spore	15	Bactericidal
7.	<i>Brevibacterium casei</i>	10–50	Anticoagulant
8.	<i>Corynebacterium</i> sp. SH09	10–15	NA
9.	<i>Escherichia coli</i>	50	NA
10.	<i>Klebsiella pneumoniae</i> , <i>Escherichia coli</i> and <i>Enterobacter cloacae</i>	50–100	NA
11.	<i>Klebsiella pneumoniae</i> , <i>Escherichia coli</i> and <i>Enterobacter cloacae</i>	28.2–122	NA
12.	<i>Lactobacillus</i> sp.	20–50	NA
13.	<i>Morganella</i> sp.	20–30	NA
14.	<i>Oscillatoria willei</i>	100–200	NA
15.	<i>Plectonema boryanum</i>	1–200	NA
16.	<i>Pseudomonas aeruginosa</i>	13	NA
17.	<i>Pseudomonas stutzeri</i> AG259	< 200	NA
18.	<i>Rhodobacter sphaeroides</i>	9.56	NA
19.	<i>Ureibacillus thermosphaericus</i>	10–100	NA

NA: not available.

The exact mechanism of AgNP formation is still not clear but a few kind of research strongly support the role of nitrate reductase as the key enzyme for nanoparticle formation in bacteria, where bioreduction of AgNO_3 could be associated with metabolic processes utilizing nitrate by reducing nitrate to nitrite and ammonium.³⁴

18.2.2 FUNGUS-MEDIATED SYNTHESIS OF AgNPs

The use of bioorganisms for the production of various therapeutically active products is an attractive process developed in the 21st century. Nowadays, the production of metal nanoparticles from their corresponding metal salts by fungi is gaining importance. It is believed that the reduction of the metal ions occurs by an enzymatic process. It is creating an avenue for the fungi-mediated synthesis of nanomaterials over a range of chemical constituents. Some of the most popular species include *Fusarium*, *Aspergillus*, and *Penicillium*.

Ahmad et al. (2003) observed that aqueous silver ions, when exposed to the fungus *Fusarium oxysporum*, are reduced in solution, thereby leading to the formation of an extremely stable silver hydrosol. The AgNPs of size 5/15 nm are stabilized in solution by proteins secreted by the fungus.³⁶ Similarly, extracellular production of AgNPs of size 20–50 nm by several strains (O6 SD, 07 SD, 534, 9114, and 91248) of the fungus *Fusarium oxysporum* have been reported. The authors concluded that the reduction of the metal ions occurs by a nitrate-dependent reductase and a shuttle quinone extracellular process.³⁷

Similar biosynthesis of highly stable spherical AgNPs of size 10–60 nm by fungus *Fusarium semitectum* from silver nitrate solution has been reported.³⁸ Likewise, an efficient, ecofriendly and simple process of AgNP biosynthesis (extracellularly) by *Fusarium solani* have been reported by Ingle et al. (2009).³⁹ The authors described that the AgNPs were found to be quite stable in solution due to the capping of AgNPs by proteins secreted by the fungus.

In a study, *Aspergillus clavatus*, an endophytic fungus was challenged with 1 mM AgNO_3 solution, resulted in the formation of extracellular, polydispersed spherical, or hexagonal particles of size 10–25 nm and having antimicrobial activity against *Candida albicans*, *Pseudomonas fluorescens*, and *Escherichia coli*.⁴⁰ Bhainsa and D'Souza (2006) investigated extracellular biosynthesis of AgNPs using *Aspergillus fumigates*

where author reported the formation of well-dispersed silver nanoparticles of size 5–25 nm.⁴¹ Jain et al. (2011) demonstrated an ecofriendly and low-cost protocol for the synthesis of AgNPs using the cell-free filtrate of *Aspergillus flavus* NJP08. The extracellular proteins present in cell extract were found to be responsible for the synthesis and stability of AgNPs.⁴²

Kathiresan et al. (2009) reported in vitro biosynthesis of AgNPs from AgNO₃ as a substrate by *Penicillium fellutanum* isolated from coastal mangrove sediment. The authors explored a single prominent protein band with molecular weight of 70 kDa in the culture filtrate, which was secreted out of the fungal biomass and was believed to be involved in the reduction of the silver ions.⁴³ AgNPs of size 52–104 nm were biologically synthesized using filamentous fungi *Penicillium* sp. isolated from the soil samples. The cell filtrate of *Penicillium* sp., when challenged with 1 mM of silver nitrate, resulted in a change of the mixture from colorless to orange–brown indicated the synthesis of AgNPs in the reaction mixture.⁴⁴ Similar experiments for AgNPs biosynthesis from *Penicillium* sp. was demonstrated by Sadowski et al (2008).⁴⁵

Generally, the synthesis of AgNPs takes place in two steps: firstly, reduction of bulk silver ions into AgNPs and, secondly, capping of the synthesized nanoparticles. The mechanism of fungal-mediated synthesis occurs in the following steps; former step involves trapping of Ag⁺ ions at the surface of the fungal cells and subsequently a 32 kDa protein which may be a reductase secreted by the fungal isolate specifically reduce silver ions into AgNPs. The later step involves 35 kDa proteins which bind with nanoparticles and confer stability.³⁹ The protein–nanoparticle interactions can play an important role in providing stability to nanoparticles. The fungal proteins proffer key role in the reduction of the metal salts into their corresponding elemental form. The proteins present in *Volvariella volvacea* are such example of natural bioreductant. In *Fusarium oxysporum*, bioreduction takes place by α -NADPH-dependent sulfite reductase (35.6 kDa) and phytochelatins components,⁴⁶ whereas, in *Penicillium brevicompactum*, compactin serves as the bioreductant.⁴⁷

A large fungus-mediated synthesis of nanoparticles has been reported. Fungi like *Cladosporium cladosporioides*, *Trichoderma Reesei*, *Chrysosporium tropicum*, *Cochliobolus lunatus*, etc., have been reported to contribute biofabrication of AgNPs. The biosynthesized metal nanoparticles have exhibited potential cytotoxic, immunomodulatory, larvicidal activities. The most common fungi used for the biosynthesis of AgNPs are listed in Table 18.2.

TABLE 18.2 Fungus-Mediated Synthesis of AgNPs.

S. no.	Fungi	Size (in nm)	Application
1.	<i>Alternaria alternata</i>	20–60	Fungicidal
2.	<i>Aspergillus clavatus</i>	10–25	Bactericidal
3.	<i>Aspergillus flavus</i>	17	NA
4.	<i>Aspergillus fumigatus</i>	5–20	NA
5.	<i>Aspergillus niger</i>	20	NA
6.	<i>Aspergillus terreus</i>	2.5	NA
7.	<i>Bipolaris tetramera</i>	54.78–73.49	Bactericidal and immunomodulatory
8.	<i>Chrysosporium tropicum</i>	20–50	Larvicidal
9.	<i>Cladosporium cladosporioides</i>	10–100	NA
10.	<i>Cochliobolus lunatus</i>	3–21	Larvicidal
11.	<i>Coriolus versicolor</i>	25–75	NA
12.	<i>Cryphonectria</i> sp.	30–70	Bactericidal
13.	<i>Fusarium acuminatum</i>	5–40	Bactericidal
14.	<i>Fusarium oxysporum</i>	5–15	NA
15.	<i>Fusarium oxysporum</i>	20–50	NA
16.	<i>Fusarium semitectum</i>	10–60	NA
17.	<i>Fusarium solani</i>	5–35	NA
18.	<i>Hormoconis resinae</i>	20–80 (triangle) 10–20 (spherical)	NA
19.	<i>Humicola</i> sp.	5–25	Cytotoxicity
20.	<i>Neurospora crassa</i>	11	NA
21.	<i>Penicillium brevicompactum</i>	23–105	NA
22.	<i>Penicillium fellutanum</i>	5–25	NA
23.	<i>Penicillium</i> sp.	52–104	NA
24.	<i>Penicillium</i> sp.		NA
25.	<i>Phaenerochaete chrysosporium</i>	50–200	NA
26.	<i>Phoma glomerata</i>	60–80	Bactericidal
27.	<i>Pleurotus djamor</i>	5–50	Cytotoxicity
28.	<i>Pleurotus sajor caju</i>	5–50	Bactericidal
29.	<i>Trichoderma asperellum</i>	13–18	NA
30.	<i>Trichoderma reesei</i>	5–50	NA
31.	<i>Trichoderma viride</i>	5–40	NA
32.	<i>Verticillium</i>	25	NA
33.	<i>Volvariella volvacea</i>	20–150	NA
34.	Yeast strain MKY3	2–5	NA

NA: not available.

18.2.3 ALGAE-MEDIATED SYNTHESIS OF AgNPs

The extensive literature on various bioorganisms has revealed that marine has abundant resources comprising of diverse biomolecules for successful biosynthesis of AgNPs. Rajesh et al. (2012) demonstrated a simple and ecofriendly biosynthesis of AgNPs of size 28–41 nm at room temperature using *Ulva fasciata* crude ethyl acetate extract as reducing and capping agent. The presence of 1-(hydroxymethyl)-2, 5, 5, 8a-tetramethyl decahydro-2-naphthalenol as reducing agent and hexadecanoic acid was found to be a stabilizing agent. The AgNPs inhibited the growth of *Xanthomonas campestris* pv. *malvacearum*, with a MIC value of $40.00 \pm 5.77 \mu\text{g/mL}$.⁴⁸ Similarly, fabrication of AgNPs using marine macroalgae *Ulva reticulata* has been reported.⁴⁹

Merin et al. (2010) employed four algal species: *Chaetoceros calcitrans*, *Chaetoceros salina*, *Isochrysis galbana*, and *Turbinaria conoides* for the synthesis of AgNPs. The AgNPs of size 53–72 nm demonstrated prospective antimicrobial activity against *E. coli*, *P. aeruginosa*, *P. vulgaris*, and *Klebsiella* sp. Similarly, bactericidal activity has been reported by AgNPs of size 96 nm biosynthesized from algae *Turbinaria conoides*.⁵⁰ Kannan et al. (2013) showed the formation of AgNPs (3–44 nm) by the reduction of the aqueous silver metal ions using macro alga *Chaetomorpha linum* extract. The authors reported that few water-soluble compounds such as amines, peptides, flavonoids, and terpenoids present in *C. linum* extract is responsible for bioreduction.⁵¹ The extract of brown Australasian marine alga *Cystophora moniliformis* was utilized to synthesize AgNPs of size 50–100 nm. Spherical and smaller particles appeared at low temperatures, and agglomeration and increased size of the particles (<2 μm) were observed at higher temperatures⁵² (Table 18.3).

18.2.4 SEAWEED-MEDIATED SYNTHESIS OF AgNPs

The literature highlights the use of extracts of seaweeds for the production of AgNPs. Aqueous extract of seaweed *Gelidiella* sp. has been employed for synthesizing 40–50 nm AgNPs which exhibited potent cytotoxic activity against Hep2 cell line⁵³. Murugan et al. (2011) reported the seaweed-mediated synthesis of AgNPs by using the frond extract of *Caulerpa scalpelliformis*. The toxicity of the formed AgNPs was assessed against the filarial vector *Culex quinquefasciatus*.⁵⁴ The formation of

AgNPs by the reduction of aqueous silver metal ions during exposure to both fresh and dry seaweed extracts of *Codium capitatum* has been reported.⁵⁵ Antimicrobial activity of AgNPs of size 20 nm synthesized from an aqueous extract of red seaweed *Gelidiella acerosa* and *Sargassum tenerrimum* has also been reported.⁵⁶ A list of seaweeds used to synthesize AgNPs has been provided in Table 18.4.

TABLE 18.3 Algae-Mediated Production of AgNPs.

S. no.	Algae	Size (in nm)	Application
1.	<i>Chaetoceros calcitrans</i> , <i>Chaetoceros salina</i> , <i>Isochrysis galbana</i> , and <i>Taterillus gracilis</i>	53–72	Bactericidal
2.	<i>Chaetomorpha linum</i>	3–44	NA
3.	<i>Chlorococcum humicola</i>	2–16	Bactericidal
4.	<i>Cystophora moniliformis</i>	50–100	NA
5.	<i>Turbinaria conoides</i>	96	Bactericidal
6.	<i>Ulva fasciata</i>	28–41	Bactericidal
7.	<i>Ulva reticulate</i>	-	Bactericidal

NA: not available.

TABLE 18.4 Seaweeds-Mediated Synthesis of AgNPs.

S. no.	Seaweeds	Size (in nm)	Application
1.	<i>Caulerpa scalpelliformis</i>	20–35	Larvicidal
2.	<i>Codium capitatum</i>	3–44	NA
3.	<i>Gelidiella acerosa</i>	22	Fungicidal
4.	<i>Gelidiella</i> sp.	40–50	Cytotoxicity
5.	<i>Sargassum tenerrimum</i>	20	Bactericidal
6.	Water hyacinth	5.69 ± 5.89 nm (pH 4), 4.53 ± 1.36 nm (pH 8), and 2.68 ± 0.69 nm (pH 11)	NA

NA: not available.

18.3 CONCLUSION

Nature has provided abundant bioresources that can reduce silver ion into the AgNP. In the field of nanotechnology, a reliable and ecofriendly process for the synthesis of AgNPs is the foremost demand. In order to achieve this goal, the use of natural sources for the green synthesis

of AgNPs becomes crucial. This approach has several advantages over conventional methods as an efficient, cost-effective, and environmentally safe. However, there are a few drawbacks associated with the biosynthesis of nanoparticles using green chemistry approach. It is relatively a slow process, slightly difficult to control the size/shape of nanoparticles using biological sources, the exact mechanism for nanoparticles formation is unknown and nonspecific conjugation of phytoconstituents/proteins during the synthesis of AgNPs. The microorganism (bacteria and fungi)-mediated synthesis is relatively easy, but there is a need to explore the biochemical and molecular mechanism of nanoparticle synthesis by these organisms. Algae and seaweeds are relatively newer bioresources and are not explored adequately and need further research. The wide variety of biological activities and imaging property of biosynthesized AgNPs may provide a basis for the development of future nanomedicine. Additionally, purification and proper characterization of these AgNPs are the essential steps to be taken into consideration before the nanomaterials to be used commercially in healthcare. In spite of all major challenges and issues, the biosynthesized AgNPs may be potential nanomedicine for the treatment of various diseases in near future.

KEYWORDS

- bioorganism
- biosynthesis
- green synthesis
- mechanism
- nanoparticle
- silver

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