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REVIEW

Cyanobacteria – A Promising Platform in Green Nanotechnology: A Review on Nanoparticles Fabrication and Their Prospective Applications

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Abstract: Green synthesis of nanoparticles (NPs) is a global ecofriendly method to develop and produce nanomaterials with unique biological, physical, and chemical properties. Recently, attention has shifted toward biological synthesis, owing to the disadvantages of physical and chemical synthesis, which include toxic yields, time and energy consumption, and high cost. Many natural sources are used in green fabrication processes, including yeasts, plants, fungi, actinomycetes, algae, and cyanobacteria. Cyanobacteria are among the most beneficial natural candidates used in the biosynthesis of NPs, due to their ability to accumulate heavy metals from their environment. They also contain a variety of bioactive compounds, such as pigments and enzymes, that may act as reducing and stabilizing agents. Cyanobacteria-mediated NPs have potential antibacterial, antifungal, antialgal, anticancer, and photocatalytic activities. The present review paper highlights the characteristics and applications in various fields of NPs produced by cyanobacteria-mediated synthesis.

Keywords: nanoparticles, nanomaterials, cyanobacteria, green synthesis, physicochemical properties

Introduction

Nanotechnology is an emerging field that includes synthesis, characterization, and development of various nanomaterials,[1,2] that have significant roles in daily life, providing valuable products that improve industrial production, agriculture, communication, and medicine.[3] Currently, around 1000 commercial nanoproducts are available in world markets.[4,5] The term "nano" denotes any particles or materials with at least one nanosized (1–100 nm) dimension. Nanoparticles (NPs) differ significantly from their bulk materials in terms of physical, chemical, and biological properties.[6] These differences are mainly due to their high surface area to volume ratio, which results in considerable differences in catalytic and thermal activities, melting point, conductivity, mechanical properties, and optical absorption. These properties make NPs applicable in almost all fields.[7]

NPs have significant roles in bio-diagnostic and optical biosensing, nanophotonics, and imaging and treatment of many diseases affecting human health.[8] Silver NPs (Ag-NPs) can interact effectively with microbe surfaces due to their small size and large surface area and are thus used as antimicrobial agents.[9] Ag-NPs synthesized using *Fusarium Keratoplasticum* and embedded in cotton fiber showed significant antibacterial activity against pathogenic bacteria.[10] Carbon nanotubes have a key role in drug

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delivery, because of their capacity to carry drugs and control their release into target cells.[11] Quantum dot NPs have been used to detect the location of malignant cells inside the body.[12] Iron oxide NPs are used in resonance imaging and diagnosis of tumors.[13] Gold NPs (Au-NPs) are in high demand for various applications in multiple fields owing to their low toxicity.[14] In addition, Au-NPs have high photothermal and photoacoustic activity, making them suitable for use in photothermal therapy for cancer. Other biogenic NPs such as copper oxide NPs,[15] zinc oxide NPs,[16] selenium NPs,[17] acted as potent anticancer agents. The variation in NP shapes, including spherical, cubic, needles, triangular, rod, etc., enables them to be used in diverse areas such as device manufacture, electronics, optics, and biofuel cells (Figure 1).[18]

The physicochemical routes used to produce NPs are often unwieldy, expensive, and result in liberation of toxic byproducts that threaten ecological systems.[19] To avoid these drawbacks, green synthesis of NPs using biogenic agents has become an alternative to chemical and physical synthesis.[20] Diatoms, mushrooms, algae, plants, fungi, bacteria, actinomycetes, lichen, cyanobacteria, and microalgae have been shown to successfully reduce metal precursors to their corresponding NPs.[21] Intra- and extracellular green synthesis techniques have been developed to reduce bulk materials to nanoforms using biological extracts.[22] These nanomaterials can be synthesized in the presence of biocompounds such as flavanones, amides, enzymes, proteins, pigments, polysaccharides, phenolics, terpenoids, or alkaloids, to aid the reduction and stabilization of NPs.[21] A high surface area to volume ratio is the target physical feature of NPs, as it confers their versatile applicability and ability to withstand harsh conditions.[23] The shape and size of NPs synthesize by microorganisms, can be controlled by various abiotic and biotic factors, including pH, temperature, the nature of the microorganisms, their biochemical activity, and interactions with heavy metals.[24–26]

In the past few years, the synthesis of NPs using cyanobacteria has become an active research field.[24,27] Cyanobacteria are a diverse group of photoautotrophic prokaryotes that exist in a wide range of ecosystems.[28] They are distinguished by their ability to fix atmospheric nitrogen (N_2) by reducing nitrogen gas to ammonia using nitrogen reductase enzymes. This is a significant advantage in their role in biotransformation of metals to NPs,[19] as they possess the ability to eliminate heavy metal ions from their surrounding environment. Furthermore, they contain various biomolecules including secondary metabolites, proteins, enzymes, and pigments that confer important biological properties such as antimicrobial and anticancer activity.[27,29,30] In addition to these features, cyanobacteria have a high growth rate that facilitates high biomass production. Thus, they represent important

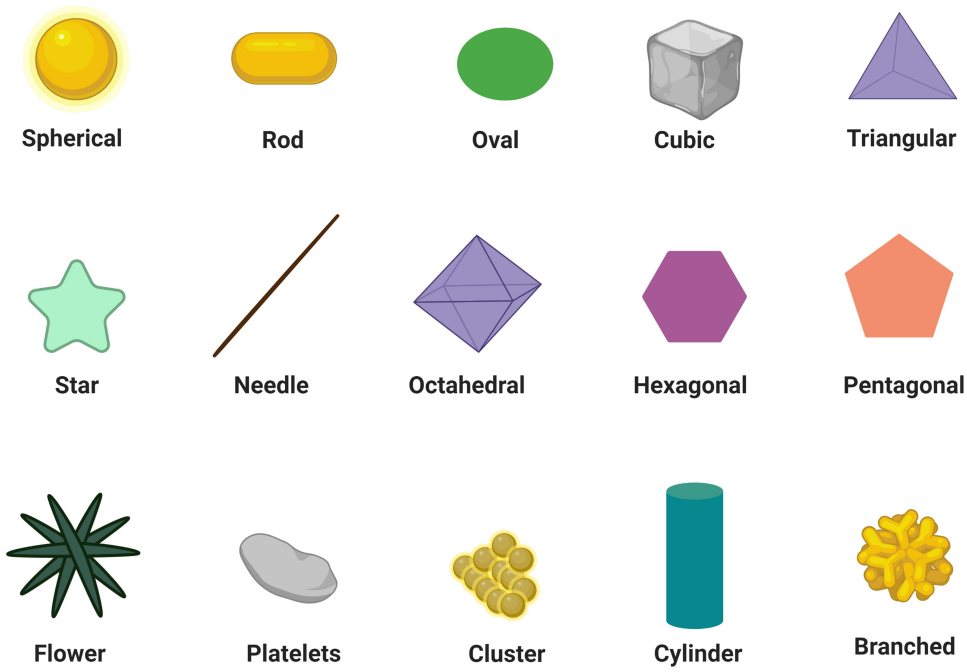


Figure 1 Various shape of nanoparticles.

nanotechnology-mediated microorganisms that can act as nanobiofactories for NPs.[31,32] Although there have been several detailed reviews of biological synthesis using microorganisms, few studies have focused on synthesis of NPs using cyanobacteria.

The current paper comprehensively reviews work on cyanobacteria-mediated fabrication of NPs, their abiotic and biotic conditions used during biosynthesis process including illumination, pH, temperature, type of synthesis process (extracellular and intracellular), followed with the factors influence on the synthesis process of NPs, the corresponding mechanisms of the biological synthesis, applications of NPs in various areas as well as the toxicity strategies of NPs against living cells.

Classification of NPs

NPs can be classified according to various factors, such as shape and dimension, phase compositions, nature, and origin (Figure 2).[33] For instance, natural NPs include those that exist in the biosphere as a result of fabrication from heavy metals by living organisms, as well as those generated incidentally by forest fires, volcanic eruptions, weathering of rocks, explosion of clay minerals, soil erosions, and sandstorms.[34] By contrast, engineered NPs are produced using chemical and physical routes. NPs can also be classified according to their chemical nature. Inorganic NPs include metal and metal oxide NPs such as silver, gold, platinum, titanium oxide, iron oxide, copper oxide, and zinc oxide NPs. Organic NPs include carbon NPs, N-halamine compounds, and chitosan NPs.[21]

Synthesis and Characterization of NPs

There are several methodologies for NP synthesis, including conventional methods such as chemical and physical approaches as well as modern methods such as biological synthesis using natural living organisms,[25] enzymes,[35] vitamins,[36] etc.[6] The chemical routes are a type of bottom-

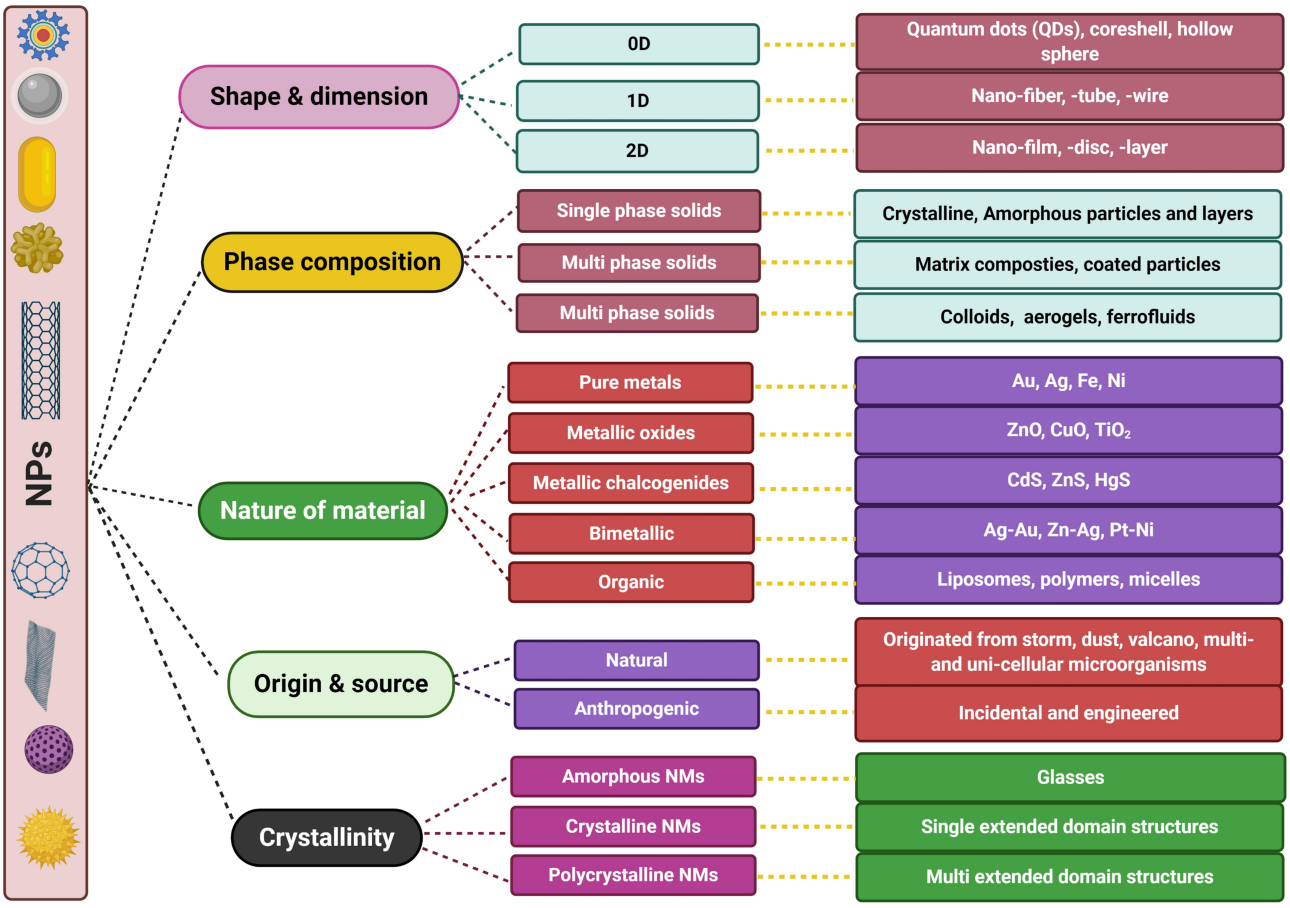


Figure 2 Nanoparticles classifications.
Note: ©2019. Dove Medical Press. Adapted from Ahmad S, Munir S, Zeb N, et al. Green nanotechnology: a review on green synthesis of silver nanoparticles–an ecofriendly approach. *Int J Nanomedicine*. 2019;14:5087[33] and adapted from *J Microbiol Methods*, 163, Khanna P, Kaur A, Goyal D. Algae-based metallic nanoparticles: synthesis, characterization and applications, page number:105656, Copyright (2019), with permission from Elsevier.[19]

up fabrication method, in which the atom assembled to nuclei and then grown to NPs.[37] In chemical methods, the main components are the precursor metals and the stabilizing and reducing agents. Reducing agents include sodium citrate, ascorbate, and sodium borohydride;[38] stabilizing agents include polyvinyl pyrrolidone, starch, and sodium carboxyl methylcellulose.[39] Physical synthesis strategies belong to top-down route, in which, the metals are converted to their nanoforms using physical approaches such as laser ablation,[40] mechanical milling,[41] and sputtering.[37,42]

The drawbacks of the physicochemical approaches include power consumption, high cost, and a slow production rate, and, most importantly, these processes are not more eco-friendly due to their toxic yields that threaten ecological systems.[6,18] Thus, there are global efforts towards development and usage of eco-friendly methods to synthesize NPs.

Green chemistry represents an advanced version of bottom-up nanotechnology approaches used to fabricate NPs.[19] But still now, biological synthesis process fights many obstacles to compete physicochemical synthesis such as obtaining uniform shape and size of NPs.[43] The aim of the biological synthesis methodology is to utilize natural sources to convert bulk material into nanoscaled particles with unique properties.[32] The natural sources used in biofabrication of NPs vary from unicellular to multicellular organisms, moreover; this process can be carried out in the presence of single proteins, enzymes, pigments, etc.[21] The unicellular organisms include bacteria,[44] cyanobacteria,[31] and diatoms,[45] while multicellular organisms include algae and plant.[46,47] The variety of potential natural sources and biomolecules facilitate the production of NPs with different unique properties. NPs are also subjected to various characterization analyses to assess their physical and chemical properties, including size, distribution, dispersion, stability, charge, and surface morphology.[48,49] These analyses use spectroscopic techniques such as ultraviolet (UV)-visible spectroscopy, Fourier transform infrared spectroscopy (FTIR), zeta potential, dynamic light scattering, and nuclear magnetic resonance spectroscopy to determine wavelength ranges,[27] and the chemical composition of biocoats surrounding biogenic NPs,[31] and to confirm the formation of NPs, as well as characterizing their charge and hydrodynamic diameter.[50] X-ray based analyses such as X-ray diffraction (XRD),[49] X-ray photo-electron spectroscopy (XPS),[23] and energy dispersive spectroscopy (EDAX or EDS) are employed to evaluate composition, structure and crystal phase, structure and crystal phase.[49] Microscopic techniques such as scanning electron microscopy (SEM), transmission electron microscopy (TEM), high-resolution TEM, and atomic force microscopy are used to determine the size and morphological appearance of NPs.[43,51] Also, there are several techniques perform to estimate the magnetic properties of NPs such as ferromagnetic resonance (FMR), vibrating sample magnetometer (VSM), etc. (Table 1).[52,53]

Potential Mechanisms of Green Synthesis Methods

The method of biofabrication of NPs differs from organism to another.[54] Moreover, differences are found among different strains of the same species.[55,56] Naturally, NPs are synthesized when microorganisms are exposed to toxic substances, in response to which they secrete extracellular substances to capture the material, or mediated through electrostatic interactions.[54,57] Mukherjee et al showed that attraction electrostatic forces were among the factors aiding the reduction process of NPs in fungal cells.[57] The biotransformation of NPs follows a general pattern wherein metal ions are trapped in the microbial cells or on the microbial surface in the presence of enzymes, and then reduced to form NPs.[54] Furthermore, the reduction of NPs by microorganisms can be classified into intracellular and extracellular synthesis (Figure 3).

Intracellular Synthesis of NPs

Intracellular formation of NPs refers to cases where the reduction of bulk material into NPs is performed inside host cells under the control of various biological factors.[20] Methods for in vivo synthesis of NPs in the laboratory involve three general steps: i) culturing the target microorganisms; ii) the interaction between the precursor solution and living cells; and iii) the separation and purification of NPs from cells for characterization using physicochemical techniques.[24] In the latter step, the mixture of living microorganisms and precipitated NPs is centrifuged at 12,000 g. The pellets are then washed multiple times with distilled water for direct examination, and/or the cells are lysed using methods such as sonication to extract NPs for analysis (Figure 4).[58]

Intracellular interactions between bulk materials and microorganisms can be achieved by two different protocols. The first involves collecting cellular biomass of target microorganisms in the logarithmic phase by centrifugation, then washing this biomass to remove any traces of

Table 1 Techniques Performed to Characterize Nanoparticles

Type Analysis	Characterization Analyses	Function	Reference
Spectroscopic techniques	Ultraviolet (UV)-visible spectroscopy	Confirm the formation of NPs and detect their wavelength ranges	27
	Fourier transform infrared spectroscopy (FTIR)	Determine the chemical composition of biocoats surrounding biogenic NPs	31
	Zeta potential	Characterize NPs charge	50
	Dynamic light scattering (DLS)	Estimate hydrodynamic diameter	50
	Nuclear magnetic resonance spectroscopy (NMR)	Determine the content and purity of NPs	145
X-ray based analyses	X-ray diffraction (XRD)	Evaluate composition, structure, and crystal phase of NPs	49
	Xray photo-electron spectroscopy (XPS)	Evaluate structure of NPs	23
	Energy dispersive spectroscopy (EDAX or EDS)	Evaluate atomic structure of NPs	49
Microscopic techniques	Scanning electron microscopy (SEM)	Determine the size and morphological appearance of NPs	43
	Transmission electron microscopy (TEM), high-resolution TEM,	Determine the size and morphological appearance of NPs	43
	Atomic force microscopy (AFM)	Determine the geometries, size, morphology, surface roughness of NPs	51,146
Magnetic techniques	Superconducting quantum interference device (SQUID), vibrating sample magnetometer (VSM), ferromagnetic resonance (FMR)	Estimate magnetization saturation, magnetization remanence, magnetic anisotropic constant, demagnetization field	52,53,147

salts from the medium.[59] The cleaned biomass is dissolved in water and mixed with a suitable concentration of precursor material solution. In the second method, microorganisms are individually cultured along with the bulk material solution and kept under culture conditions for 2 weeks.[60]

In cyanobacteria, ions are intracellularly reduced by electrons produced via the electron transport system, including energy-generating reactions in photosynthesis and, to some extent, in the respiratory electron transport system as a result of the existence of enzymes such as NADH-dependent reductases and redox reactions occur in the cytoplasm, thylakoid membranes, and cell membranes.[22,61,62]

Lengke et al showed that after reaction between *Plectonema boryanum* UTEX 485 system and silver nitrate, spherical, octahedral, and anhedral Ag-NPs were precipitated inside cells and in the culture solution.[24] They suggested that the silver ions were reduced by an intracellular electron donor or exported by a membrane transporter system. This indicates that the metabolic status (eg, respiration or photosynthesis) and the growth phase of an organism determine its ability to synthesize NPs. Remarkably, *P. boryanum* was shown to reduce gold(III)-chloride solutions to Au-NPs intracellularly.[63] The authors attributed the biorecovery mechanism of *P. boryanum* strains to either the gold(III)-chloride solution or the acidic medium, which killed cyanobacteria and liberated more organic sulfur, leading to further precipitation of gold particles. The interactions of cyanobacteria or organic material released through the cyanobacterial membrane with gold(III)-chloride enhanced the growth of metallic Au-NPs.

Kalishwaralal et al suggested that nitrate reductase enzymes may help to induce the enzyme responsible for synthesis of Ag-NPs in *Bacillus licheniformis*.[64] Another study showed that nitrogenases (nitrogen-fixing enzymes) may be potent reducing agents for fabrication of gold ions into Au-NPs.[65] Shabnam and Pardha-Saradhi reported that thylakoids extracted from *Potamogeton nodosus* (an aquatic plant) and *Spinacia oleracea* (a terrestrial plant) may

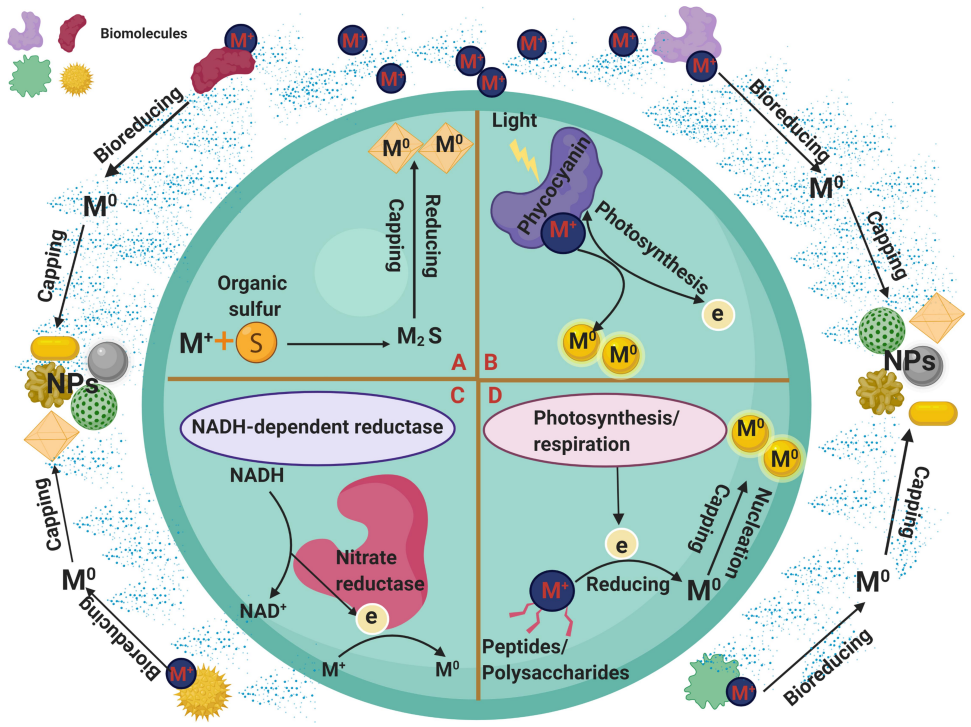


Figure 3 Potential mechanisms of green synthesis methods. (**A-D**) represented different intracellular synthesis methods. (**A**) Organic sulfur-mediated synthesis of NPs. (**B**) pigment-mediated synthesis of NPs. (**C**) Enzyme-mediated synthesis of NPs. (**D**) Biomolecules-mediated synthesis of NPs.
Abbreviations: M^+, metal; M^0, reduced NPs; e, electron; S, sulfur, M_2S, metal sulfide.

have been responsible for the fabrication of gold ions into Au-NPs during photochemical reactions.[66] Dahoumane et al suggested that polysaccharides and other macromolecules may be responsible for internal reduction and stabilization of NPs.[67] Other reports have suggested that cyanobacterial pigments act as potent bioreductant molecules that intracellularly reduce bulk material into NPs.[68,69]

Extracellular Synthesis of NPs

Extracellular synthesis takes place outside the cell, with exuded biological molecules such as pigments, ions, proteins, enzymes, hormones, and antioxidants having a significant role in the reduction process of NPs.[70,71] These biomolecules act as reducing and capping agents during the biofabrication process. Various methods exist for extracellular synthesis of NPs, including use of cell-free culture media, cell biomass extracts, and biomolecules (Figure 5).

Cell-Free Media

NPs can be synthesized using the culture media of microorganisms after removal of biomass by centrifugation. The filtrated extracellular culture media are mixed with metal precursor solutions under certain conditions to synthesis NPs. Keskin et al tested five cyanobacterial strains and showed that cell-free culture media of *Synechococcus* sp. were able to synthesis Ag-NPs under light conditions.[72] Ag-NPs were also extracellularly synthesized using the supernatant of *Pseudomonas* sp. THG-LS1.4 strain.[73] Many studies have demonstrated the vital role of biocontents such as enzymes, antioxidants, and phenolic and alkaloid compounds present in the cell-free culture in controlling the bioreduction process of NPs. Shivaji et al suggested that biomolecules such as NADH-reductases and sulfur-containing proteins in the cell-free supernatant are involved in biofabrication of metallic NPs.[74]

Cell Biomass Filtrate

Several reports describe the cell biomass filtrate synthesis approach, in which microorganism cultures are centrifuged and the pellets washed at least three times with distilled water to eliminate any excess metal from the medium.[31,32,75] Then, the cleaned pellets are freeze-dried using a lyophilizer or dried in an oven almost at 40 °C, then crushed using a mortar and pestle. The resulting fine powder is mixed with distilled water then filtrated using Whatman filter paper. Finally, the filtrate is mixed with

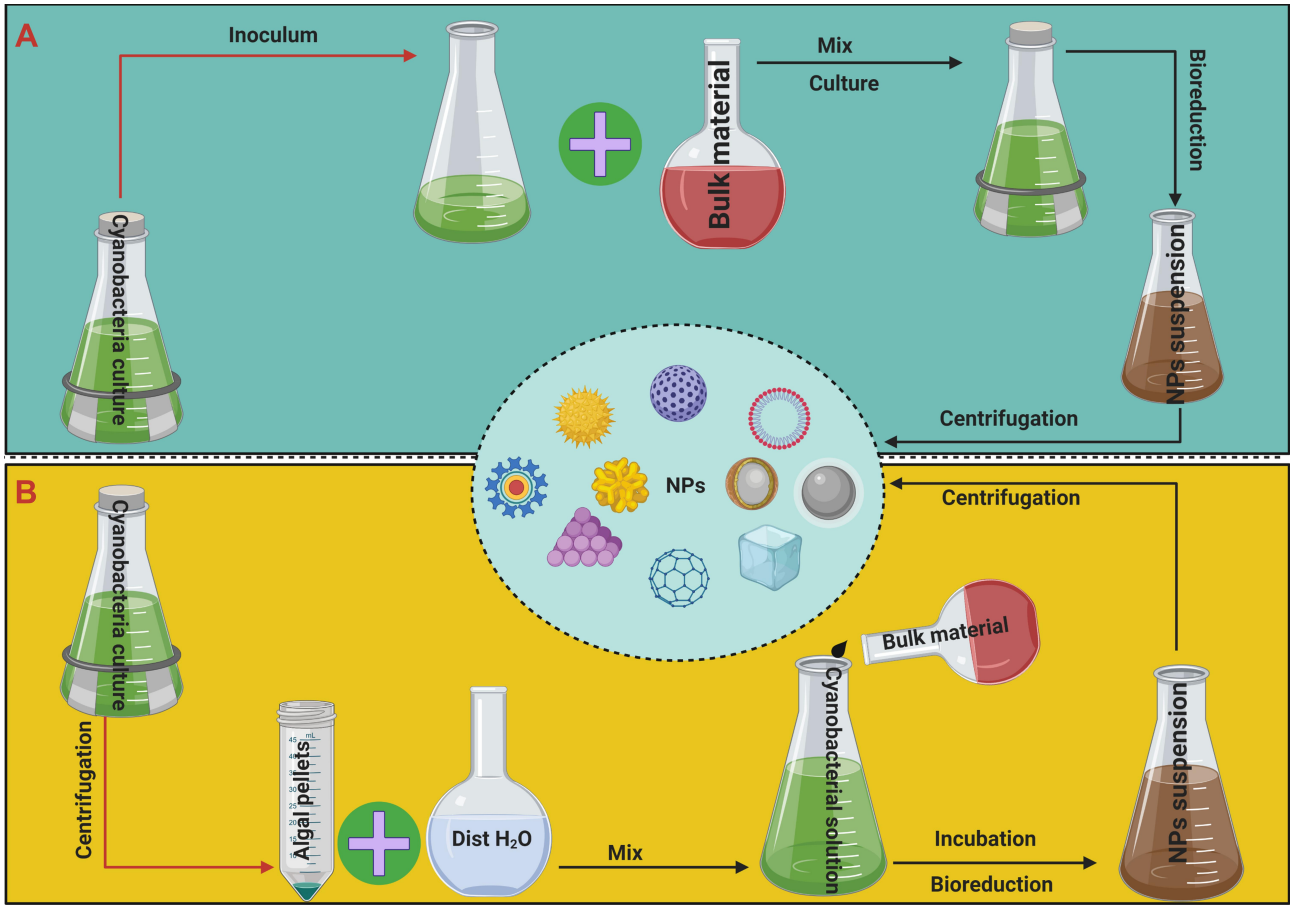


Figure 4 Potential protocols of intracellular synthesis methods.
Notes: (**A**) microorganisms are individually cultured along with the bulk material solution and kept under culture conditions. (**B**) synthesis NPs utilizing algal biomass in the logarithmic phase.

a metal precursor solution and incubated under suitable conditions. In this method, active biomoieties such as proteins and enzymes in the cells filtrate have significant roles in the biofabrication and stabilization of NPs.[31] Other route mentioned by Hassan et al in which cell biomass collected at mid-exponential phase and wash several times to exclude any trace elements then soaked in distilled water for specific time. Afterward, the mixture is centrifuged, and the supernatant is used for NPs synthesis.[15]

Biomolecule-Based NP Synthesis

Pigments

Cyanobacteria, microalgae, actinomycete, algae, etc. are distinguished by the predominance of pigments in their cells, such as carotenoid,[76] C-phycocyanin,[69] and R-phycoerythrin,[77] that are able to synthesis NPs. C-phycocyanin is a blue photosynthetic accessory pigment that forms part of phycobilisomes, structures attached to thylakoids involved in light harvesting and transferring electrons toward photosystem II reaction centers.[78,79] It has been shown that C-phycocyanin controls electron transfer and has the ability to bind to heavy metals.[80,81] Recent studies have demonstrated the role of C-phycocyanin in fabrication of NPs; Pate et al showed that utilizing C-phycocyanin extracted from two different cyanobacteria species (*Spirulina* and *Limnothrix* species) resulted in production of Ag-NPs with different shapes and sizes.[55] The authors attributed these differences in morphological features to the fact that the two C-phycocyanin preparations differed in purity and molecular weight. Also, they showed that there was a relationship between the ability of C-phycocyanin to synthesis NPs and the presence of light, as the pigment failed to reduce silver nitrate into Ag-NPs under dark conditions. Wei et al demonstrated the importance of C-phycocyanin extracted from Spirulina as a protective (capping) agent during the reduction process of silver nitrate into Ag-NPs.[82] El Naggar et al reported that a proteinaceous pigment phycocyanin

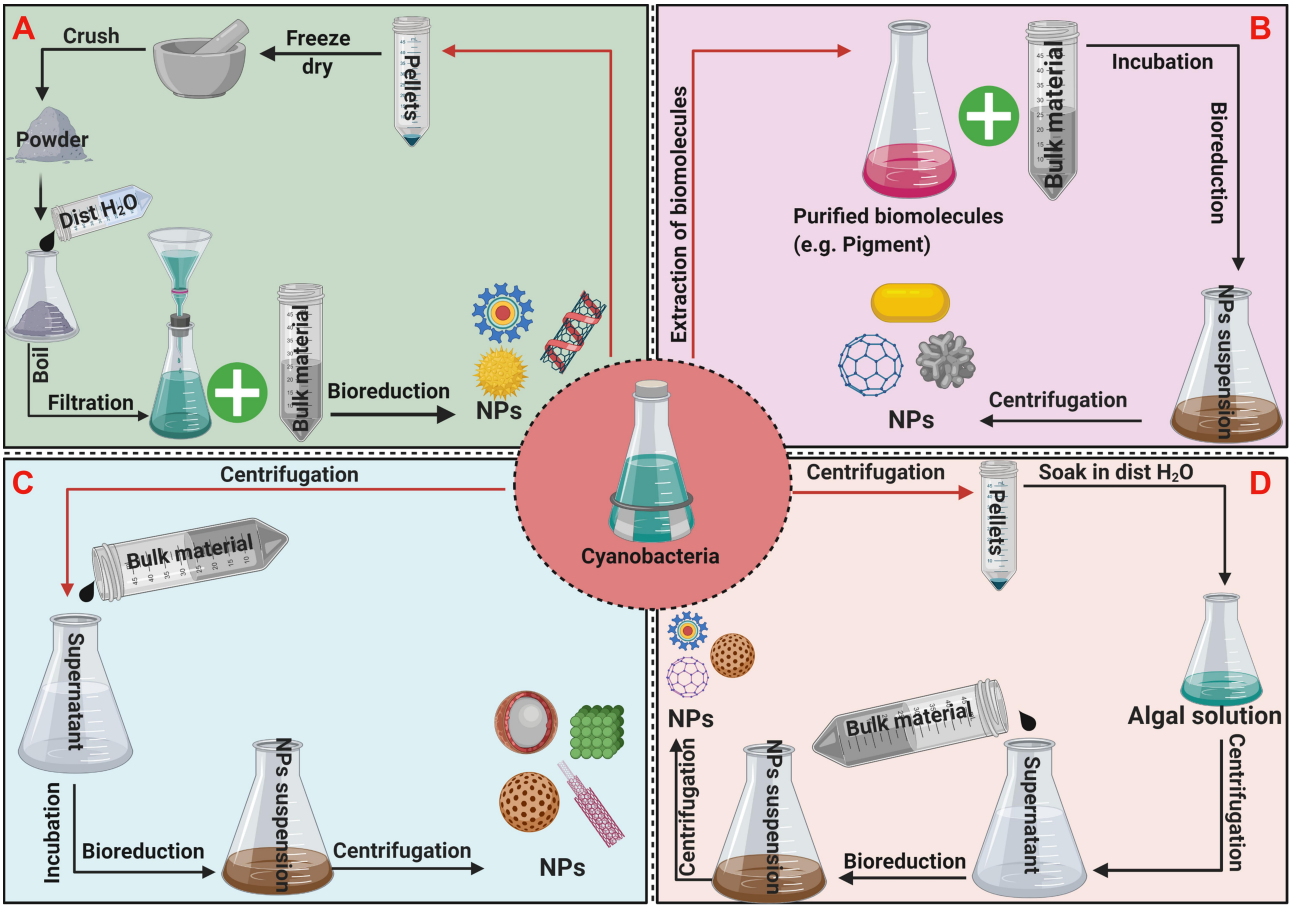


Figure 5 Potential protocols of extracellular synthesis methods.
Notes: (**A–D**) represent different protocols of extracellular synthesis of NPs. (**A**) cell biomass mediated synthesis of NPs (**B**) biomolecules mediated synthesis of NPs. (**C**) cell-free media mediated synthesis of NPs. (**D**) cell filtrate mediated synthesis of NPs.

isolated from *Nostoc linckia* reduced silver nitrate into Ag-NPs under direct illumination (2400–2600 Lux) for 24 h at room temperature.[69] In another study, phycoerythrin was extracted from *Nostoc carneum* and used as a reducing agent to synthesize Ag-NPs.[83] Mubarak Ali et al successfully synthesized cadmium sulfide (CdS) NPs using C-phycoerythrin extracted from cyanobacteria species *Phormidium tenue* NTDM05.[27] The mechanism by which C-phycocyanin mediates Ag-NPs synthesis is not clear; however, Patel et al suggest that it is similar to the mechanism of the red pigment R-phycoerythrin extracted from red algae, which can synthesize Ag-NPs without the addition of any reductant materials.[55]

Proteins

Many studies have considered the role of proteins in stabilization and reduction of NPs.[20,31,69] Bharde et al showed that cationic proteins secreted by *Verticillium* sp. and *Fusarium oxysporum* had hydrolytic activity, which enabled them to reduce and/or cap magnetite NPs.[84] Reddy et al found that a bacterial protein of molecular weight between 25 and 66 kDa contributed to the reduction process of Au-NPs, whereas a protein of molecular weight between 66 and 116 kDa was responsible for SNP fabrication.[85] Khalifa et al suggested that amino acids and proteins acted as stabilizing and reducing agents in the biofabrication process of metal nanoparticles (MNPs).[86] Mubarak Ali et al showed that the presence of amino, carboxyl, sulfate, etc. groups in the amino acid sequence of cyanobacterial proteins facilitates the bioreduction process of extremely small NPs with uniform particle size distribution.[87] Govindaraju et al performed extracellular synthesis of silver-gold core shell NPs, in addition to Ag-NPs and Au-NPs, using a single cell protein *Spirulina plantensis*.[8] They identified the FTIR bands at 1653, 1541, and 1242 cm^{-1} as amide I–III bands of polypeptides/proteins, and suggested that algal proteins played a crucial part in the stabilization process of these NPs.

Rahman et al reported that under metal stress, new or modified proteins were expressed to perform dual functions, fabricating precursor materials into CuO NPs and acting as stabilizing agents.[88] They showed that a 22 kDa protein of *Phormidium* was responsible for the reduction of copper sulfate into copper oxide NPs. Rosken et al first detected Au-NPs in the extracellular polymeric material of vegetative cells and the heterocyst polysaccharide layer of *Anabaena cylindrica*.[89]

Enzymes

Many studies have investigated the roles of various enzymes, including nitrate reductases and NADH-dependent enzymes in the bioreduction process of NPs.[65] Furthermore, Yin et al reported that superoxide dismutase has a vital role in the extracellular production of Ag-NPs using *F. oxysporum*.[54] Mostly, assimilatory type of nitrate reductases is metalloproteins having molybdenum ions as cofactor and catalyzes several reactions in nitrogen, carbon and sulfur cycle. Many studies have demonstrated the importance of these enzymes as a potent reducing agent in the biofabrication process of MNPs.[90]

Oza et al suggested that nitrate reductase aided the NADH-dependent extracellular synthesis of Au-NPs by *Chlorella pyrenoidosa*.[65] Brayner et al synthesized Au-NPs, Ag-NPs, Pt NPs, and Pd NPs in the presence of cyanobacteria using nitrogenases as reducing agents.[91] They chose three strains, *Calothrix pulvinate, Anabaena flos-aquae*, and *Leptolyngbya foveolarum*, to form the NPs. C. pulvinate synthesized Pd and Pt NPs after 30 min and 15 days, respectively, Au-NPs after a few hours, and Ag-NPs after 24 h. By contrast, when the same precursor materials and strains were incubated with nitrogenases, Pd and Pt, Au, and Ag NPs were formed after 2 h, 72 h, and 10 min, respectively.

Polysaccharides

Morsy et al used extracellular polysaccharides (EPSs) from *Nostoc commune* to reduce silver nitrate to Ag-NPs.[92] Briefly, they mixed 10 g of dried cyanobacteria with water, suspended the mixture in 100 mL of potassium phosphate buffer (pH 7), and homogenized it in a blender at medium velocity for 10 s, followed by stirring overnight at ambient temperature. The suspension was then homogenized again at least three times for 10 s and left to stand at ambient temperature for 10 min. The upper layer (polysaccharides) was removed using a spatula, and the lower aqueous layer was centrifuged at 6000 x g for 10 min at 20 °C. The pellets were discarded, and the supernatant containing the water-soluble fraction of the EPSs was dialyzed overnight against distilled water and freeze-dried using a lyophilizer. Then, 50 mL of the aqueous EPS solution (10 mg/mL) was added to 30 mM of silver nitrate solution. The reaction was autoclaved at 15 psi and 121 °C for 5 min. To precipitate biogenic Ag-NPs the mixture was centrifuged at 15,000 x g for 30 min at 20 °C. They reported that the EPSs functioned as potent reducing and capping agents, and showed that coating Ag-NPs with EPSs prevented the particles from coming into contacting with oxygen and increased their stability.

Factors Influencing Biofabrication of NPs Using Microorganisms

Many factors should be considered during biological synthesis, including illumination, time of exposure, pH, temperature, and concentration. Control of these factors can facilitate the production of NPs with suitable physicochemical properties.[22,67]

Illumination

The presence or absence of light has an important role in the biosynthesis of NPs. Some researchers report that light is needed at least to accelerate the bioreduction process for synthesis of NPs.[93] Patel et al suggested that illumination conditions are significant factors controlling the intracellular and extracellular synthesis of Ag-NPs using phototrophic cyanobacteria.[55] They found that some cyanobacteria could not produce NPs under dark conditions. However, under the same conditions but after exposure to light, the same strains were able to fabricate Ag-NPs from silver nitrate. On the other hand, other strains including *Anabaena* sp., *Limnothrix* sp., and *Synechocystis* sp. were able to produce NPs under both light and dark conditions. This can be explained by the fact that different strains produce different compounds capable of NPs synthesis, only some of which require light activation.[55] Another important point related to illumination is the light intensity. Mankad et al reported complete extracellular reduction of silver ions to Ag-NPs after exposure of a mixture of *Azadirachta indica* leaf extract and silver nitrate solution to sunlight for only 5 min.[93]

Time of Exposure

The time of reaction varies among different microorganisms, with some able to synthesize NPs within minutes

whereas others require weeks. Lengke et al reported that *P. boryanum* UTEX 485 took 28 days to synthesize Ag-NPs, whereas Zada et al showed that *Leptolyngbya* sp. JSC-1 fabricated Ag-NPs extracellularly from silver nitrate after 20 min.[94,95] A recent study showed that the dispersivity and stability of silver-NPs synthesized using *Oscillatoria limnetica* changed with increasing time. After 48 h of synthesis, the UV spectrum wavelength value was constant, and after 9 months of incubation, the optical intensity had shifted from 0.71 to 0.599 nm, indicating about the stability of Ag-NPs with low agglomeration.[26] The stability of Anabaena-mediated Ag-NPs was evaluated after 6 months of storage by Singh et al.[96] The results showed that the Ag-NPs were stable with no change in spectral absorbance, at least in the first 3 months.

pH

El Naggar et al reported that pH significantly affected the size and distribution of Ag-NPs.[83] They reported that silver-NPs extracellular synthesis using phycoerythrin was inhibited in acidic media (pH), whereas the reaction was enhanced under alkaline conditions (pH 10). In addition, smaller and more highly dispersed NPs were observed at pH 10, whereas, larger and more aggregated NPs were observed at pH 12.

Temperature

Lengke et al reported the first successful alternative to abiotic chemical approaches for fabricating NPs.[97] They screened the ability of *P. boryanum* UTEX 485 to form extra-, intracellular platinum NPs. The results demonstrated the effects of a variable range of temperatures on NP formation, showing that crystallization and recrystallization of NPs depend on temperature. Decreasing temperature resulted in amorphous distribution, while a crystalline structure was dominant at higher temperatures.

Concentration of Precursors and Natural Reducing Agents

The concentration of bioreductant materials has an important influence on the features of NPs, including shape and size.[26] The synthesis of NPs is dose dependent and is also related to the type of algae used.[65,67] Hamouda et al showed that increasing the concentration of cyanobacteria *Oscillatoria limnetica* increased the absorbance of the resulting peaks.[26] Moreover, they reported that peaks shifted in position from 420 to 430 nm, accompanied by broadening of peaks, indicating an increase in the size of particles. They also found that the extracellular biofabrication reaction of Ag-NPs was dependent on the dose of silver nitrate. Overall, increasing the concentration of precursor materials resulted in an increased optical intensity recorded by UV spectrophotometry.

Nature of Microorganisms

The nature of microorganisms is related to their biomolecular contents and the types of these molecules, such as polysaccharides, peptides, and pigments.[21,87] Thus, different microorganisms vary in their ability to form NPs. Brayner et al screened the reduction activity of three cyanobacteria cultures and observed that the size and shape of NPs varied according to the genus of cyanobacteria used.[91] Moreover, different strains from the same species were found to produce NPs with different physicochemical and biological characteristics. Recent studies used different strains from the same *Nostoc* species, including *Nostoc* sp. Bahar M,[32] *Nostoc* HKAR-2,[98] and *Nostoc muscorum* NCCU-442,[56] resulting in different nanosize ranges (8.5–26.44, 51–100, and 42 nm, respectively) of the resulting Ag-NPs.

Other factors may control NP features, including the microorganisms' habitats and their ability to eliminate metals from their environment.[21] Blue-green algae are distinguished by their ability to accumulate heavy metals from the surrounding environment and degrade these metals into NPs.[20] Husain et al showed that 30 cyanobacteria strains isolated from a marine habitat had significant potential to extracellularly reduce silver nitrate to Ag-NPs.[56] By contrast, other Eubacteria known to be resistant to heavy metals such as *Aphanizomenon* sp. could not fabricate Ag-NPs from silver metal under laboratory conditions.[55]

Cyanobacteria as Biomachinery for NPs Synthesis

The blue-green algae (cyanobacteria) are the only known oxygen-producing prokaryotes. All cyanobacteria are microscopic and widespread in aquatic environments, with some terrestrial species. The aquatic forms mostly occur in fresh water and few are marine.[99] Cyanobacteria contain non-membrane-bound organelles including chloroplasts, unstacked thylakoids, phycobiliprotein pigments, and cyanophycean starch and peptidoglycan matrices or walls. In

addition, they are a rich source of biomolecules such as proteins, enzymes, antioxidants, vitamins, and polysaccharides.[27] Although there have been many reports of biological synthesis with different micro- or macro-organisms, using plants, algae, bacteria, and fungi to obtain NPs of various sizes and shapes, few studies have used cyanobacteria as the biological machinery for NP fabrication.[12] Cyanobacteria are considered to be important biofactories that can be used to synthesize NPs by either extracellular or intracellular methods, owing to their ease of culture at ambient temperature and under atmospheric pressure, their high growth rate, the variable biocompounds inside their cells, their capacity to take up heavy metal ions, and the environmental safety of their products.[20] Different studies have demonstrated the capacity of different cyanobacterial strains to form different types of NPs, including metallic NPs such as Ag-NPs and Au-NPs, and metal oxide NPs such as ZnO NPs and CuO NPs, as well as other nanomaterials such as Ag-Au nanoalloys and semiconductor NPs such as CdS NPs (Figure 6).[2,63,99,100]

Silver Nanoparticles (Ag-NPs)

Silver-NPs are the most commonly used MNPs in various fields and can be found in many industrial and medical products including dressings, surgical instruments and masks, detergents, and care products.[101,102] Conventionally, Ag-NPs have been fabricated by chemical and physical approaches. Due to the drawbacks of these routes include their high cost, high energy requirements, and toxic byproducts, green synthesis methods have been developed to produce clean NPs and avoid the harmful effects of physicochemical techniques.[6,12] For instances, Kim et al mentioned that the injection rate and reaction temperature are crucial factors to synthesize Ag-NPs using polyol process

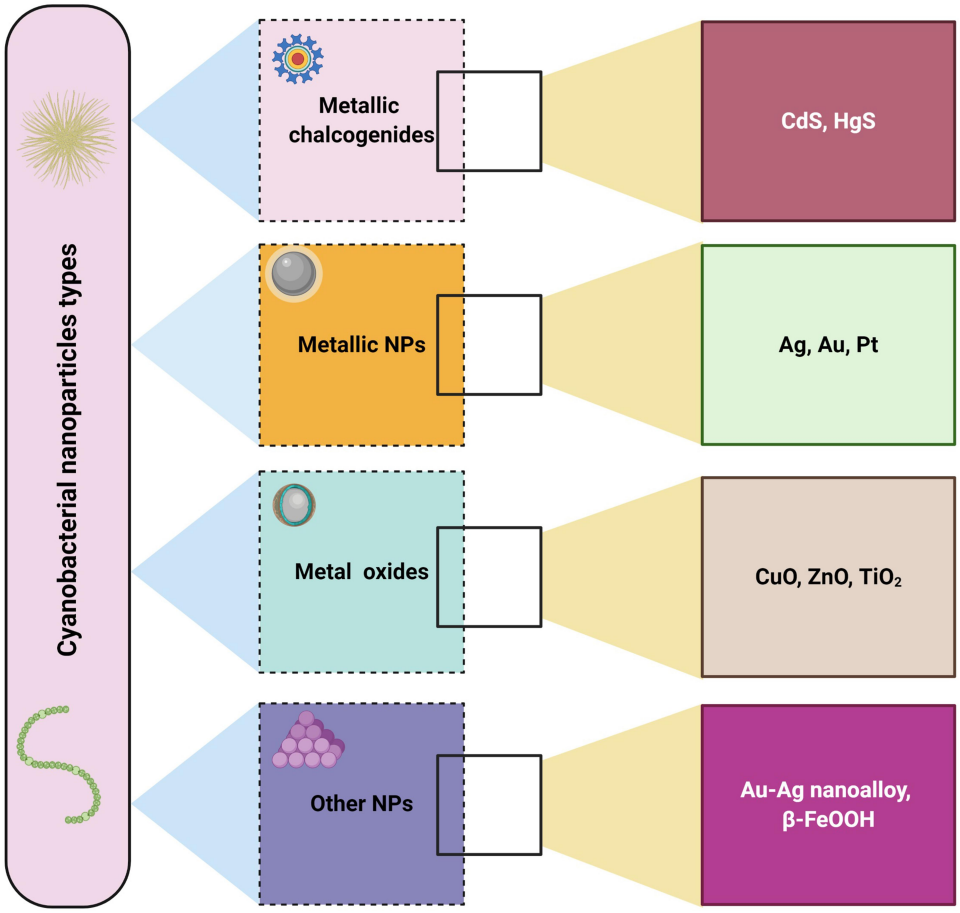


Figure 6 Type of metallic NPs synthesized by cyanobacteria.
Abbreviations: Cds, cadmium sulfide; HgS, mercury sulfide; Au, gold; Ag, silver; Pt, platinum; CuO, copper oxide; ZnO, zinc oxide; β-FeOOH, akaganéite.

and a modified precursor injection approach.[103] They generated spherical Ag-NPs with nanosize of 17 nm at 100 °C. In contrast, many studies using neutral organisms could synthesis Ag-NPs with smallest size ranged from 10, 10–15, 14.9 nm at room temperature.[32,91,104] Also, Jin et al synthesized Ag-NPs utilizing photoinduced route.[105] They found that Ag-NPs have triangular shape with size range between 30 and 120 nm. The scholars used chemically stabilizing agents such as citrate and poly (styrene sulfonate) to obtain stable Ag-NPs. While *Arthrospira maxima SAE* and *Arthrospira platensis* were able to generate triangular Ag-NPs (61 and 46 nm, respectively) at 30 °C for 24 h without needing to any stabilizing agents.[56]

Ecofriendly synthesis research has expanded rapidly to discover new microbes with hydrolytic capacity to synthesize NPs. Among these biological entities, blue-green algae provide a straightforward route for producing the desired Ag-NPs. *Desertifilum* IPPAS B-1220 was explored for the fabrication of Ag-NPs for the first time by Hamida et al,[31] who extracellularly synthesized Ag-NPs using a cell biomass extract under direct illumination for 24 h at room temperature. The formation of D-SNPs confirmed by UV-absorption peak at 421 nm. XRD diffraction pattern exhibited five 2 θ degree at 29.7, 38.4, 44.6, 64.7and 77.7 indicates the nanocrystallinity of D-SNPs. FTIR data demonstrated different IR peaks at 601.81 cm^{-1}, 1042.35 cm^{-1}, 1626.05 cm^{-1}, 2353.23 cm^{-1}, and 3453.72 cm^{-1} for D-SNPs. According to dominant FTIR spectra, the scholars reported the main biomolecules responsible for the bioreduction and stabilization processes were proteins and polysaccharides. Also, they found that *Desertifilum* IPPAS B-1220 sp. could produce spherical silver-NPs with sizes ranging from 4.5 to 26 nm.

Lengke et al used *P. boryanum UTEX 485* for the first time for both intracellular and extracellular synthesis of Ag-NPs.[106] They found that Ag-NPs have octahedral and spherical shapes with nanosize ranged from 1 to 200 and 10 nm, respectively. EDS and XPS indicated the association of trace of iron, phosphorus, and sulfur with silver nanoparticles. They reported that the biofabrication process of silver nitrate could be linked with metabolic process using nitrate by reducing nitrate to nitrite and ammonium which is fixed as glutamine before cyanobacterial death. However, liberating of organic materials after bacterial death resulted in precipitation of Ag-NPs in solution. A recent study investigated the hydrolytic activity of a new strain of cyanobacteria, *Nostoc* sp. Bahar M, to extracellularly fabricate silver-NPs from silver nitrate.[32] The authors mentioned that the plasmon resonance of *Nostoc*-mediated silver-NPs was at 403 nm, indicating about the smaller size of these NPs. Also, XRD pattern confirmed the face-centered cubic crystalline structure of silver-NPs. TEM and SEM showed that silver-NP produced by *Nostoc* sp. Bahar M was uniformly distributed and spherical in shape, with average nanosize of 14.9 nm. Also, FTIR data exhibited that protein molecules play important role in the biofabrication process of Ag-NPs. Recently, an aqueous extract of *Oscillatoria limnetica* biomass was also used to synthesize Ag-NPs at room temperature for 18 h.[26] The Ag-NPs were spherical in shape and have diverse size ranged between 3.30 and 17.97 nm. Also, the authors studied variable abiotic factors such as pH, time, and concentration of natural reducing materials and silver nitrate to determine the optimal conditions for silver-NP synthesis. They found that the most suitable conditions to produce Ag-NPs from *Oscillatoria limnetica* are at pH of 6.7 and for 18 h as well as the synthesis process is dose-dependent manner for both silver nitrate and cyanobacterial extract concentrations.

Thirty cyanobacterial species were screened for extracellular synthesis of Ag-NPs.[56] The results showed that all 30 cyanobacteria were able to form Ag-NPs from their precursor materials, with variable size ranges. *Cylindrospermum stagnale* performed the best, producing the smallest Ag-NPs with nanosizes of 38–40 nm. Similarly, Sudha et al screened the Ag-NP fabrication ability of several cyanobacteria species isolated from Muthupet mangroves, including *Aphanothece, Oscillatoria, Microcoleus, Aphanocapsa, Phormidium, Lyngbya, Gloeocapsa, Spirulina*, and *Synechococcus*.[68] Of all the tested microorganisms, only *Microcoleus* sp. could reduce silver nitrate and form spherical Ag-NPs, with an average diameter of 55 nm.

Patel et al performed both extracellular and intracellular synthesis of Ag-NPs with light and dark incubation using different cyanobacterial isolates, including *Anabaena* sp., *Aphanizomenon* sp., *Cylindrospermospsis* sp. 121–1, *Cylindrospermopsis* sp. USC CRB3, *Lyngbya* sp., *Limnothrix* sp., *Synechocystis* sp., and *Synechococcus* sp. With the exception of *Aphanizomenon* sp., all tested cyanobacteria reduced silver nitrate into Ag-NPs under direct light exposure using either cell-free culture liquids or cell biomass extracts. In addition, only the cell biomass extracts of *Anabaena* sp., *Limnothrix* sp., and *Synechocystis* sp. were able to synthesis Ag-NPs under dark incubation. Only *Aphanizomenon* sp. failed to tailor the bulk material into its nanoform (Table 2).[55]

Table 2 Cyanobacteria-Mediated Synthesis of Silver Nanoparticles (Ag-NPs)

Strains	Size	Shape	Mode of Synthesis	Illumination	Temperature (°C)	pH	Time	Application/Activity	Reference
Arthrospira platensis NEERI	46	Triangular	–	Light	30	NM	24 h	NM	56
Arthrospira platensis	7–16	Spherical	–	NM	37	5.6	120 h	NM	8
Arthrospira platensis	4–42	NM	+,-	Light	RT	Toward alkalinity	48h	NM	148
Arthrospira indica PCC7940	48	Spherical	-	Light	30	NM	24 h	NM	56
Arthrospira indica SAE-85	67	Spherical	-	Light	30	NM	24 h	NM	56
Arthrospira indica SOSA-4	48	Spherical	-	Light	30	NM	24 h	NM	56
Arthrospira maxima SAE-49-88	61	Triangular	-	Light	30	NM	24 h	NM	56
Anabaena flos-aquae (ALCPB24)	40, 25.2	Spherical	+, -	Light	NM	NM	Few hours	NM	91
Anabaena ambigua (NCCU-1)	48	Spherical	-	Light	30	NM	24 h	NM	56
Anabaena variabilis (NCCU-441)	50	Spherical	-	Light	30	NM	24 h	NM	56
Anabaena sp. *66–2*	24.13	Irregular	+, -	Light, dark	25	7	72 h	Antibacterial agent	55
Anabaena doliolum	10–50	Spherical	-	Dark	25	7	72 h	Antibacterial, antitumor agent	122
Anabaena sp. *PCC 7120*	NM	NM	+	NM	NM	NM	NM	NM	149
Aphanizomenon sp.*127–1*	—	—	+, -	Light, dark	25	7	72 h	—	55
Aphanothece sp.	—	—	+,-	Dark	RT	NM	24	—	68
Aphanocapsa sp.	—	—	+,-	Dark	RT	NM	24	—	68
Aulosira fertilissma sp.	58	Spherical	-	Light	30	NM	24 h	NM	56
Calothrix brevissema sp. *NCCU-65*	42	Cubic	-	Light	30	NM	24 h	NM	56
Calothrix pulvinata	15, 10	Spherical	+, -	Light	NM	NM	Few hours	NM	91

(*Continued*)

Table 2 (Continued).

Strains	Size	Shape	Mode of Synthesis	Illumination	Temperature (°C)	pH	Time	Application/Activity	Reference
Chroococcus NCCU-207	48	Spherical	-	Light	30	NM	24 h	NM	56
Chrococcus cohaerens	—	—	-	NM	NM	NM	72 h	NM	126
Cylindrospermum stagnale NCCU	38–40	Pentagonal	-	Light	30	NM	24 h	NM	56
Cylindrospermospsis sp. *121–1*	NM	NM	+, -	Light	25	7	72 h	Antibacterial agent	55
Cylindrospermopsis sp. *USC CRB3*	NM	NM	+, -	Light	25	7	72 h	Antibacterial agent	55
Dolichospermum sp.	10	Spherical	+	NM	NM	NM	NM	NM	104
Desertifilum sp. IPPAS B-1220	4.5–26	Spherical	-	Light	RT	NM	24 h	Anticancer, antibacterial agent	31,123
Gloeocapsa gelatinosa NCCU-430	88	Spherical	-	Light	30	NM	24 h	NM	56
Gloeocapsa sp.	NM	NM	+,-	Light/dark	25	NM	24, 48, 72h	NM	150
Gloeocapsa sp.	NM	NM	+	Dark	25	NM	28 days	NM	151
Gleocapsa sp.	—	—	+,-	Dark	RT	NM	24 h	—	68
Hapalosiphon fontinalis sp. *NCCU-339*	50	Triangular	-	Light	30	NM	24 h	NM	56
Lyngby asp.15–2	NM	NM	+, -	Light	25	7	72 h	Antibacterial agent	55
Limnothrix sp.*37-2-1*	31.86	Elongated	+, -	Light, dark	25	7	72 h	Antibacterial agent	55
Lyngbya majuscule CUH/Al/ MW-150	20–50	Spherical	+	Dark	RT	4	72 h	Antileukemic, antibacterial agent	121
Lyngby asp.	—	—	+,-	Dark	RT	NM	24 h	—	68
Leptolyngbya valderianum	2–20	Spherical	+	Dark	RT	3.86	72 h	Antibacterial agent	152
Leptolyngbya JSC-1	5–50	Spherical	-	NM	RT	NM	20 min	Anticancer, antibacterial agent	94
Lyngbya NCCU-102	54	Spherical	-	Light	30	NM	24 h	NM	56

Microchaete NCCU-342	40	Spherical	-	Light	30	NM	24 h	NM	56
Microcoleus sp.	40–80	Spherical	+,-	Dark	RT	NM	24 h	Antibacterial agent	68
Microchaete NCCU-342	60–80	Spherical	-	Light	60	5.5	60 min	Dye decolorization ability	128
Nostoc sp.	NM	NM	+	Dark	25	NM	28 days	NM	151
Nostoc sp.	NM	NM	-	NM	30	NM	NM	Antibacterial agent	75
Nostoc Bahar M	8.5–26.44	Spherical	-	Dark	RT	NM	24 h	Anticancer, antibacterial agent	32,124,153
Nostoc Linckia	9.39–25.89	Spherical	-	Light	RT	10	24 h	Antibacterial, anticancer agent	69
Nostoc carneum	7.1–26.68	Spherical	-	Light	RT	10	24 h	Anticancer, antibacterial, antihemolytic agent	83
Nostoc muscorum NCCU-442	42	Spherical	-	Light	30	NM	24 h	NM	56
Nostoc sp. *strain HKAR-2*	51–100	Spherical	-	Dark	25	7	120 h	Anticancer, antifungal, antibacterial agent	97
Nostoc commune	15–45	Spherical	-	NM	121	NM	5 min	Antifungal, antibacterial agent	92
Nostoc sp.	20.3	Spherical	+,-	NM	25	7	24 h	Antibacterial agent	127
Oscillatoria sp. *NCCU-369*	80	Spherical	-	Light	30	NM	24 h	NM	56
Oscillatoria limnetica	3.30–17.97	Quasi-spherical	-	Light	35	6.7	48 h	Antibacterial, anticancer agent	26
Oscillatoria willei NTDM01	100–200	Spherical	+	Dark	25	4.7, 5	28 days	NM	87
Oscillatoria sp.	—	—	+,-	Dark	RT	NM	24	—	68
Oscillatoria sp.	NM	NM	+	Dark	25	NM	28 days	NM	151
Oscillatoria Lemmermanni	100–200	Spherical	-	NM	NM	NM	72 h	Antibacterial agent	126
Oscillatoria ornate	100–200	Spherical	-	NM	NM	NM	72 h	Antibacterial agent	126
Oscillatoria pseudogeminata	100–200	Spherical	-	NM	NM	NM	72 h	Antibacterial agent	126
Phormidium tenue	—	—	-	NM	NM	NM	72 h	NM	126
Phormidium sp.	—	—	+,-	Dark	RT	NM	24 h	—	68

(*Continued*)

Table 2 (Continued).

Strains	Size	Shape	Mode of Synthesis	Illumination	Temperature (°C)	pH	Time	Application/Activity	Reference
Phormidium sp.	NM	NM	+	Dark	25	NM	28 days	NM	151
Phormidium sp.	5–10	Spherical	-	NM	30	NM	NM	Antibacterial agent	75
Plectonema boryanum UTEX 485	10, 1–200	Spherical, Octahedral	+,-	Dark	25–100	5–4.7	28 days	NM	24
Plectonema sp. *NCCU-204*	61	Spherical	-	Light	30	NM	24 h	NM	56
Phormidium sp. *NCCU-104*	48	Cubic	-	Light	30	NM	24 h	NM	56
Scytonema sp. *NCCU-126*	70	Spherical	-	Light	30	NM	24 h	NM	56
Scytonema sp.	NM	NM	-	NM	30	NM	NM	Antibacterial agent	75
Stigonema turfaceum	—	—	-	NM	NM	NM	72 h	NM	126
Synechocystis NCCU-370	80	Spherical	-	Light	30	NM	24 h	NM	56
Synechocystis sp.*48–3*	14.64	Irregular clusters	+, -	Light, dark	25	7	72 h	Antibacterial agent	55
Synechococcus sp.*146–6*	NM	NM	+, -	Light	25	7	72 h	Antibacterial agent	55
Synechococcus sp.	—	—	+,-	Dark	RT	NM	24 h	—	68
Synechococcus sp	15.2–266.7	Spherical	+, -	Light	22	6	72, 24 h	Photocatalytic, antibacterial agent	72
Synechococcus elongatus	> 100–77.3	Cubic	+	Dark	25	NM	28 days	NM	151
Spirulina CFTRI	47	Hexagonal	-	Light	30	NM	24 h	NM	56
Spirulina NCCU-477	49	Cubic	-	Light	30	NM	24 h	NM	56
Spirulina NCCU-479	52	Spherical	-	Light	30	NM	24 h	NM	56
Spirulina-481	64	Spherical	-	Light	30	NM	24 h	NM	56
Spirulina NCCU-482	42	Spherical	-	Light	30	NM	24 h	NM	56
Spirulina NCCU-483	51	Pentagonal	-	Light	30	NM	24 h	NM	56
Spirulina platensis NCCU-S5	46	Spherical	-	Light	30	NM	24 h	NM	56
Spirulina platensis	< 100	Spherical	+	Light	NM	7	2 weeks	Antialgal agent	154

Spirulina platensis	30–50	Spherical	-	NM	60	4.7–5	10 min	Antibacterial agent	[155]
Spirulina platensis	10–200	Spherical	-	NM	27	NM	NM	Anticancer agent	[156]
Spirulina platensis	12	Spherical	+	Light	24	NM	12 h	NM	[157]
Spirulina platensis	5–20	Spherical	-	NM	NM	NM	1–5 days	NM	[158]
Spirulina platensis	12.77	Spherical	+, -	Dark	RT	NM	2 days	NM	[159]
Spirulina platensis	—	—	+,-	Dark	RT	NM	24 h	—	[68]
Spirulina platensis	11.5	Spherical	+,-	NM	25	7	24 h	Antibacterial agent	[127]
Spirulina platensis	11.6	Fcc	+	NM	25	7	24 h	NM	[160]
Tolypothrix tenuis sp.	44	Spherical	-	Light	30	NM	24 h	NM	[56]
Westiellopsis prolifica sp.	52	Spherical	-	Light	30	NM	24 h	NM	[56]
Westiellopsis sp.	< 20 and 5 µm	NM	+	Dark	27	NM	48 h	NM	[161]

Abbreviations: (-), extracellular; (+), intracellular; NM, not mentioned; (—), no NPs formed; RT, room temperature.

Gold Nanoparticles

Au-NPs are known to be good heat conductors and low toxicity NPs against normal cells that are suitable for use in photothermal therapy to treat cancer.[107] As well as physiochemical methods, biological synthesis can be used to synthesize Au-NPs in an ecofriendly manner. The first investigation of the ability of *Anabaena laxa* to catalyze the conversion of hydrogen tetrachloroaurate (III) into Au-NPs was performed by Lenartowicz et al.[108] They reported that *A. laxa* were able to intracellularly fabricate Au-NPs with diverse morphologies and sizes using three different concentrations of auric chloride ($HAuCl_4$; 0.1, 0.5, and 1 mM). The authors reported that the maximum UV spectra peak was formed at 545 and 560 nm for 0.5 and 1 mM of $HAuCl_4$. Three 2θ degree (38.2°, 44.3° and 64.6°) were detected by X-ray diffraction analysis indicating the crystallinity of Au-NPs. Also, TEM micrographs showed that the Au-NPs appearing at 0.5 mM were spherical, however, few NPs with other shapes (triangular, hexagonal, and irregular) were observed. The size of these NPs ranged from 0 to 30 nm; however, the largest particles have size range from 30 to 100 nm. At higher concentration (1 mM of $HAuCl_4$), triangular, hexagonal, and irregular shapes of Au-NPs appeared with nanosize range from 20 to 50 nm. In addition, living cyanobacteria cultures were able to form Au-NPs more efficiently than dead ones, indicating a role of metabolic activity in the bioreduction process of Au-NPs.

Similarly, Dahoumane et al and Brayner et al demonstrated the bioreduction ability of *A. flos-aquae* to intracellularly synthesize Au-NPs.[22,91] Rosken et al showed that *A. cylindrica* and other *Anabaena* sp. reduced gold ions to Au-NPs without releasing toxic anatoxin-a.[89,109] They mentioned that *A. cylindrica* were able to intracellularly produce Au-NPs after 4 h under direct illumination incubation. XRD pattern of Au-NPs showed that these NPs have ellipsoidal shape with an aspect ratio of 1.15. The biosynthesized Au-NPs were spherical, and their average size was 10 nm. Moreover, TEM micrographs showed that the Au-NPs mainly distributed in vegetative cells (50%) in comparing with heterocysts and found to be located along the thylakoid membranes. The scholars suggested that heterocysts are not as important for NPs fabrication, due to their results showed that more than 10 vegetative cells contained Au-NPs while only one heterocysts contained NPs. The bioreduction activities of three species of cyanobacteria, *Phormidium valderianum, P. tenue*, and *Microcoleus chthonoplastes*, were screened against $HAuCl_4$ solution at different pH values by Parial et al.[14] They reported that all three tested cyanobacterial strains were able to synthesis Au-NPs; however, only *P. valderianum* was able to produce Au-NPs of different shapes and sizes, including nanospheres (15 nm) and triangular (24 nm) and hexagonal (25 nm) NPs, in response to variations in pH. *Gloeocapasa* sp. were exploited for intracellular synthesis of Au-NPs using cleaned whole cells;[110] 90 mL of 10^{-3} $HAuCl_4$ solution was mixed with 10 mL of *Gloeocapasa* culture and incubated with stirring at ambient temperature. After a few hours, Au-NPs had formed, and their UV absorbance was 547 nm. Moreover, FTIR results showed that algal proteins were responsible for the bioreduction process that formed these NPs, as strong peaks were observed at 3424.96 cm^{-1}, corresponding to N-H stretching, and at 1640.16 cm^{-1}, corresponding to amide I. In addition, SEM and TEM micrographs showed that the Au-NPs had spherical shape and diameters of less than 100 nm (Table 3).

Other Nanomaterials

The ability of cyanobacteria to reduce metallic NPs is not limited to Ag-NPs and Au-NPs, but extends to other metals including platinum, palladium, and cadmium, as well as metal oxides including copper oxide and zinc oxide. Lengke et al screened the ability of *P. boryanum UTEX 485* to form platinum and palladium NPs under variable temperatures.[96,111] The scholars mentioned that Pd NPs formed after incubation with *P. boryanum* for 28 days at 25–100 °C. TEM micrographs of Pd NPs showed that these particles have spherical and elongated shapes, but at 100 °C only spherical palladium hydride appeared. XRD analysis of Pd NPs synthesized at 100°C and 60°C showed different peaks at a Bragg angle (2θ) of 46.9, 54.5, and 81.2 indicates the nanocrystalline of Pd NPs, however, at 25 °C there no diffraction peaks detected. Similarly, different physicochemical analysis of Pt NPs synthesized by *P. boryanum UTEX 485* at 25–100 °C for 28 days and at 180 °C for 1 day were performed by Lengke et al XPS results showed the association of sulfur, phosphorus and nitrogen with platinum(II), and EDX analysis indicated the present of sulfur with platinum. So, the authors speculated that these organic elements play significant role in the reduction process of platinum ions into Pt NPs. Brayner et al intracellularly synthesized Au-NPs, Ag-NPs, Pt NPs, and Pd NPs utilizing the biomass of *C. pulvinata, A. flos-*

Table 3 Cyanobacteria-Mediated Synthesis of Gold Nanoparticles (Au-NPs)

Strains	Size	Shape	Mode of Synthesis	Illumination	Temperature (°C)	pH	Time	Application of NPs	Reference
Anabaena sp. *SAG 12.82*	9	Spherical	+	Light	22	7.3	2 h	NM	[109]
Anabaena cylindrica SAG 1403.2	10	Spherical	+	Light	22	7.3	4 h	NM	[89]
Anabaena laxa	3–5	Spherical, triangular, hexagonal, irregular	+	Light	23	NM	24 h	NM	[109]
Anabaena sp. *PCC 7120*	10–30	Spherical	+, -	Light	RT	NM	1–4 weeks	NM	[162]
Anabaena sphaerica	Spherical, triangular, hexagonal	1–35, 1–50	+,-	NM	RT	4	7–10 days, 24 h	NM	[163]
Anabaena flos-aquae, ALCP B24	12, 25	Spherical	+, -	Light	NM	NM	Few hours	NM	[91]
Coleofasciculus chthonoplastes BDU 61,001	10–30	Spherical	+	Light	20	5	Up to 3 h	Anticancer, antibacterial agent	[164]
Calothrix pulvinate	5.4, 5.7	Spherical	+, -	Light	NM	NM	Few hours	NM	[91]
Cyanothece sp.	80–129	Non spherical, spherical	+	NM	RT	NM	60 min, 24 h	Anti-myocardial infarction properties	[130]
Dolichospermum sp.	23	Spherical	+	NM	NM	NM	NM	Spherical	[104]
Gloeocapsa sp.	NM	NM	+	Dark	25	NM	28 days	NM	[151]
Gleocapsa sp.	<100	Spherical	+	NM	RT	NM	Few hours	Antitumor agent	[110]
Lyngbya majuscula	2–25	Spherical and hexagonal	+	Light	20	5	72 h	NM	[165]
Lyngbya majuscula	< 20	Spherical	+	NM	NM	6	72 h	NM	[166]
Lyngbya majuscule	41.7	Spherical	+	Light	23	NM	24 h	Anti-myocardial infarction properties	[129]

(*Continued*)

Table 3 (Continued).

Strains	Size	Shape	Mode of Synthesis	Illumination	Temperature (°C)	pH	Time	Application of NPs	Reference
Leptolyngbya	6	Spherical	-	Light	NM	NM	NM	NM	91
Leptolyngbya tenuis (BDU 20,391)	NM	NM	+	Light	20	5	1–5 days	Anticancer, antibacterial agent	164
Microcoleus Chthonoplastes sp	NM	NM	+	NM	20	5, 7	72 h	NM	14
Nostoc sp. *PCC 7422*	10–30	Spherical	+, -	Light	RT	NM	1–4 weeks	NM	162
Nostoc sp. *PCC 9229*	10–30	Spherical	+, -	Light	RT	NM	1–4 weeks	NM	162
Nostoc sp. *PCC 6310*	10–30	Spherical	+, -	Light	RT	NM	1–4 weeks	NM	162
Nostoc sp. *PCC 9305*	10–30	Spherical	+, -	Light	RT	NM	1–4 weeks	NM	162
Nostoc sp.	NM	NM	+	Dark	25	NM	28 days	NM	151
Nostoc ellipsosporum	8–42, 60 × 18.5	Spherical, Rod, oval to irregular shape,	+	Light	20	5	Up to 3 h	Anticancer, antibacterial agent	164
Nostoc ellipsosporum	137 to 209 length and 33 to 69 diameter	Rod	+	Light	20	4.5	48 h	NM	167
Oscillatoria sp.	NM	NM	+	Dark	25	NM	28 days	NM	151
Phormidium valderianum	15, 411 × 3225, 17, 24, 25	Spherical, Rods, Spherical, triangular, hexagonal	+	NM	20	5, 7, 9	72 h	NM	14
Phormidium tenue	14.84	Spherical	+	NM	20	5	72 h	NM	14
Plectonema boryanum UTEX 485	<10–25, 1–10 µm	Cubic, Octahedral platelets	+, -	Dark	25–100, 200	1.9–2.2	30 days, 1 day	NM	25

Plectonema boryanum UTEX 485	10–6 µm	Octahedral platelets	+,-	NM	25	1.9–2.2	24 h	NM	[63]
Phormidium willei sp.	25	Spherical, hexagonal and triangular	+	Dark	NM	NM	1 hr	Antioxidant agent	[2]
Phormidium sp.	NM	NM	+	Dark	25	NM	28 days	NM	[151]
Spirulina subsalsa	5–30	Spherical, few nanorods	+	Light	20	5	72 h	NM	[165]
Spirulina subsalsa	NM	NM	+	NM	NM	6	72 h	NM	[166]
Synechocystis sp. *PCC 6803*	13	Spherical	+	Light, dark	20, 20, 4	NM	16 h	NM	[61]
Synechococcus elongatus	70–85	Cubic	+	Dark	25	NM	28 days	NM	[151]
Synechocystis sp. *PCC 6803*	—	—	+, -	Light	RT	NM	1–4 weeks	—	[162]
Synechococcus sp. *PCC 7942*	—	—	+, -	Light	RT	NM	1–4 weeks	—	[162]
Spirulina platensis	6–10	Spherical	-	NM	37	5.6	120 h	NM	[8]
Spirulina platensis	2–8	Spherical	-	NM	RT	NM	48 h	Antibacterial agent	[125]
Spirulina platensis	15–60	Spherical	+	Light	RT	NM	5 days	Pharmaceutical, medical purposes	[58]

Abbreviations: (-), extracellular; (+), intracellular; NM, not mentioned; (—), no NPs formed; RT, room temperature.

aquae, and *L. foveolarum*.[91] They suggested that polysaccharides were responsible for NP stabilization.

CdS NPs are well-known and widely studied semiconductors. They have been synthesized using various microorganisms, including yeasts, algae, and fungi.[112–114] C-phycoerythrin (CPE) pigment extracted from *P. tenue* was also used to synthesis 5 nm CdS NPs from their precursors, using an aqueous mixture of $CdCl_2$ and Na_2S (Table 4).[27] The CdS NPs were formed after incubation with C-phycoerythrin pigment for 24 h at 37 °C. The formation of CdS NPs was confirmed by the absorption peak at 470 nm. FTIR analysis demonstrated new bands at 1543, 1364, 1223 cm^{-1} appeared only in CPE-coated CdS NPs indicates a new vibration due to C\S band. Other bands seen at 1364 and 1034 cm^{-1} was related to the C-N stretching vibrations of the aromatic amino amines. Furthermore, EDAX analysis confirmed the existence of both Cd and S in biosynthesized CdS NPs.

Metal Oxides and Akaganéite NPs

Nostoc sp.[99] and *Anabaena* sp.[95] have been used to generate ZnO NPs, whereas copper oxide (CuO) NPs were produced by *Phormidium cyanobacterium* and *S. plantensis* respectively (Table 4).[88,100] Brayner et al synthesized beta-iron oxyhydroxide (β-FeOOH) NPs using *A. flos-aquae, C. pulvinata*, and *Klebsormidium* sp.[115] They found that there were two basic mechanisms by which iron was acquired higher plants, denoted strategy I and strategy II. Strategy I involves soil acidification and formation of lateral roots and specific transfer cells in the rhizodermis, as well as induction of an Fe^{3+}-chelate reductase and of Fe^{2+} transporters. This strategy was used in all plants except grasses. Grasses followed strategy II, in which iron is taken up as a Fe^{3+}-siderophore complex. Based on these observations, the authors proposed that the mechanism of iron oxide fabrication by cyanobacteria followed strategy II (siderophore-based iron acquisition). Owing to limited availability of iron, the cells released organic Fe^{3+} metal-chelating molecules (siderophores) that could solubilize and scavenge iron ions from the environment and internalize them into the cells. Similarly, Dahmoune et al biologically generated akaganeite NPs using *A. flos-aquae*.[116] They showed that XRD analysis of freeze-dried cyanobacteria after reaction with iron salts exhibited the existence of tetragonal akaganeite NPs with some amorphous phase related to the cyanobacteria biomass. TEM ultrathin sections of treated cyanobacteria with iron precursors showed distribution of dark β-FeOOH akaganeite nanorods inside the bacterial cells. However, HR-TEM provided more information about the distribution pattern of akaganeite NPs inside the cells, in which the nanorods appeared as a complex arrangement of pores forming a spongelike structure.

Bimetallic NPs

Bimetallic NPs include a combination of two different metals, the ratio of which can be varied to provide novel physicochemical features derived from the constituting metals (Table 4). [8,12] These NPs are attractive for various applications due to the extra degree of freedom they afford. Govindaraju et al used extracellular synthesis to produce silver-gold core shell NPs, in addition to Ag-NPs and Au-NPs, using single-cell protein *S. plantensis*.[8] The spectral wavelength of silver-gold bimetallic NPs was 509 nm and their size was 17–25 nm. Roychoudhury et al exposed *Lyngbya majuscula* to an equimolar solution of gold and silver (1 mM, pH 4) for 72 h to produce an Au-Ag nanoalloy.[117] They reported that *Lyngbya* sp. acted as environmentally friendly factories for Au-Ag nanoalloy fabrication. The UV absorbance of the nanoalloy was 481 nm, with a nanosize ranging from 5 to 25 nm.

Applications of NPs Synthesized by Cyanobacteria

Many studies demonstrated the bioactivity of NPs synthesized by different strains of cyanobacteria. These bioactivities are including anticancer, antimicrobial, antioxidant activities (Figure 7).

Antitumor Activity

Cancer is among the leading causes of death in humans.[118] The incidence of cancer is increasing because of various factors, including aging, an increasing population, and lifestyles that predispose to individuals to the disease.[118,119] Advances in nanoscience have led to new methods to prevent tumor progression and metastasis.[31,32] For example, magnetic iron oxide NPs have improved cellular imaging,[13] increasing the quality and speed of diagnostic process. Intravenous injection of Au-NPs can enhance radiotherapy (X-rays), with increased survival of test mice (86%) compared with those treated with X-rays alone (20%).[120] There have been many reports of the biological synthesis of NPs using cyanobacteria and their activities against different cancer cell lines (Table 2–4). Green Ag-NPs synthesized by novel *Desertifilum* sp. induced a drastic loss of viability in HepG2 liver, MCF-7

Table 4 Cyanobacteria-Mediated Synthesis of Other Nanomaterials (NMs)

Strains	NPs	Size (nm)	Shape	Mode of Synthesis	Illumination	Temperature (° C)	pH	Time	Application of NPs	Reference
Anabaena strain L31	ZnO	70–100	Spherical	–	Dark	25	7	72 h	Ecofriendly sunscreen agent	[95]
Anabaena flos-aquae	β -FeOOH	100 (length)	Nanorods	+	Light	20	7	28 days	NM	[115]
Anabaena flos-aquae, ALCP B24	β-FeOOH	NM	Nanorods	+	Light	20	7	28 days	"one-pot" hybrid biofilms	[116]
Anabaena flos-aquae, ALCP B24	Pt	NM	NM	+	Light	NM	NM	15 days	NM	[91]
Anabaena flos-aquae, ALCP B24	Pd	NM	NM	+	Light	NA	NA	30 min	NM	[91]
Nostoc sp. *EA03*	ZnO	50–80	Star	-	Light	RT	9	2 h	Antibacterial, antibiofilm and anticancer agent	[99]
Calothrix pulvinate	β-FeOOH	100 (length)	Nanorods	+	Light	20	7	28 days	NM	[115]
Calothrix pulvinate	Pd	3.5	Spherical	+, -	Light	NA	NA	30 min	NM	[91]
Calothrix pulvinate	Pt	3.2	Spherical	+, -	Light	NA	NA	15 day	NM	[91]
Lyngbya majuscula	Au-Ag nanoalloy	5–25	Spherical	+	Light	NM	4	72 h	NA	[117]
Phormidium tenue NTDM05	CdS	5.1	Spherical	-	Light	NM	NM	5 days	biolabel	[27]
Phormidium cyanobacterium	CuO	10–40	Quasi-spherical	-	Light	28	NM	42 h	NM	[88]
Plectonema boryanum UTEX 485	Pt	30 nm-0.3 μm	Spherical	+, -	Dark	25–100 and 180	4,7,10	28, 1 days	NM	[96]
Plectonema boryanum UTEX 485	Pd	> 30	Spherical and elongated	-	Dark	25–100 and 180	4,7,10	28, 1 days	NM	[111]
Spirulina platensis	CuO	30–40	Spherical	-	Light	100–120	NM	24 h	Antibacterial agent	[100]
Spirulina platensis	Au-Ag bimetallic	17–25	Spherical	-	Light	37	5.6	120 h	NM	[8]

Abbreviations: (-), extracellular; (+), intracellular; NM, not mentioned; (—), no NPs formed; RT, room temperature.

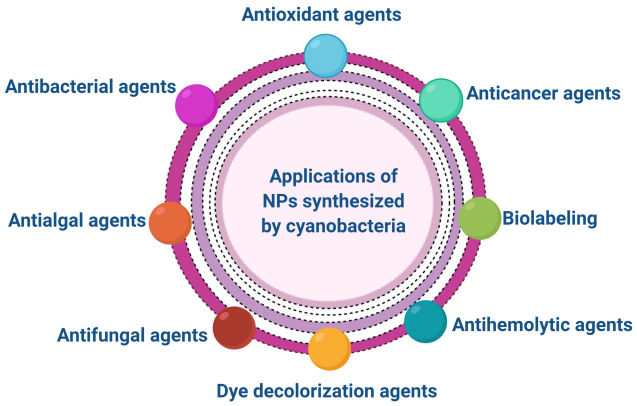


Figure 7 Different applications of NPs synthesized by cyanobacteria.

breast, and Caco-2 colon cancer cell lines, with half-maximal inhibitory concentration (IC_{50}) values of 32, 58, and 90 µg/mL, respectively,[31] suggested that they may have applications as potent anticancer agents. Bin-Meferij et al reported that *Nostoc*-mediated silver-NPs (N-SNPs) reduced Caco-2 cell viability by 50%, with an IC_{50} of 150 µg/mL.[32] The authors mentioned that N-SNPs resulted in morphological changes including cell shrinkage, clustering, cell detachment. They speculated that the cytotoxic effect of N-SNPs toward Caco-2 cells resulted from interaction of N-SNPs with different organelles such as mitochondria and endoplasmic reticulum as well as biomolecules such as DNA and proteins. Similarly, a recent study assessed the anticancer activity and biocompatibility of silver-NPs formed by *Nostoc* sp. against normal and tumor cells.[83] Ag-NPs suppressed the proliferation of MCF-7 cancer cells seven-fold compared with normal human lung fibroblast (WI38) and human amnion (WISH) cells. By contrast, the same concentration (13.07 ± 1.1 µg/mL) of a standard antitumor drug, 5-fluorouracil, had a greater cytotoxic effect against WI38 and WISH cells than against malignant cells. Thus, green Ag-NPs appear to be safer to normal cells than 5-fluorouracil. Moreover, the scholars exhibited that after injection of mice bearing Ehrlich ascites carcinoma with 5 mg of Ag-NPs lead to significant reduction in the tumor volume, tumor cells, WBCs count and body weight. Roychoudhury et al found that biosynthesized, ecofriendly, highly stable Ag-NPs showed appreciable antiproliferative effects against leukemic cells, especially the lymphoblastic leukemia (REH) cell line.[121] The Ag-NPs (100–1000 µg/mL) showed no effect on peripheral blood mononuclear cells. However, at the same concentrations of Ag-NPs, REH cell line was the most sensitive toward Ag-NPs than other leukemia cell lines including myeloblastic leukemia and lymphoblastic leukemia with IC_{50} of 620 ± 3.73, 1000 ± 2.79 and 1000 ± 4.38 µg/mL, respectively. Also, the scholars studied the nuclear morphological changes of REH treated with Ag-NPs using DAPI staining assay and observed that Ag-NPs resulted in nuclear damage, shrinkage, chromatin condensation and chromatin margin. A recent publication reported that *Anabaena* sp. could produce Ag-NPs with strong antitumor activities against Dalton's lymphoma and colo205 cancer cells.[122] They found that low concentration of SNP was able to reduce the proliferation of both cell types via inducting the production of reactive oxygen species (ROS) and DNA damage led to cell death. The antitumor properties of Ag-NPs biosynthesized by *Nostoc* sp. HKAR-2 were screened against the MCF-7 cell line.[97] The Ag-NPs killed tumor cells effectively as their concentrations increased, suggesting potential applications in the treatment of cancerous cells. Ebadi et al found that a 50 µg/mL concentration of ZnO NPs eliminated 50% of cancerous A549 lung cancer cell line, while the same concentration killed less than 50% of normal (MRC-5) cells.[99]

Antioxidative Activity

Singh et al tested the toxicity of biogenic ZnO NPs fabricated by cell extracts from *Anabaena* strain L31 and biogenic ZnO NP–shinorine conjugates in vivo.[95] They monitored the formation of ROS using DCFH-DA as a probe. Under a fluorescence microscope, they observed that ROS reached maximum activity 12 h after incubation with ZnO NPs, in contrast to control cells incubated with DCFH-DA alone. By contrast, ROS production decreased in cells spiked with the ZnO NP–shinorine conjugate. The authors suggested that biogenic ZnO NP–shinorine conjugates have antioxidative properties and could be used as non-toxic sunscreen agents. MubarakAli et al showed that Au-NPs synthesized by *Phormidium* sp. exhibited stronger antioxidant properties than citric acid.[2] They also found that increasing the concentration of Au-NPs increase their scavenging activity (Table 3).

Antimicrobial Activity

Antibacterial Activity

NPs are attractive for medical applications due to their high surface area to volume ratio.[12] Smaller NPs have a large surface area that increases the interaction between NPs and target bacterial cells.[123] Keskin et al reported that Ag-NPs synthesized by *Synechococcus* sp. have

antibacterial properties against various bacterial strains, including *Bacillus subtilis, Staphylococcus aureus*, and *Escherichia coli*, of which *B. subtilis* was the most sensitive to biogenic Ag-NPs.[72]

Hamida et al found that 1.54 mg/mL of silver-NPs synthesized from *Desertifilum* sp. (D-SNPs) had significant antibacterial activity against five strains of Gram-negative and Gram-positive bacteria: *Pseudomonas aeruginosa, Bacillus cereus, B. subtilis, Shigella flexneri*, and *Salmonella enterica* (clinical isolates).[31] *S. flexneri* showed the greatest response to D-SNPs, with an inhibition zone (IZ) diameter of 22.7 ± 0.3. In another recent study, *E. coli, Salmonella typhimurium*, drug-resistant *Klebsiella pneumoniae, Streptococcus mutans*, and methicillin-resistant *S. aureus* (MRSA) (clinical isolates) were treated with 1.5 mg/mL of an aqueous solution of silver-NPs synthesized by *Desertifilum* sp.[123] The D-SNPs were more effectual antibacterial agents than silver nitrate against all tested bacteria; MRSA showed the greatest response to D-SNPs, with an IZ of 23.7 ± 0.08. Treating MRSA with D-SNPs also resulted in ultrastructural changes, including bacterial membrane disruption, cytoplasmic lashing, and atrophy of cells leading to bacterial cell death. Also, the authors suggested that the potential mechanism of D-SNPs against MRSA via direct interaction between NPs and biomolecules such as proteins, enzymes, antioxidants and nucleic acids or/and indirect interaction through enhancing the generation of ROS leading to bacterial death. Ag-NPs (5mM) synthesized by phycocyanin extracted from *N. linckia* showed significant inhibitory activity against various pathogenic bacterial strains, including *S. aureus, P. aeruginosa, E. coli*, and *K. pneumoniae*.[69] The highest IZ diameter (10 mm) was observed in both *P. aeruginosa* and *E. coli*, while the IZ diameter of *S. aureus* and *K. pneumoniae* was (9 mm). The authors reported that Ag-NPs produced by *N. linckia* has ability to suppress the Gram-positive and Gram-negative bacteria.

In a recent study, the inhibitory activity of silver-NPs synthesized utilizing *Nostoc* sp. (N-SNPs) was assessed against drug-resistant *K. pneumoniae*.[124] The results demonstrated for the first time the relationship between biogenic silver-NPs and genes related to a bacterial secretion system. N-SNPs resulted in downregulation of the *hns, hcp-1, VgrG-1*, and *VgrG-3* genes responsible for inducing the secretion system. Interactions of Au-NPs with Gram-positive organisms (*B. subtilis* and *S. aureus*) were investigated using TEM. The TEM micrographs of *B. subtilis* showed that the Au-NPs damaged the bacterial cell wall, resulting in pits at the exterior of the cell and deformation of the cell membrane, thereby disrupting bacterial functions such as respiration and permeability.[125]

The antibacterial activity of Ag-NPs produced by *Oscillatoria* sp. was observed against pathogens *E. coli, Klebsiella* sp., *Salmonella sp*., and *Pseudomonas* sp. using the disc diffusion method. The maximum antibacterial effects were observed against *Pseudomonas* sp. (15 mm), and a minor antibacterial effect was recorded against *E. coli* (10 mm), indicating resistance to Ag-NPs.[126] Ag-NPs synthesized from *Anabaena* sp. showed strong antibacterial activity,[122] which was tested against three multi-drug-resistant bacteria, *K. pneumoniae, E. coli*, and *S. aureus*, isolated from foot ulcers of diabetic patients. Sonker et al investigated the inhibitory activities of silver-NPs synthesized using a cyanobacterial extract of *Nostoc* sp. against two plant-pathogenic bacteria, *Ralstonia solanacearum* and *Xanthomonas campestris*.[97] The result showed that Ag-NPs (5, 10, 15 µg/mL) lead to suppress the growth of two bacterial strains with IZ ranges of 15 ± 4.5, 25 ± 4, 25 ± 5 and 18 ± 1.5, 23 ± 4, 23 ± 10, respectively.

Patel et al found that Ag-NPs synthesized from different species of cyanobacteria had bactericidal activity against *Bacillus megaterium, E. coli, B. subtilis, S. aureus, P. aeruginosa*, and *Micrococcus luteus*.[55] They also reported that all tested bacteria showed resistance to Ag-NPs fabricated by *Limnothrix* sp., while SNP synthesized by *Anabaena* sp. was the most significant one, with an IZ of 22 mm. Ahmed et al reported that Ag-NPs synthesized from *Spirulina* sp. and *Nostoc* sp. suppressed bacterial growth of the tested bacteria (including *S. aureus, Staphylococcus epidermidis, K. pneumoniae, E. coli* and *P. aeruginosa*) more strongly than silver nitrate,[127] and that *P. aeruginosa* resisted Ag-NPs synthesized by two isolates.

Roychoudhury et al reported that the synthesized non-toxic, highly stable Ag-NPs synthesized by *Lyngbya majuscula* exhibited significant biocidal activity against *P. aeruginosa*.[121] The authors subjected the *P. aeruginosa* with 50 µL of different concentration of Ag-NPs including 1, 0.5, and 0.1 mg/mL for 24 h at 37 °C. The maximum IZ (8 mm) was resulted from treating *P. aeruginosa* with 0.5 mg/mL of Ag-NPs. Another study found that Ag-NPs synthesized by *Nostoc* sp., *Scytonema* sp. and *Phormidium* sp. were potent antibacterial agents against various pathogens including *S. aureus*, MRSA, *P. aeruginosa, E. coli*.[75] Seventy microliters of the Ag-NPs synthesized by *Nostoc*

sp., *Scytonema* sp. and *Phormidium* sp. inhibited the bacterial growth of all previous tested microbes with IZ diameter of (10, 2, 9, 9 mm), (7, 12, 9, 9.5 mm) and (9, 11.5, 8, 10 mm) respectively. *Nostoc*-mediated ZnO NPs showed antibiofilm activity against *P. aeruginosa*, and *S. aureus*. Atomic force microscopic analysis showed that ZnO NPs destroyed the biofilms of the tested bacteria such that they protruded outward or were sunken inwards (Tables 2–4).[99]

Antialgal Activity

El-Sheekh et al studied the inhibitory activity of Ag-NPs synthesized by *S. platensis, Chlorella vulgaris*, and *Scenedesmus obliquus* against *Microcystis aeruginosa*.[129] *M. aeruginosa* are well known to be harmful microalgal, which secrete toxins that induce liver cancer. The results of this work encouraged the use of Ag-NPs as antialgal agents to reduce the harmful effect of *M. aeruginosa*. As the concentration of Ag-NPs increased, the viability of *Microcystis* cells decreased; at 10 mg/L, Ag-NPs caused a 92% reduction of viable cells, compared with a 30% reduction at 1 mg/L (Table 2).

Antifungal Activity

A recent study showed that Ag-NPs produced by *Nostoc* sp. HKAR-2 resulted in inhibition of *Aspergillus niger* and *Trichoderma harzianum* fungal activity with IZ ranges of 3–5 and 4–5, respectively.[97] Morsy et al studied the antifungal activity of Ag-NPs synthesized by EPSs of *N. commune* against different fungal strains infecting seeds of sorghum, maize, soybean, and sesame.[92] They sterilized the grain surface with Ag-NPs then grew the seeds in Dichloran chloramphenicol peptone agar at 25 °C by the direct plate method. Complete inhibition of *Fusarium nygamai* was observed on sorghum grains and soybean seeds with Ag-NP sterilization, compared with 17.24% and 14.63% of total *Fusarium* and 7.5% and 8.7% of total fungi with NaOCl sterilization, respectively (Table 2).

Photocatalytic Activity

Keskin et al reported that Ag-NPs produced from *Synechococcus* sp. had photocatalytic activity.[72] These Ag-NPs caused photodegradation of methylene blue; after 4 h, the decolorization of the organic pigment reached 18 ± 0.3% for 20 mg L^{-1} of aqueous dye solution. Similarly, Ag-NPs fabricated by *Microchaete* sp. NCCU-342 degraded methyl red dye (84.60%) within 2 h more effectively than cyanobacterial extract (49.80%) (Table 2).[128]

Other Applications

Bakir et al and Younis et al reported that Au-NPs synthesized by *L. majuscule* have anti-myocardial infarction properties.[129,130] They showed that Au-NPs alone or with cyanobacterial extract inhibit the isoproterenol-induced changes in serum cardiac injury markers, ECG, arterial pressure indices, and antioxidant capabilities of the heart. Also, Ag-NPs synthesized by phycobiliproteins extracted from *Nostoc* sp. showed antihemolytic activity.[83] The authors used 2, 2′-azobis (2-amidinopropane) dihydrochloride (AAPH) to induce complete erythrocyte hemolysis (100%) of blood extracted from a rat. They mixed the mixture with Ag-NPs and observed that Ag-NPs inhibit hemolytic activity with inhibition of 96.4% (erythrocyte hemolysis was decreased to be 3.6%) which was similar to those caused by vitamin C (96%). Also, the scholars mentioned that the possible mechanism of antihemolytic activity of Ag-NPs is due to *Nostoc* material (such as amino compounds ($-NH_2$), phenols (Ar-OH)) capped Ag-NPs which have the antihemolytic and antioxidants activity.

MubarakAli et al showed that C-phycoerythrin-CdS NPs could be used as fluorescence probes in biolabeling for ultrasensitive detection of DNA.[27] Similarly, Au-NP synthesized by *Phormidium willei* and *Coelastrella* sp. was proven to be used as a biolabeling by MubarakAli (Tables 3 and 4).[2] The scholars showed that at higher concentration, the green Au-NPs synthesized by *Coelastrella* sp only were actively binding to DNA.

Killing Strategies of NPs Against Living Cells

The exact killing mechanism of NPs against living cells such as microbial and cancer cells is still under investigation. However, several studies attributed the toxic effect of NPs against cells to two general strategies: (i) indirect influence in which NPs enhancing the production of ROS results in intensive oxidative stress leading to DNA damage, protein degradation, imbalance in enzyme activities resulting in metabolic toxicity and cellular dysfunctions that finally cause cell death;[131,132] (ii) direct influence in which NPs directly interact with cellular structures (such as cellular borders and organelles) as well as cellular components (such as proteins, enzymes, antioxidants, nucleic acids, etc.) led to activate cell death pathways (Figure 8).[123,133]

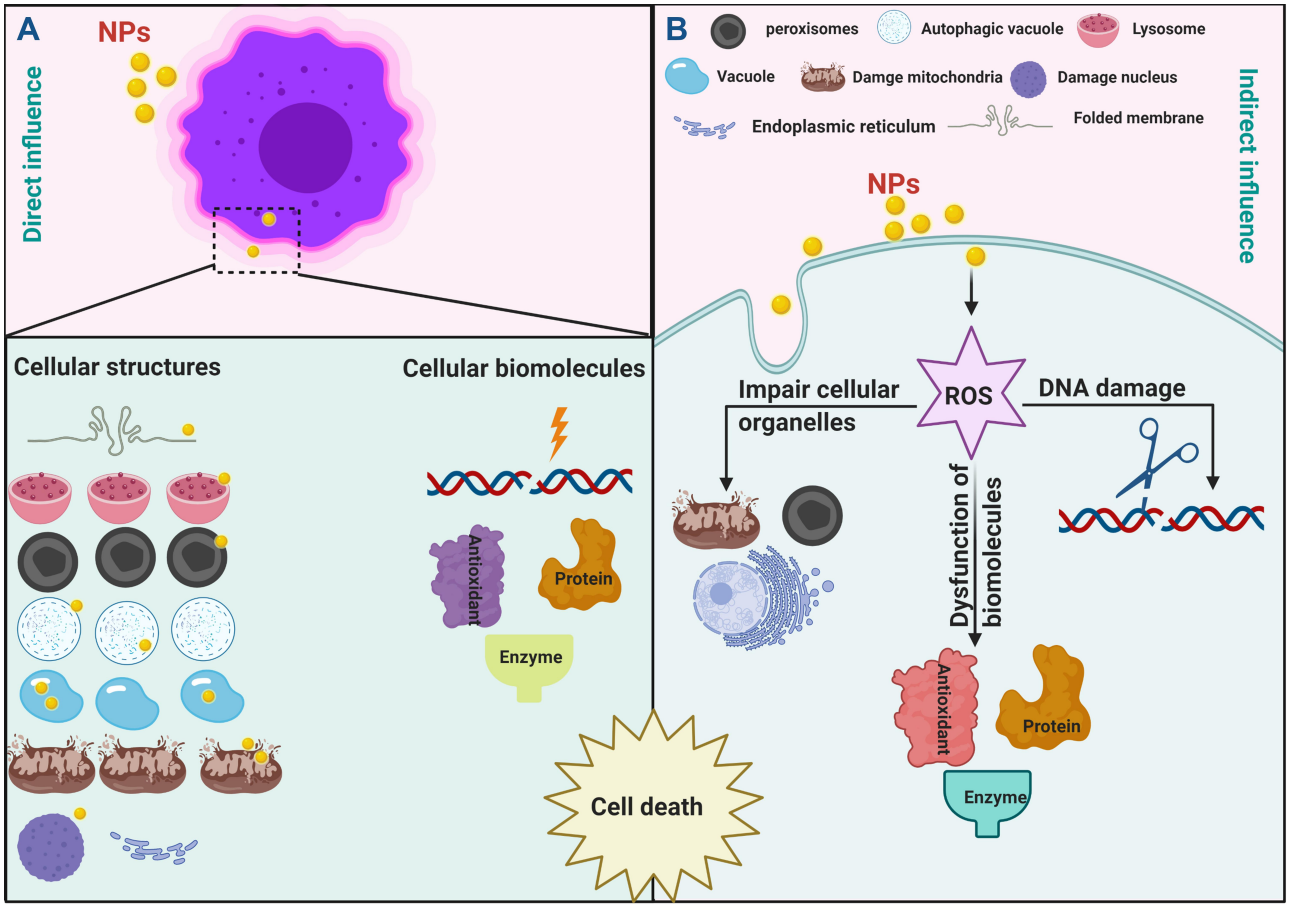


Figure 8 The killing strategies of NPs against living cells. (**A**) illustrating the direct influence of NPs, in which NPs interact directly with cellular structures and biomolecules led to cell death. (**B**) illustrating the indirect influence of NPs, in which NPs inducing the generation of reactive oxygen species (ROS) led to cell death.

Oxidative stress is the dominant key of NP-induced cellular injury. Different factors control the oxidative stress-mediated by NPs including acellular factors (such as particle size, concentration and the chemistry of their surface) and cellular responses (such as mitochondrial respiration, NP-cellular interaction and immune cell stimulation) are responsible for ROS-mediated damage. The induction of oxidative stress by NPs is torch bearers for further pathophysiological influences such as genotoxicity, inflammation, proteins denaturation, enzyme and antioxidants dysfunction demonstrated by stimulation of associated cell signaling pathways causing cell death.[132]

Many scholars reported that NPs stimulate the production of ROS such as superoxide anion ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2), hydroxyl radicals ($OH^{\cdot}$), etc.[132,134] This abundance of reactive oxygen species have the potentiality to impair the cellular functions causing oxidative stress. It results from the imbalance between ROS production and the capacity of cells to detoxify or repair the damage caused by free radical intermediates.[135] For illustration, the decrease in GSH level after exposure the cells to NPs lead to accumulation of ROS causing oxidative stress.[124] Similarly, the imbalance in antioxidant enzymes such as GPx,[123] superoxide dismutase, catalase, etc., results in oxidative stress causing cellular dysfunction and led to cell death.[136] On the other side, other studies suggested that the direct interaction between NPs and cellular targets (such as mitochondrial respiration, metabolism, inflammation, etc.) results in direct induction of oxidative stress.[124,132,137]

In prokaryotic and eukaryotic cells, cellular membranes are the protective barriers against the external stress and controlling the transport of nutrients in/out the cells.[37] When NPs injected to the cells, it was observed that these particles attracted to cellular membranes may be due to charge of NPs and their surface chemistry.[123,138] This direct interact between NPs and cellular membranes results in irregular, folded, pored membranes and sometimes causes completely lysed membranes affecting the membrane integrity and permeability, causing cell death.[138,139] TEM micrographs taken by Hamida et al showed that N-SNPs attached to plasma membranes of *MRSA, K. pneumoniae*.[123,124]

After NPs well ingested into cells, result in cytoplasmic dissolution and nuclear damage including nucleoagglomeration, chromatin condensation and DNA damage.[133] On the other hand, NPs impaired with biomolecules including enzymes (such as adenosine triphosphatase (ATPase) causing metabolic toxicity),[123] antioxidants and antioxidant enzymes (such as GSH, GPx result in induction of oxidative stress),[124] proteins (such as membrane proteins causing protein denaturation led to influence biological activities),[123] nucleic acids (such as DNA causing DNA damage),[140,141] enhancing cellular death pathways.

A recent study demonstrated the direct interaction between NPs and cellular organelles such as LDs, endosomes, mitochondria, etc.[142] Barkhade et al showed that cells treated with titanium dioxide NPs exhibited swallowing mitochondria and influence the mitochondrial membrane permeability.[143] Also, it was found that Au-NPs increase number of mitochondria and decrease the number of lipid droplets indicating that cells produce more energy in trial to remove the stress caused by NPs.[142] Furthermore, the high incidence of, autophagic vacuoles, endosomes, cytoplasmic vacuoles were observed after treatment cancer cells with Ag-NPs.[142,144] Another study showed that Ag-NPs and copper NPs resulted in increasing lipid droplets that may be return to nanotoxicity that impaired the lipid catabolic activity. The authors reported also that high incidence of peroxisomes as well as lysosomes and low distribution of endoplasmic reticulum indicating necrosis.[144]

Future Remarks

Green nanotechnology is considered a promising domain of modern science. This technology facilitates the synthesis of NPs by ecofriendly and inexpensive processes, resulting in high yields. Various natural resources are used to biosynthesize NPs, including plants, fungi, bacteria, cyanobacteria, and algae. However, some aspects still require more detailed investigation; for instance, many cyanobacterial strains remain unexplored. Further studies are needed to discover the biocatalytic activities of these cyanobacteria and their abilities to biotransform precursor metals into nanoforms.

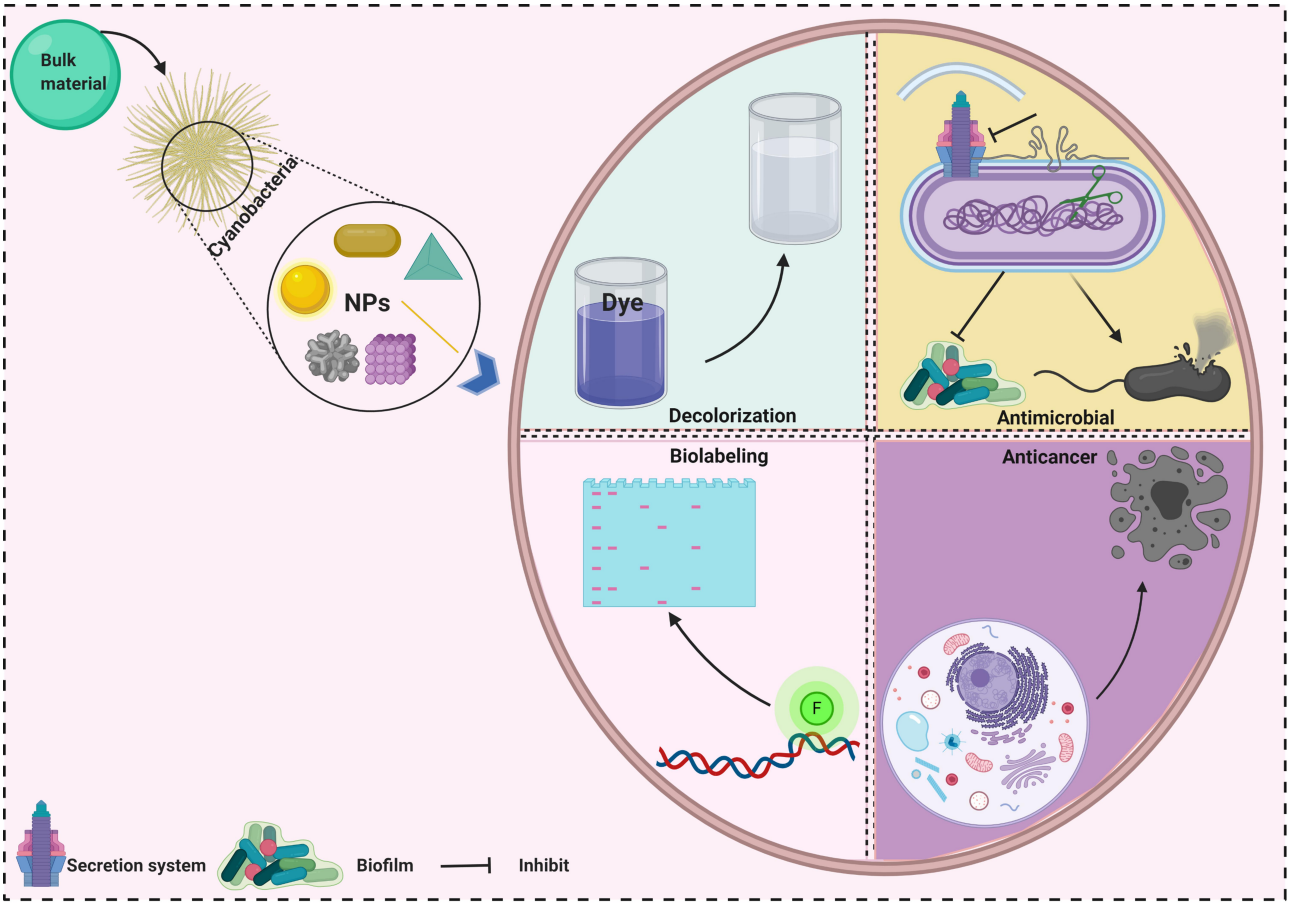


Figure 9 The potentiality of cyanobacteria to reduce various shape of NPs with potent biological and chemical applications.

Although many hypotheses have been proposed, the exact mechanism of NP synthesis using living organisms has not yet been elucidated. Thus, it will be necessary to further explore how microorganisms synthesize NPs and determine why different strains from the same species result in morphologically diverse NPs. Furthermore, studying the effects of biotic and abiotic conditions such as electrostatic force, metabolic status, growth conditions, and biomolecules (enzymes, pigments, proteins, etc.) on the green fabrication process will enable control of the physicochemical and biological properties of NPs. The emergence of serious diseases that threaten human health will motivate research to screen the activity of green NPs in various medical domains, including developing new antimicrobial and anticancer agents. In this respect, this review recommends that future studies focus on the cyanobacteria-nanotechnology field.

Conclusions

The use of cyanobacteria as bio-fabrication machinery to synthesize NPs has tremendous value, as it enables safe eco-friendly synthesis, as well as being inexpensive and saving energy, and produces novel NPs with varied shape and size. Cyanobacteria-mediated NPs have various biological, physical, and chemical features that provide versatile applicability. Many studies have shown that these NPs can serve as antimicrobial, anticancer, photocatalytic agents, etc. Cyanobacterial strains such as *Desertifilum* sp. and *Nostoc* sp. have been screened and used to synthesize Ag-NPs with significant anticancer activity against various cancer cell lines. Furthermore, Ag-NPs and Au-NPs fabricated using *Spirulina* sp. and *Anabaena* sp. show broad-spectrum inhibitory activity against Gram-positive and Gram-negative bacteria. Development and improvement of biosynthetic processes using cyanobacteria may lead to the discovery of new biogenic NPs with unique properties to serve various needs. Their incorporation into medical treatments could increase efficacy and diminish side effects (Figure 9).

Highlights

- The use of cyanobacteria as bio-fabrication machinery to synthesize NPs has tremendous value, as it enables safe eco-friendly synthesis, as well as being inexpensive and saving energy, and produces novel NPs with varied shape and size.
- Cyanobacteria-mediated NPs have various biological, physical, and chemical features that provide versatile applicability.
- Development and improvement of biosynthetic processes using cyanobacteria may lead to the discovery of new biogenic NPs with unique properties to serve various needs.

Abbreviations

NPs, nanoparticles; SNPs, silver nanoparticles; $AgNO_3$, silver nitrate; nm, nanometer; min, minute; µL, microliter; mg, milligram; mL, milliliter; µg, microgram; mM, millimolar; h, hour; cm^{-1}, inverse centimeter; rpm, revolutions per minute, SEM, scanning electron microscope; TEM, transmission electron microscope; DLS, dynamic light scattering; FTIR, Fourier-transform infrared spectroscopy; XRD, X-ray diffraction; kV, kilovolt; kb, kilobase; SPR, surface plasmon resonance; UV-vis, ultraviolet–visible spectroscopy.

Data Sharing Statement

The data supporting this article are available in Figures 1–9 and Tables 1–4. The data sets analyzed in the present study are available from the corresponding authors on reasonable request.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest in this work.

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