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REVIEW

Biomedical Applications of Biosynthesized Nickel Oxide Nanoparticles

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Abstract: Nickel oxide nanoparticles have gained tremendous attention recently in a variety of scientific domains thanks to their characteristic chemical, physical, optical, and biological properties. Due to the diversity of applications in various fields, different physicochemical methods have been used to synthesize nickel oxide nanoparticles. However, most conventional methods use hazardous chemicals during synthesis and become liable for potential health risks, while others are expensive and require a lot of energy to synthesize nanoparticles. As a result, the nanoparticles become less biocompatible and biologically inefficient. Biogenic synthesis of nanoparticles is currently proposed as a valuable alternative to the physical and chemical methods, as it is a simple, non-toxic, cheap, green and facile approach. This synthetic method uses biological substrates such as plant extracts, microorganisms, and other biological products to synthesize nickel oxide nanoparticles. The various phytochemicals from plant extracts, enzymes or proteins from microorganisms, and other biological derivatives play as reducing, stabilizing, and capping agents to provide bioactive and biocompatible nickel oxide nanoscale material. This review discusses current findings and trends in the biogenic synthesis of nickel oxide nanoparticles and their biological activities such as antibacterial, antifungal, antileishmanial, and anticancer, with an emphasis on antimicrobial and anticancer activity along with their mechanistic elucidation. Overall, this thorough study provides insight into the possibilities for the future development of green nickel oxide nanoparticles as therapeutic agents for a variety of ailments.

Keywords: nickel oxide nanoparticles, biogenic synthesis, antimicrobial activity, antileishmanial activity, anticancer activity

Introduction

The design, production, surface analysis, and application of nanoscale materials, typically with diameters ranging from 1 to 100 nm, are the focus of the rapidly expanding field of nanotechnology. These nanoscale materials, also known as nanoparticles, differ significantly from their bulk counterparts in terms of their physicochemical and biological properties. This is because of their incredibly small size and high surface-to-volume ratio.[1–3] Nanoparticles' amazing and intriguing qualities have made it possible to conduct multidisciplinary research and find solutions to a variety of issues. They have improved many aspects of human existence, including food production, pharmaceuticals, cosmetics, sensor, electronics, catalysis, energy production, medical care, and the environment.[4–7] In the medical field, they have been utilized for drug delivery, formulations of innovative medications, disease diagnostics, and treatment.[8–10]

Over the past decades, many inorganic nanoparticles have been studied extensively on account of their practical applications in different areas such as magnetic devices, sensors, photocatalysis, and biomedicine.[11–13] Among the numerous available nanomaterials, nickel oxide (NiO) nanoparticles have gained a great deal of attention mostly because of their superb stability and outstanding magnetic, electronic, optical, and catalytic properties[14,15] as well as their multifarious applications, including gas sensors,[16] electrochromic devices,[17] dye-sensitized solar cells,[18] batteries,[19] fuel cell,[20] solar energy absorber,[21] and magnetic recording devices.[22] Furthermore, NiO nanoparticles, unlike other metal oxide nanoparticles, are extremely inexpensive, non-toxic, and highly stable conductive materials with a broad bandgap of 3.6–4.0 eV.[23,24] These nanoparticles were utilized for medical applications, including imaging, drug delivery,

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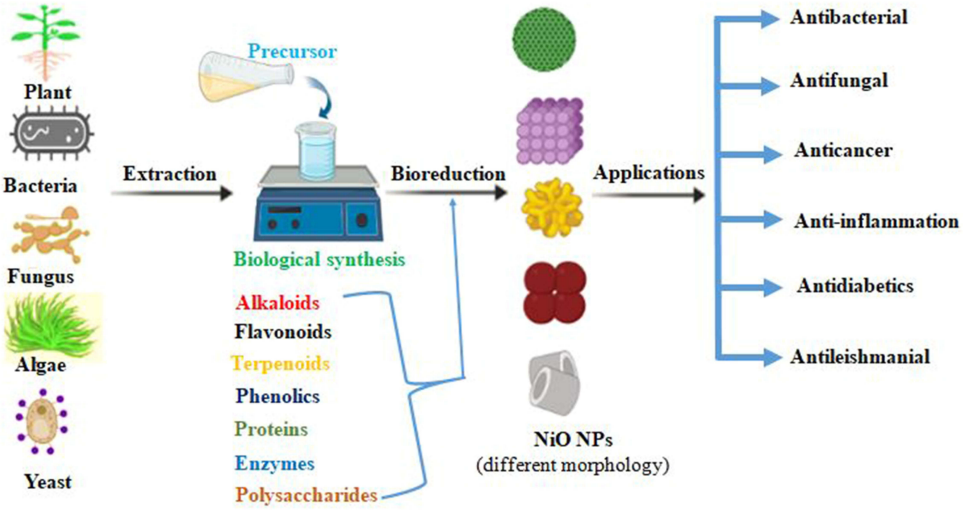
Graphical Abstract



biomedical detection, and antibiotics.[25,26] Apart from the previously mentioned usage, NiO NPs can also be successfully utilized for the removal of organic and inorganic pollutants, as a result, they play a crucial role in environmental protection. Photocatalytic degradation of Evans blue, methylene blue, 4-chlorophenol, cyanide, etc., through NiO nanoparticles, has been reported.[15,27–29] NiO nanoparticles can also promote seed germination. These are known to increase the growth rate of seedlings.[30] In doing so, they confirm their ability to modernize agriculture.

Recently, the distinctive nature of nanoparticles has prompted many researchers to develop inexpensive, environmentally friendly, time-efficient, and sustainable protocols for producing technologically important nanomaterials. Among the various synthesis routes utilized to fabricate NiO nanoparticles, biogenic synthesis (also called green synthesis), has received more attention, mainly due to its availability, simplicity, cost-effectiveness, and environment-friendly approach.[31–33] Biological synthesis of nanoparticles is economically advantageous and offers natural reducing, capping and stabilizing agents, thereby preventing the agglomeration of nanoparticles.[34] Green synthesized NiO nanoparticles have demonstrated considerable antibacterial, antioxidant, anticancer, and anti-inflammatory properties, making them promising tools for biomedical applications.[35–37] NiO nanoparticles have been found to have fungicidal activity against many fungal strains.[35] Several studies have described the anticancer activities of green synthesized NiO nanoparticles, including cytotoxicity studies towards HT-29, MCF-7, HepG2, A549, and Hela cancer cell lines.[38–40] Furthermore, these nanoparticles have shown excellent antiparasitic properties towards Leishmania tropica.[41] Other studies have also revealed the anti-diabetic, anti-inflammatory, and antioxidant nature of NiO nanoparticles.[42,43] The biocompatibility of green synthesized NiO nanoparticles was examined against freshly isolated macrophages and RBCs and found to be safe at a lower concentration.[28,35] NiO nanoparticles have shown toxicity towards different microbes and cancer cell lines by producing excess reactive oxygen species (ROS) and releasing nickel (II) ions that result in apoptosis.[44] Few reviews dealing with the synthesis of NiO nanoparticles have been published in the last decade.[45–49] However, most of these reviewers focus on several physicochemical and green synthetic methods, characterization techniques, and their applications. This review, unlike the previous reviews, provides a detailed overview of the biological synthesis, synthesis conditions, formation mechanisms, and biomedical applications, and predicts the antimicrobial and anticancer mechanism of NiO nanoparticles. In addition, the knowledge gaps, limitations, challenges and perspectives are pointed out to direct further research.

Synthesis of Nickel Oxide Nanoparticles

In general, the methods involved in the preparation of nickel oxide nanoparticles can be divided into "top-down" and "bottom-up" approaches (Figure 1). In the top-down pathway, nanoparticles are produced by decomposing bulk materials into nanosized materials through various chemical and physical methods.[50] Examples of this method are pyrolysis, mechanical milling, laser ablation, sputtering, and nanolithography. A major advantage of the top-down approach is the ability to synthesize nanomaterials in large quantities in a short period. But the disadvantage associated with this approach is surface imperfections of nanomaterials, which can affect their surface chemistry and physical properties.[3,51] Consequently, scientists prefer a bottom-up pathway where nanomaterials are prepared by self-assembly of small particles such as atoms, molecules, or clusters. Chemical methods such as sol-gel, precipitation, hydrothermal, solvothermal, and so on as well as biological synthesis are examples of bottom-up methods. The greater possibility of obtaining nanoparticles with minimum defect, homogeneous chemical composition and surface structure is the major benefit of the bottom-up approach.[3]

Synthesis of nickel oxide nanoparticles using several physicochemical and biological methods has been reported. Physical methods include mechanical milling,[52,53] sputtering,[16] spray pyrolysis,[54] chemical vapor deposition,[55] laser ablation,[56–58] and so forth. Among the physical methods, pulsed laser ablation has received much attention owing to its capability to monitor the shape, size and physicochemical properties of the nanoparticles. Moreover, unlike other methods of synthesis, pulsed laser ablation does not need high-vacuum pumping systems, costly chambers and post-synthesis purification of nanoparticles.[57,58] In this method, a pulsed high-power laser is essential for sample surface ablation. Variations of the laser ablation parameters played a major role in the fabrication of nanoparticles of desired morphology and size.[56,57] Pulsed laser ablation was used for the synthesis of NiO NPs using Ni as a precursor.[57] The NiO nanoparticles along with amoxicillin had a synergetic effect against different bacterial pathogens. Among other methods, NiO nanoparticles of average particle size 25 to 30 nm were prepared using spray pyrolysis of nickel chloride hexahydrate.[59] Chemical vapour deposition technique was utilized for the preparation of NiO nanoparticles.[55] NiO nanoparticles with a spherical shape and an average size of 25 nm have been successfully synthesized using the anodic arc plasma method.[60] Nevertheless, the majority of the above methods demand a large amount of energy, robust equipment and skilled manpower, which pose major obstacles to the synthesis of NiO nanoparticles.

Chemical methods, such as hydrothermal,[61] sonochemical,[62] solvothermal,[63–65] chemical reduction,[66,67] sol-gel,[68,69] microemulsion,[70] and so on have also been utilized for the fabrication of NiO nanoparticles. Amongst the aforesaid methods, the sol-gel technique is the most popular for the synthesis of NiO nanoparticles because it is simple, inexpensive, and has relatively mild conditions of synthesis. In this method, the formation of the nickel-containing

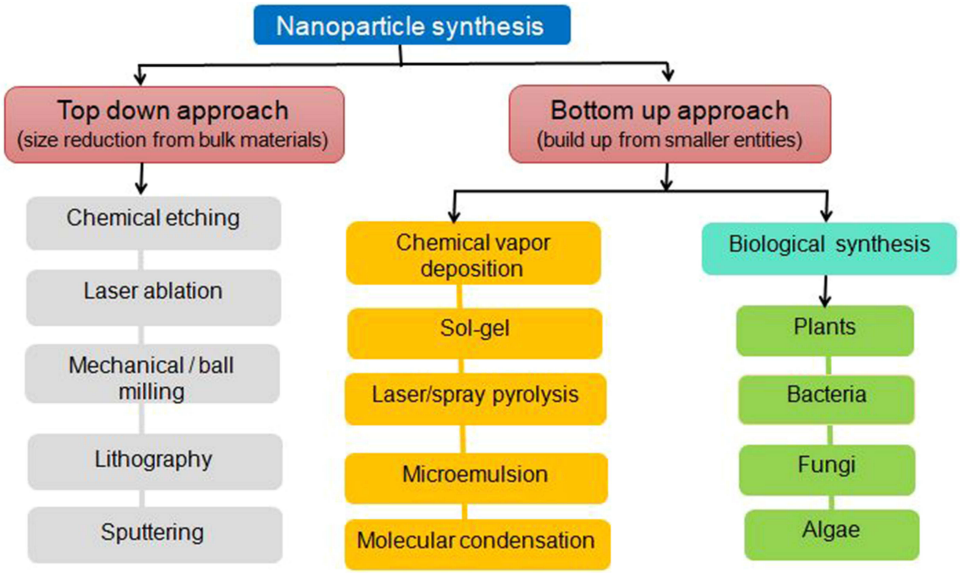


Figure 1 General methods of nanoparticles synthesis.

gels is monitored by using chemical reagents and the gel is then exposed to heat treatment up to 1000 °C to produce NiO nanoparticles. Cubic NiO nanoparticles were formed by utilizing chemical stabilizers like ethylene glycol and isopropanol and nickel nitrate hexahydrate as a precursor.[71] In this study, surfactant TritonX-100 detergent was added to avoid aggregation. In other studies, Yang et al[72] and Li et al[73] described the synthesis of NiO nanoparticles using malic acid and citric acid, respectively without adding any surfactants and reducing agents. NiO nanoparticles of size 25 nm were fabricated using $Ni(octa)_2$-oleylamine complex by thermal decomposition at 200 °C.[74] It was reported that oleylamine ($C_{18}H_{37}N$) and triphenylphosphine ($C_{18}H_{15}P$) were used as surfactants and the $C_{18}H_{37}N$ was used as both the medium and the stabilizing agent. Alcohols and hydrazine were also used as complexing agents during the production of NiO nanoparticles.[75] NiO nanoparticles were synthesized by simple solvothermal synthesis protocol using nickel nitrate as a precursor and citric acid as a chelating agent.[65] Abdullah et al[76] synthesized NiO nanoparticles by chemical precipitation without using stabilizing, capping agent or surfactant. In another study, Srikesh et al synthesized NiO nanoparticles through combustion by utilizing organic fuels.[77] However, many of the mentioned methods are time taking, labour-intensive, and require special conditions (eg, high temperature and pressure).[78–80] Another drawback of chemical synthesis methods is the use of harmful chemicals, combustible organic reagents, and non-biodegradable materials, which can be hazardous to humans and the environment. Moreover, the conventional physicochemical methods are not environmentally friendly, mainly due to the high production costs, low reaction yield, harmful side products, and high energy demands.[81–83] Additionally, the nanoparticles produced in this way cannot be used medically for health reasons, as these aggressive chemicals are adsorbed on their surface. Thus, recently there is a growing need to produce nanoparticles that are free of harmful side products. This can be achieved by green synthesis which is considered a sustainable, safe and inexpensive method.

Biological Synthesis of Nickel Oxide Nanoparticles

Biological synthesis is an example of a bottom-up approach that synthesizes nanoparticles using natural reducing and stabilizing agents. This process uses natural substrates such as microorganisms, plant extracts and biomolecules instead of chemical reducing agents and stabilizers. Most often, the reduction and stabilization of metal ions occur via various biomolecules present in these extracts, including enzymes/proteins, polysaccharides, amino acids, and vitamins.[84] The biological method is eco-friendly, sustainable, and low-cost, and the nanoparticles so generated do not contain toxic chemicals and are suitable for biomedical applications (Figure 2).[84,85] The development and significant interest of this

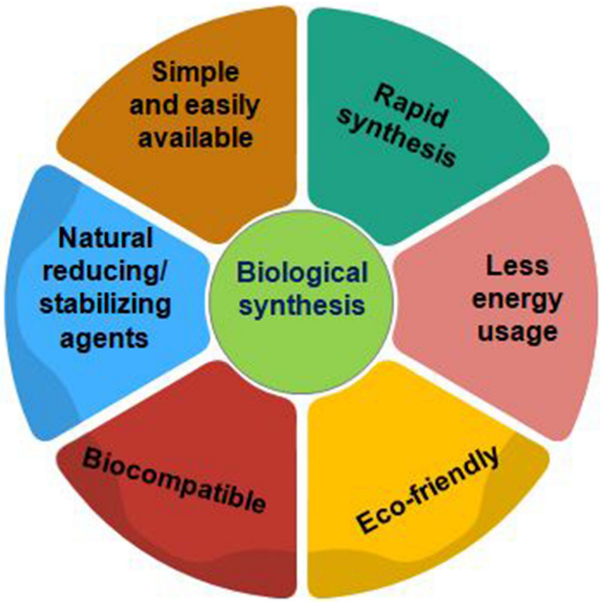


Figure 2 Benefits of biological synthesis of nanoparticles.

method is not only due to the absence of toxic chemicals or because of its low energy consumption compared to some physicochemical synthesis methods but also because it can be used to produce nanoparticles with well-defined size and morphology.[81,86]

Plant-Mediated Synthesis of NiO Nanoparticles

The utilization of plant and plant extracts to generate nanoparticles has received a lot of attention in recent years because it is simple, rapid, inexpensive, and eco-friendly. Numerous plant species have been described for the biological fabrication of NiO nanoparticles. In this process, the reduction of nickel ions occurs by the phytochemicals present in the extracts.[28,36] For instance; the polyphenols and hydroxyl group of flavonoids as well as the carbonyl and hydroxyl groups of amino acids serve as reducing agents and stabilize the synthesized nanoparticles. During the preparation of NiO nanoparticles, solutions of nickel salt and plant extracts are mixed and heated with constant stirring. Centrifuge the mixture after the reaction is complete. The clear supernatant solution is then discarded and the remaining pellets are washed, oven-dried, and calcined to obtain NiO nanoparticles. Finally, the formed nanoparticles were analyzed using various spectroscopic and microscopic techniques, such as dynamic light scattering (DLS), differential thermal analysis (DTA), energy-dispersive X-ray spectroscopy (EDX), UV-Vis spectrophotometer, Fourier-transform infrared spectroscopy (FT-IR), high-resolution scanning electron microscopy (HR-SEM), energy dispersion analysis of X-ray (EDX), high-resolution transmission electron microscopy (HR-TEM), X-ray diffraction (XRD), X-ray photoelectron microscopy (XPS), photoluminescence analysis (PL), particle size analyzer (PSA), selective area electron diffraction (SAED), and thermal gravimetric analysis (TGA) (Figure 3).

NiO nanocrystals of size about 50 nm were successfully prepared using *Nephelium lappaceum L.* extract.[85] The phenolic compounds present in the extract were responsible for the formation of NiO nanocrystals. Furthermore, the nanocrystals treated cotton fabric showed strong antibacterial properties. *Moringa oleifera* leaf extract was utilized for the biosynthesis of NiO NPs.[39] The TEM and EDX analysis indicated the production of spherical nickel oxide nanoparticles. Moreover, the resultant NiO showed significant antibacterial activity and cytotoxic activity. Oblong-shaped NiO NPs with 12 nm size were prepared using *Azadirachta indica extract* and showed outstanding antibacterial activity against *E. coli* and *S. aureus*.[87]

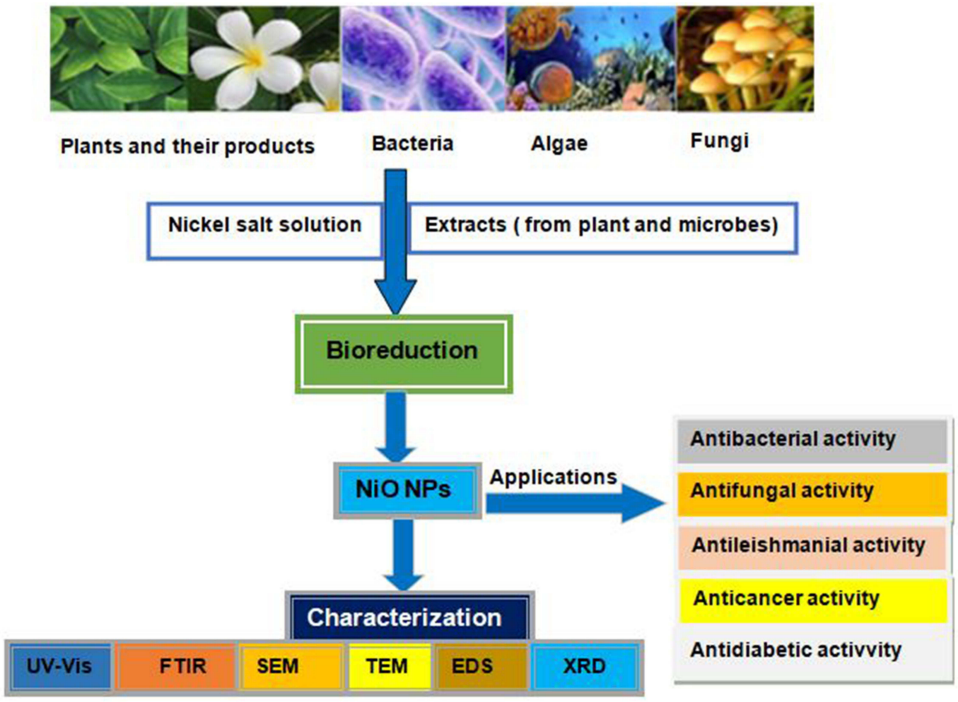


Figure 3 Schematic illustration of the biological synthesis of NiO NPs.

NiO NPs have been produced using a green and cost-effective method utilizing an aqueous leaf extract of *Aegle marmelos*.[28] The plant extracts have been suggested to play as capping and reducing agents. Spectroscopic and microscopic examinations revealed the formation of spherical NiO nanoparticles ranging in size from 8 to 10 nm. Moreover, the nanoparticles showed considerable anticancer activity against A549 cell lines. Until now, several plant extracts with distinct compositions have been exploited for the biosynthesis of NiO NPs of different shapes and sizes (Table 1). Although different plants and plant extracts have been utilized for this purpose, the variation in the concentration of nickel ion and plant extract, temperature, pH and contact time may result in the formation of NiO

Table 1 Plant Extracts Used for the Biosynthesis of NiO Nanoparticles with Their Size, Morphology, and Brief Experimental Conditions

Plant	Precursor(s)	Synthesis Conditions	Characterization	Morphology	Size (nm)	Ref.
A. conyzoides	$Ni(NO_3)_2.6H_2O$	Reaction: 80 °C, 6h; Drying: 120 °C, Calcination: 450 °C, 2h	UV-Vis, FTIR, XRD, TEM, PSA	Cubic	8–15	[88]
A. paniculata	$Ni(CH_3COO)_2.4H_2O$	Reaction: room temp., 2h; Microwave irradiation: 800W, 2.45 GHz, 20 min; Calcination: 400 °C, 3h	FTIR, XRD, SEM, EDS, HRTEM, UV-Vis	Spherical	24	[38]
A. linearis	$NiCl_2.6H_2O$	Reaction: room temp., 30 min; Drying: 90 °C, 1h; Annealing: 200, 500 °C, 2h	XRD, TEM, SEM, SAED, CV	Quasi-spherical	31.8	[89]
C. gigantea	$Ni(NO_3)_2.6H_2O$	Reaction: 400 °C; 10 min Calcination: 500 °C, 3h	UV-Vis, FTIR, TEM, SEM, XRD	Asymmetrical	31	[90]
E. heterophylla	$Ni(NO_3)_2.6H_2O$	Reaction: room temp., 24h; Calcination: 300 °C, 3h;	UV, FTIR, XRD, SEM-EDX, TEM	Rhombohedra	12–15	[40]
E. globules	$Ni(NO_3)_2.6H_2O$	Reaction: 70 °C, pH 8; Drying: 60 °C, 12h;100 °C, 24h	UV-Vis, FTIR, XRD, EDX	Pleomorphic	10–20	[91]
G. wallichianum	$Ni(NO_3)_2.6H_2O$	Reaction: 60 °C, 2h, pH 6.92; Drying: 100 °C, 3h; Calcination: 500 °C, 3h	XRD, SEM, TEM, FTIR, EDS, DLS, UV	Spherical	21	[36]
G. sylvestre	$Ni(NO_3)_2.6H_2O$	Reaction: 60 °C, 3h Calcination: 400 °C, 6 h	XRD, FESEM, EDX, HRTEM, FTIR, PSA	Spherical	14–18	[37]
L. acidissima	$Ni(CH_3COO)_2.4H_2O$	Reaction: room temp., 2h; Microwave irradiation: 850 W, 2.45 GHz, 15 min; Calcination: 600 °C, 4h	UV-Vis, FTIR, XRD, EDX, SEM	Spherical	20	[15]
M. burkenea	$Ni(NO_3)_2.6H_2O$, ethyl-glycol; citric acid	Reaction: room temp., 1h; Drying: 80°C; Calcination: 400 °C;	FTIR, EDX, SEM, HRTEM, XRD	Spherical	20	[92]
N. lappaceum	$Ni(NO_3)_2.6H_2O$	Reaction: 80 °C, 2h; Calcination: 500 °C, 2h	XRD, FESEM, TEM, CPS, UV-Vis	Spherical	15–20	[93]
R. triquetra	$Ni(NO_3)_2$	Reaction: 70 °C, 2h; Drying: 100 °C, 2h;	UV-Vis, XRD, FTIR, SEM, TEM, EDS	Spherical	25	[42]
R. virgata	$Ni(NO_3)_2$	Reaction: 60 °C, 2h Drying: 100 °C, 2h Calcination: 500 °C, 3h	UV-Vis, XRD, FTIR, SEM, EDS, TEM, DLS, *RS*	Spherical; 24 nm		[35]

(*Continued*)

Table 1 (Continued).

Plant	Precursor(s)	Synthesis Conditions	Characterization	Morphology	Size (nm)	Ref.
P. Americana	$Ni(NO_3)_2.6H_2O$	Reaction: 50 °C, 3h; Drying: 80 °C, 24h; calcination: 500 °C, 2h;	UV-Vis, FTIR, XRD, TEM, EDS	Spherical	11	[29]
P. persica	$Ni(NO_3)_2.6H_2O$	Reaction: 60 °C, 1h, pH 8; Drying: 80 °C, overnight; Calcination: 500 °C, 4h	UV-Vis, FTIR, XRD, SEM	Spherical	28	[94]
S. thea	$Ni(NO_3)_2$	Reaction: 60 °C, 1h; Drying: 100 °C, 2h; Calcination: 500 °C	XRD, FTIR, EDS, SAED, HRTEM/SEM, *RS*	Spherical	18	[41]
S. macrosiphon	$Ni(NO_3)_2.6H_2O$	Reaction: 80 °C, 6h; Drying: 100 °C, 2h; Calcination: 300–500 °C, 2h	UV-Vis, FTIR, XRD, FE-SEM, TGA/DTA	Spherical	27	[95]
S. rebaudiana	$Ni(CH_3COO)_2.4H_2O$	Reaction: 100 °C., 2h Annealing: 500 °C, 2h	UV-Vis, XRD, FESEM, FTIR, TEM	Spherical	20–50	[43]
T. erotina	$Ni(NO_3)_2.6H_2O$	Reaction: 115 °C, 1.5h; Calcination: 400 °C, 1h	FTIR, UV-Vis, XRD, TEM, VSM, BET	Spherical	10–14	[96]
Z. officinale	$Ni(NO_3)_2$	Reaction: 90 °C, 2h, pH 12; Drying: 90 °C, overnight	UV-Vis, FTIR, XRD, XPS, EDS, SEM, TEM	Spherical	16–52	[97]
O. ficus indica	$Ni(NO_3)_2.6H_2O$	Reaction: 80 °C, until color change; Annealing: 500 °C, 2h	XRD, EDS, SEM, Raman spectroscopy	Spherical	20–35	[98]

NPs of different morphologies and sizes. For instance, the crystal size of NiO NPs was increased from 32.14 nm to 33.24 nm when the annealing temperature was increased from 350 °C to 450 °C.[87]

Microbes-Mediated Biosynthesis of NiO Nanoparticles

Microbial-mediated fabrication of nanoparticles occurs via either intracellular or extracellular approaches. Intracellular synthesis generally involves the transport of metal ions into the microbial cell and the formation of nanoparticles by proteins, coenzymes, and heterocyclic derivatives present within the cell. In extracellular synthesis, metal ions are trapped on the surface of the microbial cell and the enzymes and/or proteins present on the surface reduce the metal ions and are involved in the stabilization of the nanoparticles.[12,99] Green syntheses of NiO NPs by microorganisms is a simple, inexpensive and environmentally friendly approach because no toxic and dangerous chemicals are used in the synthesis.[15] Various microbes such as algae, bacteria, fungi, and yeasts were used for the green synthesis of nickel oxide nanoparticles. For example, *Mycobacterium sp* isolated from an electroplating waste solution was used for the extracellular fabrication of NiO NPs.[100] The produced NiO NPs were flower-like and ranged in size from 100 to 500 nm. *Mycobacterium sp* cells were found to have a nickel removal efficiency of 95% using a nickel-containing industrial effluent. This demonstrates the significant impact of *Mycobacterium sp* cells in the bioremediation of nickel-containing wastewater and their ability to produce NiO NPs.

Fungi are a potential candidate for nanoparticle production because it has limited toxicity, do not require nutrients or growth media, and can be stored for long periods. In addition, it can withstand metal toxicity by attaching metal ions on the cell wall composed of hydroxides, phospholipids, amino-based phosphates, chitin, chitosan, sulfates, and so forth.[101,102]

NiO NPs in film form were synthesized using *Aspergillus aculeatus*.[101] Among the three types of fungal biomass used in the experiments, the dead biomass was found to exhibit the highest adsorption capacity and thus the greatest resistance to nickel toxicity. The NiO NPs synthesized were predominantly spherical with a size of 5.8 nm. XPS and EDS analysis demonstrated the presence of proteins that are supposed to be involved in the capping and/or stabilizing and organization of the nanoparticles. In another study,[102] the fungus *Hypocre lixii* has been used to synthesize NiO NPs. The TEM results

indicated the presence of spherical nanoparticles inside and outside the cells. The additional peaks of C, N, and O in the EDS spectra of the resulting nanoparticles showed the existence of macromolecules in the fungal cell wall, which acts as a capping material. *Rhizopus nigricans*, as a reducing agent and stabilizer, was also used for the fabrication of NiO NPs using nickel nitrate as a metal precursor.[103]

Another green and inexpensive method for synthesizing NiO NPs was reported by Sabouri et al[104] They synthesized membranous Ni/NiO NPs via *Rhodotorula mucilaginosa* yeast. The Ni/NiO NPs were found to be spherical with a size of 5.5 nm. The authors suggested that yeast proteins play a crucial role in organizing the nanoparticles into films.

In addition to bacterial-, fungi-, and yeast-based synthesis of NiO NPs, algae-mediated synthesis has also been described. Spherical NiO NPs with a size of 32.64 nm were formed by red marine algal extract and $NiCl_2.6H_2O$ solution as a precursor.[105] Additionally, the nanoparticles were found to be an efficient catalyst for the preparation of pyridopyrimidine derivatives. In another study, *spirogyra sp* was utilized for synthesizing quasi-spherical NiO NPs.[106] The biosynthesized NiO NPs exhibited strong bactericidal activity.

Other Green Source-Mediated Syntheses of NiO Nanoparticles

In addition to the synthesis of NiO NPs via plants and microorganisms, researchers have explored other low-cost, benign, and environmentally friendly methods using tannic acid, gums, chitosan, polysaccharides, amino acids, etc. (Table 2). An environmentally benign and biodegradable natural substance has been utilized for the biogenic synthesis of spherical NiO NPs and Ag-NiO nanocomposite.[107] It was reported that tannic acid act as stabilizing agent and NiO NPs exhibited excellent photocatalytic activity towards methyl violet. A similar method of synthesis has been reported for NiO nanostructures.[108] TEM spectra revealed the production of spherical NiO NPs with particle sizes of about 10–12 nm. Guar gum, a polysaccharide substance, was used as a stabilizing and capping agent during the synthesis of NiO NPs.[109] FTIR analysis indicated that the hydroxyl, carbonyl and carboxyl groups of the gum were involved in the reduction of the metal ions as well as stabilization of the nanoparticles. Moreover, the nanoparticles demonstrated tremendous

Table 2 Biomolecules or Other Green Sources Used for Biosynthesis of NiO Nanoparticles with Shape, Size, and Brief Experimental Conditions

Biological Derivatives	Precursor	Synthesis Condition	Characterization	Shape	Size	Ref.
Tannic acid	$Ni(CH_3COO)_2$	Reaction: 100 °C, until color change Annealing: 600 °C, 2h	UV-vis, FTIR, XRD, HRTEM, TGA, SAED	Spherical	10–12 nm	[108]
	$Ni(NO_3)_2.6H_2O$	Reaction: room temp., 2h	UV-vis, FTIR, SAED, EDAX, HRTEM	Spherical	7–10 nm	[107]
Arabic gum	$Ni(NO_3)_2.6H_2O$	Reaction: 180 °C, 2h Calcination: 300 −600 °C, 3h, 2h	UV-vis, FTIR, XRD, FESEM/EDX, TGA/DTA, VSM	Spherical	59 nm	[110]
Guar gum	$NiSO_4.6H_2O$	Reaction: room temp., until color change Annealing: 500 °C, 1h	UV-vis, FTIR, XRD, SEM, TEM, TGA-DTA	Spherical	3 nm	[109]
Starch	$Ni(NO_3)_2.6H_2O$	Reaction: 80 °C, 30 min Calcination: 500 °C, 3h	UV-vis, FTIR, XRD, HRTEM, FESEM, TGA	Flakes	28 nm	[113]
Chitosan	$Ni(NO_3)_2.6H_2O$	Reaction: 80 °C, 6h Drying: 120 °C, 6h Calcination: 400 and 500 °C, 2h	UV-vis, FTIR, XRD, FESEM/ EDX, TGA/DTA, CSM	Cube	126 and 250 nm	[114]
	$Ni(NO_3)_2.6H_2O$	Reaction: 60 °C, 6h Calcination: 500 and 600 °C, 5h	FTIR, TEM, XRD, FESEM, TGA, Raman spectroscopy	Spherical	10–30 nm	[111]
Egg white	$Ni(NO_3)_2.6H_2O$	Reaction: 80 °C, 12h Drying: 120 °C, 6h Calcination:300 −600 °C, 3h	UV-vis, FTIR, XRD, FESEM, EDX, PSA, TGA	Cube	-	[112]

photocatalytic effects towards nitroarenes. Arabic gum was used to fabricate NiO NPs of spherical shape and an average size of about 59 nm.[110] The produced NiO NPs exhibited strong anticancer activity against U87MG cells, revealing the significant therapeutic potential of the nanoparticles. An eco-friendly, biocompatible, non-toxic approach was followed for the green synthesis of NiO NPs using chitosan as a green template.[111] Chitosan has been reported to play a key role in polymerization and as an endpoint agent in the particle growth stage. It also minimizes toxicity, increases stability and prevents accumulation. NiO NPs having cubic morphology with uniform particle distribution were prepared using Egg white.[112] Furthermore, the nanoparticles exhibited considerable cytotoxicity against U87MG cells. Table 2 represents some of the biomolecules and other biological products that have been employed for the biosynthesis of nickel oxide nanoparticles.

Mechanism of Bio-Mediated Nanoparticles Production

In recent years, several plant extracts and microbes were utilized for the biosynthesis of metal and metal oxide nanoparticles. In plant-mediated synthesis, the phytochemicals/secondary metabolites of the plant extracts are responsible for the reduction and stabilization of metal ions into their respective metal/metal oxide nanoparticles.[81,115] However, the difference in concentration and composition of these biologically active compounds as well as pH, reaction time, temperature, and concentration of analyte has an extensive influence on the size and morphology of the synthesized nanoparticles.[116] The plant-mediated biosynthesis of nickel nanoparticles follows three phases, namely, the activation phase, growth phase and termination phase. The activation phase involves the reduction of nickel ions by the action of plant metabolites followed by the nucleation of the reduced atoms. This is followed by the growth phase that involves the spontaneous coalescence of the seceded metal atoms into larger-sized nanoparticles and further bioreduction of metal ions (Ostwald ripening), which in turn, increases the thermodynamic stability of nanoparticles. On the other hand, the increase in the duration of the growth phase leads to the aggregation of nanoparticles. The last step in the plant-mediated biosynthesis of nanoparticles is the termination phase. In this step, the nanoparticles acquire the most energetically favorable morphology, with this process being strongly influenced by the ability of a plant extract to stabilize metal nanoparticles.[2,117] In the case of metal oxides, the final product is oxidized by subjecting to air drying/calcination to get metal oxide nanoparticles.[48] Regarding the biosynthesis of NiO NPs, published research suggests that the active compounds present in the plant extract react with a nickel salt to reduce or form complexes with the metal ion.[85,93,98] For instance, the hydroxyl groups present in the phenolic compounds (such as corilagin, geranin, ellagic acid, and ellagitannins) of the plant extract are bound with the nickel ions to form a nickel phenolate complex (nickel-ellagate complex) through chelating effect. The formed complex undergoes decomposition during calcination and forms NiO nanoparticles.[93] The polyphenols of *Nephelium lappaceum* peel extract were found to chelate with nickel(II) ions and form a metal coordinated complex that is further thermally treated to form NiO NPs.[85] The antioxidants present in *Aspalathus linearis* extract also chelate with nickel(II) ions and form nickel oxide nanoparticles after thermal treatment.[118] The possible mechanism for plant-mediated biosynthesis of nickel oxide nanoparticles is shown in Figure 4.

The microbial-mediated synthesis mechanism of metal and metal oxide nanoparticles is also described in three steps: (1) Electrostatic interactions between negatively charged cell walls and positively charged metal cations trap metal ions in the cell walls of bacteria and fungi. (2) The cell wall then releases the enzyme reductase, which reduces the metal cation to a metal atom. (3) These atoms assemble to form metal nanoparticles. The nanoparticles formed can be capped by bacterial or fungal biomolecules, preventing further aggregation of the metal nanoparticles and allowing the eventually formed nanoparticles to diffuse out of the cell wall.[119] For metal oxide nanoparticles, the final product is air dried or air calcined to obtain the final metal oxide nanoparticles. Figure 5 shows a proposed mechanism of the microbes-mediated synthesis of nanoparticles.

Biomedical Applications

Antimicrobial Activity

In impoverished countries with slow socio-economic growth, infectious diseases brought on by microorganisms pose a severe threat to public health. Many drugs in the form of antibiotics have been developed to treat such infections, but

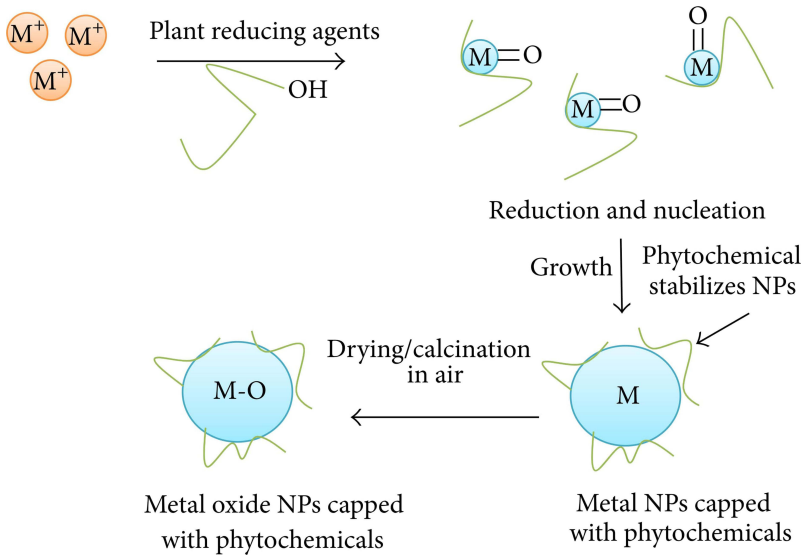


Figure 4 Mechanism of plant-mediated synthesis of Ni/NiO NPs. Reproduced from Imran Din M, Rani A. Recent advances in the synthesis and stabilization of nickel and nickel oxide nanoparticles: a green adeptness. Int J Anal Chem. 2016;2016:1–14.[48]

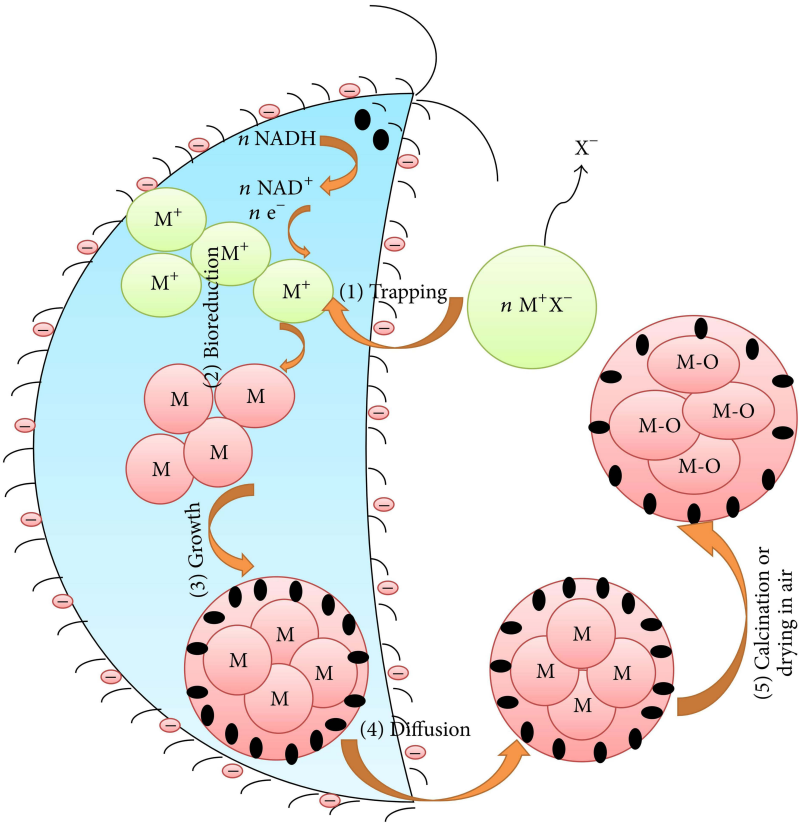


Figure 5 Mechanism of microbe-mediated synthesis of Ni/NiO NPs. Reproduced from Imran Din M, Rani A. Recent advances in the synthesis and stabilization of nickel and nickel oxide nanoparticles: a green adeptness. Int J Anal Chem. 2016;2016:1–14.[48]

the development of resistance to another class of antibiotics has limited the ability of conventional drugs to fight against microbial infections. Therefore alternative antimicrobial treatments are urgently needed.[120] Recently, nanotechnology-based therapies have been extensively utilized to diagnose and treat diseases and formulate novel drugs.[2,121] Among the various kinds of nanoparticles, NiO NPs have been screened against different human pathogenic microorganisms and

showed substantial outcomes.[28,91] NiO NPs biosynthesized using the leaves extract of *Moringa Oleifera* exhibited strong bactericidal potential towards multidrug-resistant gram-positive and gram-negative bacteria.[39] NiO NPs synthesized using *Aegle marmelos* leaf extract also showed similar bactericidal activity towards the same bacterial strains.[28] This variation may be due to the polarity difference between their membranes. Gram-positive bacteria have excess positive charge than Gram-negative bacteria, resulting in easy penetration of negatively charged-free radicals, causing more cell damage and cell death in Gram-positive than Gram-negative bacteria.[122,123] Another possible reason could be the structural complexity of the cell wall in Gram-negative bacteria. Gram-positive bacteria have a membrane surrounding the cell and a cell wall consisting of multiple layers of thick peptidoglycan, whereas Gram-negative bacteria have a single layer of thin peptidoglycan and an outer membrane consisting mainly of lipopolysaccharide. Thus, in Gram-negative bacteria, the outer membrane acts as a permeability barrier that reduces the entry of ROS into the cell.[124]

The antibiofilm and bactericidal activities of green synthesized nickel oxide nanoparticles towards *S. aureus, P. aeruginosa*, and *E. coli* were well established.[91] NiO NPs treated bacterial cells showed shrinking, fragmentation, and disorganization of outer surfaces including the formation of pits and gaps, revealing the substantial inhibitory effect of the nanoparticles. Furthermore, *P. aeruginosa* showed higher morphological change compared to *S. aureus* which may be due to the disparity in their peptidoglycan layer. In another study, cotton fabrics inoculated with *S. aureus* and *E. coli* were used to examine the antibacterial activity of NiO nanocrystals.[85] The findings showed a higher zone of inhibition against *S. aureus* (35 mm) than *E. coli* (25 mm). Furthermore, a significant antibacterial potential was observed even after repeated washing of the NiO nanocrystal-treated cotton fabrics. *Calotropis gigantea* was utilized for the biosynthesis of NiO NPs and displayed almost similar bactericidal activity with standard drug chloramphenicol towards *P. aeruginosa*, implying the potential of these nanoparticles as reliable antibacterial agents.[125] The *Sageretia thea* leaf extract-mediated synthesized NiO NPs were evaluated against six pathogenic bacterial strains with and without UV illumination.[41] Among the strains tested, *B. subtilis* was the most sensitive, whereas *K. pneumonia* and *P. aeruginosa* were the least susceptible bacterial strains. Additionally, an increasing antibacterial impact was observed after exposure to UV light. Similarly, the antibacterial effect of *Rhamnus virgata*-mediated NiO NPs significantly increased on UV illumination.[82] The MIC value of *P. aeruginosa* before and after UV illumination was found to be 125 µg/mL and 31.5 µg/mL, respectively. The highest bactericidal effect of NiO NPs under UV illumination may be because of the mass generation of reactive oxygen species. NiO NPs prepared using *R. triquetra* and *G. wallichianum* also showed similar results.[36,42] Table 3 summarizes the antibacterial effect of NiO NPs synthesized using various biological entities.

The antifungal properties of bio-inspired nickel oxide nanoparticles have rarely been investigated compared to their antibacterial activity. The biosynthesis of NiO NPs using *Sageretia thea* leaf extract was reported and the formed nanoparticles were examined against five pathogenic fungal strains.[41] The findings showed that the fungal strains were suppressed by the green-produced NiO NPs in a dose-dependent manner. Furthermore, *A. flavus* was the least sensitive strain, whereas *R. solani and M. racemosus* were determined to be the most sensitive, as demonstrated by inhibition rates of 63.2% and 64%, respectively. As a result of the nanoparticles being internalized, ROS were produced, which damaged mitochondria and DNA, contributing to the antifungal action. NiO NPs showed remarkable antifungal efficacy against a variety of fungal strains, including *A. flavus, A. niger, C. Albicans, F. solani, M. racemosus*.[35] Among the fungal strains, *M. racemosus* was found to be the most susceptible, and *A. flavus* was the least susceptible. In another study,[42] NiO NPs synthesized using *Rhamnus triquetra* exhibited a concentration-dependent fungicidal activity against the same fungal strains. The study revealed that *A. niger* was the most susceptible strain, while *A. flavus* was the least susceptible. According to a review article, NiO NPs have been shown to have antimicrobial activity against various bacteria.[127] However, there are some challenges associated with using NiO NPs as antimicrobial agents. One of the challenges is that the NiO nanoparticles can cause oxidative stress and inflammation in human cells.[128] Another challenge is that the nanoparticles can cause oxidative stress in bacterial cells. This can lead to the development of resistance in bacteria. Additionally, nanoparticles can be unstable and can aggregate in solution.[128] Another study found that NiO nanoparticles can cause lung inflammation and fibrosis in rats.[129] Therefore, it is important to use caution when handling NiO NPs and to follow proper safety protocols. Table 4 summarizes the antifungal activity of NiO NPs produced using plants, microorganisms and other natural sources.

Table 3 Antibacterial Effect of Biosynthesized NiO Nanoparticles

Bacterial Species	NiO NPs			Method	ZOI (mm)	Ref.
	Size (nm)	Shape	Concentration/Amount			
B. subtilis	7–40	Spherical	1µL of 0.1 mg/mL	Disc diffusion	12	[43]
	21	Spherical	MIC: 21.875 µg/mL	Disc diffusion	–	[36]
	24	Spherical	MIC: 15.6 µg/mL	Disc diffusion	–	[35]
E. coli	7–40	Spherical	1µL of 0.1 mg/mL	Disc diffusion	16	[43]
	14–18	Spherical	1g of 20 mL extract + 80 mL of 0.1mM Ni $(NO_3)_2.2H_2O$	Disc diffusion	28.5±1.9	[37]
	31	Asymmetrical	500µg/mL	Agar well diffusion	2.95±0.48	[90]
	8–10	Spherical	20 mL extract + 80 mL of 0.1 mM Ni $(NO_3)_2.2H_2O$	Disc diffusion	11	[28]
	12–15	Rhombohedral	100 µg/mL	Agar well diffusion	15.37±0.17	[15]
	32	Cubic	5 mg/mL	Agar well diffusion	11	[126]
	9.69	Spherical	20 mL extract + 80 mL of 0.1mM Ni $(NO_3)_2.2H_2O$	Disc diffusion	10	[39]
	24	Spherical	MIC: 62.5 µg/mL	Disc diffusion	–	[35]
E. Hermannii	8–10	Spherical	20 mL extract + 80 mL of 0.1 mM Ni $(NO_3)_2.2H_2O$	Disc diffusion	6	[28]
	9.69	Spherical	20 mL extract + 80 mL of 0.1mM Ni $(NO_3)_2.2H_2O$	Disc diffusion	5	[39]
K. pneumonia	21	Spherical	MIC: 175 µg/mL	Disc diffusion	–	[36]
	12–15	Rhombohedral	100 µg/mL	Agar well diffusion	13.80±0.29	[15]
	24	Spherical	MIC: 125 µg/mL	Disc diffusion	–	[35]
P. aeruginosa	21	Spherical	MIC: 175 µg/mL	Disc diffusion	–	[36]
	14–18	Spherical	1g of 20 mL extract + 80 mL of 0.1mM Ni $(NO_3)_2.2H_2O$	Disc diffusion	31.6±1.4	[37]
	12–15	Rhombohedral	100 µg/mL	Agar well diffusion	13.67±0.29	[15]
	24	Spherical	MIC: 125 µg/mL	Disc diffusion	–	[35]
S. aureus	21	Spherical	MIC: 87.5 µg/mL	Disc diffusion	–	[36]
	12–15	Rhombohedral	100 µg/mL	Agar well diffusion	14.67±0.17	[15]
	14–18	Spherical	1g of 20 mL extract + 80 mL of 0.1mM Ni $(NO_3)_2.2H_2O$	Disc diffusion	33.4±1.3	[37]
	31	Asymmetrical	500 µg/mL	Agar well diffusion	4.63±0.41	[90]
	8–10	Spherical	20 mL extract + 80 mL of 0.1 mM Ni $(NO_3)_2.2H_2O$	Disc diffusion	16	[28]
S. aureus	32	Cubic	5 mg/mL	Agar well diffusion	12	[126]
	9.69	Spherical	20 mL extract + 80 mL of 0.1mM Ni $(NO_3)_2.2H_2O$	Disc diffusion	15	[39]
	24	Spherical	MIC: 62.5 µg/mL	Disc diffusion	–	[35]
S. pneumonia	7–40	Spherical	1µL of 0.1 mg/mL	Disc diffusion	14	[43]
	8–10	Spherical	20 mL extract + 80 mL of 0.1 mM Ni $(NO_3)_2.2H_2O$	Disc diffusion	12	[28]
	9.69	Spherical	20 mL extract + 80 mL of 0.1mM Ni $(NO_3)_2.2H_2O$	Disc diffusion	12	[39]

Abbreviations: ZOI, Zone of inhibition; MIC, minimal inhibitory concentration.

Table 4 Antifungal Activity of Green Synthesized NiO Nanoparticles

Fungal Species	NiO NPs			Method	ZOI (mm) / Inhibition (%)	Ref.
	Size (nm)	Shape	Concentration/ Amount			
Alternaria alternate	31.44	Rhombohedral	1000 μg/mL	Poisoned food method	71.25%	[30]
Aspergillus flavus	21	Spherical	MIC: 175 μg/mL	Disc diffusion	–	[36]
	24	Spherical	MIC: 125 μg/mL	Disc diffusion	–	[35]
	25	Spherical	MIC: 275 μg/mL	Disc diffusion	–	[42]
	18	Spherical	2 μg/mL	Disc diffusion	58%	[41]
Aspergillus fumigatus	7–40	Spherical	–	Disc diffusion	6 mm	[43]
	18	Spherical	2 μg/mL	Disc diffusion	62.6%	[41]
Aspergillus niger	21	Spherical	MIC: 43.75 μg/mL	Disc diffusion	–	[36]
	24	Spherical	MIC: 31.25 μg/mL	Disc diffusion	–	[35]
	7–40	Spherical	–	Disc diffusion	6 mm	[43]
	18	Spherical	2 μg/mL	Disc diffusion	62	[41]
	31.44	Rhombohedral	1000 μg/mL	Poisoned food method	39.51%	[30]
Candida albicans	21	Spherical	MIC: 43.75 μg/mL	Disc diffusion	–	[36]
	24	Spherical	MIC: 62.5 μg/mL	Disc diffusion	–	[35]
	25	Spherical	MIC: 68.75 μg/mL	Disc diffusion	–	[42]
Fusarium solani	21	Spherical	MIC: 21.87 μg/mL	Disc diffusion	–	[36]
	24	Spherical	MIC: 31.25 μg/mL	Disc diffusion	–	[35]
	25	Spherical	MIC: 68.75 μg/mL	Disc diffusion	–	[42]
Fusarium oxysporum	31.44	Rhombohedral	1000 μg/mL	Poisoned food method	15.39%	[30]
Mucor racemosus	21	Spherical	MIC: 21.87 μg/mL	Disc diffusion	–	[36]
	24	Spherical	MIC: 31.25 μg/mL	Disc diffusion	–	[35]
	25	Spherical	MIC: 68.75 μg/mL	Disc diffusion	–	[42]
	18	Spherical	2 μg/mL	Disc diffusion	62%	[41]
Rhizopus solani	18	Spherical	2 μg/mL	Disc diffusion	63.2%	[41]

The actual mechanism for the antimicrobial activity of green synthesized NiO NPs is not clearly understood and is still under investigation. Nevertheless, many ways of action such as 1) generation of reactive oxygen species due to light illumination, 2) direct contact of NiO NPs with microbial cells, resulting in plasma membrane destruction, and 3) release of antimicrobial ions mainly nickel (II) ions have been suggested (Figure 6).[35,41,85] Researchers have unveiled that the stress elicited by the creation of ROS is the main cause for the antimicrobial potential of NiO NPs.[35,36,39,41] Generation of reactive oxygen species such as superoxide (O_2^-), hydrogen peroxide (H_2O_2) and hydroxyl radical (OH) is attributed to the activation of NiO NPs by ultraviolet and visible light.[35,85] Superoxide and hydroxyl radicals consist of excess negative charge and therefore do not penetrate the cell membrane; however, hydrogen peroxide readily enters cells[85] and induces cell death by disrupting cell membrane integrity and damaging DNA, mitochondria, and proteins within the cell.[42,85] The antimicrobial impact of NiO NPs depends on their surface area, morphology, and surface defects. For example, the larger the surface areas of NiO NPs, the more ROS are produced on the surface and thus the greater antimicrobial property.[28,37] Besides the ROS generation, the direct contact of NiO NPs with the bacterial membranes and damage to the microbial surface have been described as factors responsible for the antimicrobial property of these nanoparticles.[39] The cytotoxic behaviour of NiO NPs led to the formation of pores, shrinking and cell membrane fragmentation.[91] Likewise, surface defects in the nanoparticles' symmetry and adsorption of nanoparticles on the surface of cells can also cause injury to cells and account for the antibacterial potential.[36,43]

In addition to the aforementioned mechanism, the significant antimicrobial impact of NiO NPs was also thought to be a result of the intermolecular interactions between the nickel (II) ions and the cell surface.[41] Ezhilarasi et al studied the

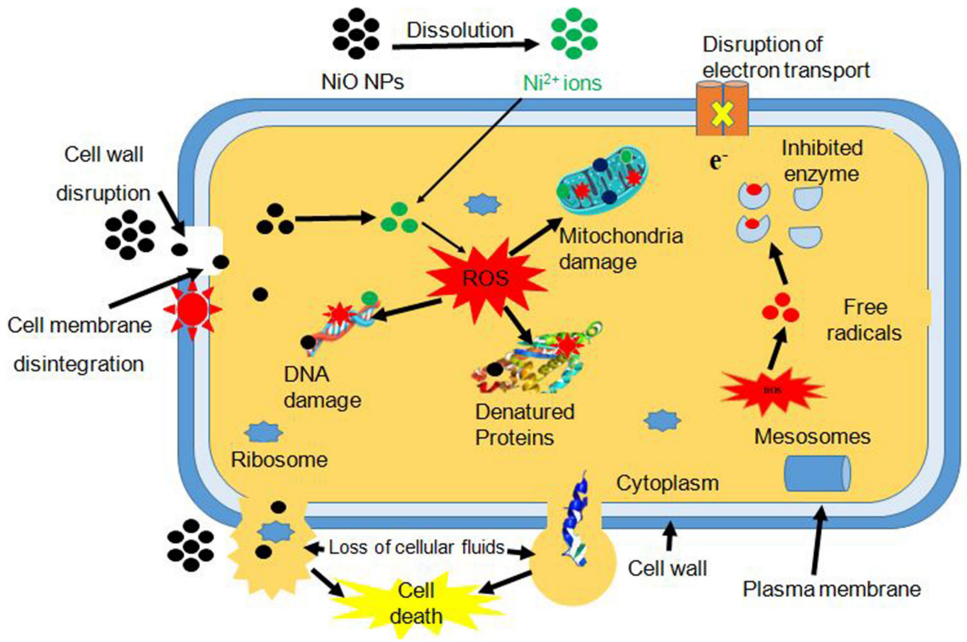


Figure 6 Antimicrobial mechanism of green synthesized NiO NPs.

antimicrobial effect of NiO NPs and pointed out that the binding of nickel (II) ions on the cell surface is more likely to affect membrane permeability, enable nanoparticle uptake, and ultimately inhibit cell growth.[39] The nickel (II) ion that enters the microbial cell interrupts transmembrane electron transport, thereby inhibiting the growth of the microbial species.[39,40,126] The internalization of NiO NPs into the microbial cells intensifies the inhibition of microbial growth by interfering with electron transport, damaging DNA by rupturing proteins by changing the tertiary structure and harming the mitochondria by generating ROS. This ultimately results in cell death.[43] Moreover, the uncoupling of ATP production, the loss of protein motive force, and the interference with the phosphate efflux mechanism brought on by the interaction of NiO NPs with thiol groups of cellular proteins results in the separation of the cell membrane from the cytoplasm.[91] The condensation of genetic materials, loss of replication, and finally the release of intracellular contents may result from these processes occurring alone or together. Generally speaking, NiO NPs' bactericidal potential is ascribed to their tiny size, unique morphology, low band energy, and strong electrostatic properties. Despite the increasing knowledge on the antimicrobial activity of NiO nanoparticles, much remains unknown about their exact mechanism of encountering bacteria, toxicity, in vivo studies, and environmental concerns, which need to be addressed before utilizing them for clinical settings.

Anticancer Activity

Biosynthesized NiO NPs showed substantial anticancer properties, especially against colon, breast, liver, and lung cancers (Table 5).[36,38,40] The anticancer properties of NiO NPs prepared with *Geranium wallichianum* were investigated against liver cancer cells using 3 - (4, 5 – dimethylthiazol - 2 - yl) - 2, 5 - diphenyltetrazolium bromide (MTT) assay.[36] In their study, the cancer cells were maintained at 37 °C with a continuous supply of 5% CO_2 in their respective media and seeded in a 96-plate before treatment. Exposure of human hepatocarcinoma (HepG2) cells to various concentrations of NiO NPs (500–3.9 µg/mL) for 24 hr showed concentration-dependent inhibition of the cell lines. NiO NPs prepared using *Andrographis paniculata* leaf extract also showed a dose-dependent inhibition against human breast cancer (MCF-7) cell lines.[38] NiO NPs fabricated with *Moringa Oleifera* exhibited higher cytotoxicity against human colorectal adenocarcinoma cancer (HT-29) cell lines, and a gradual decrease in cell viability was observed with increasing nanoparticle dose.[39] The significant anticancer activity of these nanoparticles towards HT-29 cell lines was attributed to their large surface area to volume ratio. Moreover, the level of nickel (II) ions released was found to be high, thereby

Table 5 Anticancer Effects of Biosynthesized NiO Nanoparticles

Types of Cells/Cell Lines	NiO NPs		Method	Toxicity (IC_{50}) (μg/mL)	Ref.
	Size (nm)	Shape			
Breast cancer					
MCF-7	32	Cube	MTT assay	55	[126]
	24	Cube	MTT assay	44.91	[38]
Cervical cancer					
HeLa	–	Cube	MTT assay	120	[84]
Liver cancer					
HepG2	21	Spherical	MTT assay	37.84	[36]
	12–15	Rhombohedra	MTT assay	344.26	[40]
	24	Spherical	MTT assay	29.68	[35]
	25	Spherical	MTT assay	20.73	[42]
HuH7	25	Spherical	MTT assay	11.3	[42]
Lung cancer					
A549	12–15	Rhombohedra	MTT assay	353.16	[40]
	5–15	Hexagonal and rhombohedral	MTT assay	93.35	[130]
Glioblastoma cancer					
U87MG	–	Cube	MTT assay	15.62	[112]
	18–43	Sheet, plate, cube	MTT assay	125	[131]
	59	Spherical	MTT assay	37.84	[110]
Esophageal					
FLO-1	60.39	Spherical	MTT assay	380	[132]
ESO26	60.39	Spherical	MTT assay	263	[132]
OE33	60.39	Spherical	MTT assay	229	[132]
KYSE-270KYSE-270	60.39	Spherical	MTT assay	251	[132]

inducing the massive generation of ROS through mitochondria dysfunction, and subsequently, cell death. The *Euphorbia heterophylla* leaf extract-mediated synthesized NiO NPs showed a concentration-dependent anticancer activity towards HepG2 and human lung cancer (A549) cell lines.[40] *Rhamnus virgata* extract orchestrated NiO NPs were examined for their anticancer potential towards HepG2 cell lines.[35] Findings showed the anticancer activity of NiO NPs increased with increasing doses. Furthermore, the biosynthesized NiO NPs exhibited remarkable cytotoxicity towards brine shrimps with an IC_{50} value of 43.73 μg/mL. The biocompatible nature of the NiO nanoparticles to freshly isolated macrophages and human RBCs was also investigated and revealed that NiO NPs at a concentration of 2 μg/mL were biocompatible and could be used in different treatments. Green synthesized NiO NPs demonstrated a dose-dependent cytotoxic effect and fluorescence microscopic analysis confirmed the nanoparticles induced apoptosis, which might be due to the production of ROS.[126] The *Salvia macrosiphon* extract-mediated synthesized NiO NPs exhibited dose-dependent toxicity toward Neuro2A cell lines.[95] The significant toxicity of NiO NPs could be due to their tendency to release nickel (II) ions inside the cell ultimately leading to cell death. NiO NPs synthesized using egg white also showed significant cytotoxicity towards U87MG cell lines, with an IC_{50} value of 15.62 μg/mL.[112]

The anticancer mechanism of nanoparticles is quite complex and still under investigation. Many studies proposed that the plausible anticancer mechanism of NiO nanoparticles could be due to the reactive oxygen species-dependent and caspase-mediated apoptosis in cancer cell lines (Figure 7).[28] When the nanoparticles come into contact with the cancer cell membrane, the cell surface triggers nanoparticle invagination via endocytosis to generate intracellular

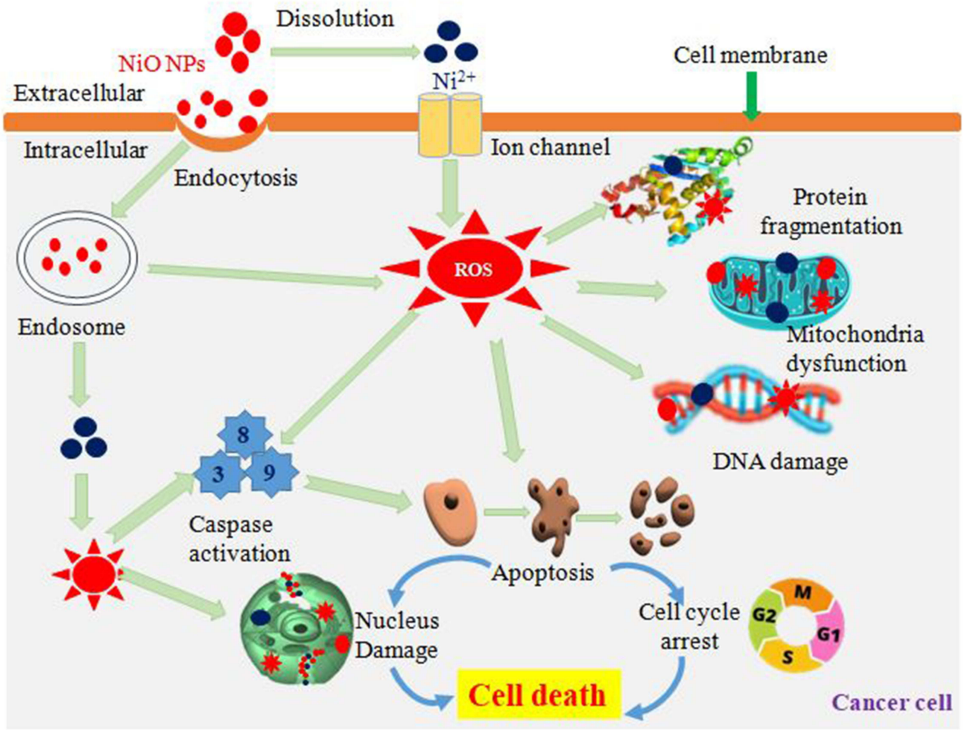


Figure 7 Anticancer mechanism of green synthesized NiO NPs.

membrane-bound vesicles.[133] This allows the endocytosed nanoparticles to enter the intracellular space without being eliminated. They are then released to generate ROS which causes mitochondria dysfunction, nuclear destruction, protein oxidation, DNA damage, decreasing major non-protein free radical scavengers and finally apoptosis.[28,134] Particularly, the ROS are likely to cause cell cycle arrest during growth and preparation for the mitosis and meiosis phases.[135] This process is completed by stimulating caspases-3, −8, and −9 (proteins associated with apoptosis). Many studies have also shown that ROS increases levels of the tumor protein P53, which is known to inhibit cancer cells.[135,136] Another possible reason could be the internalization of nickel ion into the cells which activates the calcium-dependent cascades that disrupt the DNA repair pathways and ultimately causes apoptosis.[28,137] The amount of nickel (II) ions released will be higher for nanosized compared to the micron-sized particles. Thus, the smaller particle size of NiO NPs may be the reason for the higher cytotoxic activity towards A549 cell lines.[28] Based on the aforementioned mechanism, NiO nanoparticles may significantly contribute to cancer cell killing by reactive oxygen agents.

Antileishmanial Activity

The parasite Leishmania tropica is the source of the neglected disease caused by Leishmania tropica. The commonly used antileishmanial medications have some drawbacks, including toxicity, side effects, and decreased efficacy due to drug resistance.[138] Nowadays, many researchers are engaged in developing alternative routes for its treatment. Recently, the antileishmanial activity of bio-inspired NiO NPs was tested against amastigote and promastigote cultures of *Leishmania tropica* using MTT cytotoxic assay.[41] The IC_{50} values against promastigotes and amastigotes cultures were 24.13 µg/mL and 26 µg/mL, respectively, indicating that both cultures were efficiently suppressed in a dose-dependent manner. Similarly, NiO NPs synthesized using *Rhamnus virgata* showed considerable antileishmanial potential against amastigotes and promastigotes with IC_{50} values of 10.62 µg/mL and 27.58 µg/mL respectively.[35,36] NiO NPs prepared using *R. triquetra* also showed a dose-dependent antileishmanial activity.[40] The concentration-dependent and lower IC_{50} values of the nanoparticles indicated that they could be used in future medicine for potent drug delivery against Leishmania.

Anti-Diabetic Activity

NiO nanoparticles synthesized using *Averrhoa bilimbi* exhibit potent anti-diabetic activity on α-amylase inhibitory effectiveness with IC_{50} of 311.26 µg/ mL.[139] Similarly, the as-synthesized NiO NPs also showed significant anti-diabetic activity compared to Metformin.[130] These findings suggest the potential of biogenic NiO Nanoparticles for the treatment of various diseases in the future.

Challenges and Future Perspectives

In recent years, nanoparticles have been used in biomedicine as antimicrobials, anticancer, and drug delivery agents by encapsulating drugs or binding therapeutic agents for more effective delivery to target tissues or cells.[140,141] They are produced with a very small size so that they can move freely within the human body and target cancer cells.[142] The Food and Drug Administration (FDA) has approved several nanoparticles, such as Au, Ag, zinc oxide, nickel oxide, and silica nanoparticles, for biomedical applications for the treatment of chronic diseases and cancers.[142,143] These nanoparticles are used to treat liver, breast, cervical, and lung cancers.[143]

Research results on the green synthesis of nanoparticles have grown gradually within the last few decades. However, the focus is primarily on antimicrobials, with less emphasis on anticancer agents.[144] Extensive in vitro studies have shown the therapeutic potential of biologically synthesized NiO nanoparticles, but these nanoparticles are still far from clinical trials due to limited in vivo data. Further detailed studies on the toxicity of these nanoparticles should be undertaken before they can be utilized in clinical settings. Since nanomaterials exhibit much more variable behavior than bulk materials, during biosynthesis the variables affecting the physicochemical and biological properties of NiO nanoparticles need to be monitored to better understand the underlying influencing mechanisms. Additionally, the underlying mechanism of NiO nanoparticles in various disease models should be investigated. The biggest obstacle limiting the application of nanoparticles is the lack of standardized regulations required for their use. Their uncontrolled use without uniform regulation will cause many unavoidable consequences. These challenges need to be addressed before large-scale commercialization of NiO nanoparticles can be made. Despite these challenges, the current promising data demonstrate the potential of NiO nanoparticles for the treatment of cancer and other disease in the future.

Conclusions

Nanotechnology is a highly developing field due to its extensive application in various fields of science and technology. Various physicochemical methods have been used to synthesize NiO nanoparticles. However, conventional chemical and physical methods have certain limitations in the form of chemical impurities during the synthesis process or in subsequent applications. Various chemicals (reducing agents) are used to chemically reduce NiO nanoparticles, most of which are toxic and cannot be easily discarded for environmental reasons. In many other cases, synthesis takes place at high temperatures, requires high energy and is very expensive. In recent years, the biological method of NiO nanoparticle synthesis is increasingly being developed and is gradually replacing the physicochemical methods with economic, environmental and safety advantages. In this paper, we have reviewed the recent trends and understandings of biogenic NiO NPs for possible use in biomedical applications, with a particular emphasis on antimicrobial and anticancer activity. Different types of natural extracts (such as plants, bacteria, algae, and fungus) and other biological products have been discussed with their synthesis condition and mechanism of formation. From this review, it can be seen that microbe-mediated synthesis is not industrially viable due to the requirement of strong sterile conditions and their maintenance. Therefore, the use of plant extracts for this purpose is more beneficial than microbes due to their ease of modification, fewer biological hazards, and laborious process of maintaining cell cultures. Furthermore, the use of plant extracts also reduces the cost of isolating micro-organisms and their culture media, making them more cost competitive compared to microorganism-mediated nanoparticle synthesis. Soon, nanoparticles fabricated using plant extracts may be integrated into large-scale production as they are reliable, eco-friendly, simple, and cost-effective. These strengths may open up new commercial opportunities for biological nanoparticles, hence lowering the production cost. The superior properties, small size, and biocompatibility nature of NiO NPs have led to their wide use in biomedical fields. They have shown promising results against multidrug-resistant microbes and may be used as a potential antimicrobial agent against such intractable

pathogens in the future. In addition, these nanoparticles have also shown remarkable antioxidant, anti-diabetic, antileishmanial, and anticancer effects, however, further studies need to be conducted in vivo models to clarify the full mechanism and side effects. Furthermore, a detailed study on the future application of biogenic NiO NPs in magnetic resonance imaging, cell separation, drug delivery and biomedical detection is highly needed. Hence, understanding the current progress in the biosynthesis of NiO NPs and their biomedical applications will help drive future research on NiO NPs and their large-scale production.

Abbreviations

NiO NPs, Nickel oxide nanoparticles; UV-Vis, Ultraviolet-visible spectroscopy; SEM, Scanning electron microscopy; FE-SEM, Field emission scanning electron microscopy; TEM, Transmission electron microscopy; HR-TEM, High-resolution transmission electron microscopy; FTIR, Fourier-transform infrared spectroscopy; EDS, Energy dispersive X-ray analysis; DLS, Dynamic light scattering; PSA, Particle size analyzer; XPS, X-ray photoemission spectroscopy; SAED, Selective area electron diffraction; TG/DTA, Thermal gravimetric/differential thermal analysis; ROS, Reactive oxygen species; ZOI, Zone of inhibition; MIC, Minimum inhibitory concentration.

Disclosure

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this manuscript.

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