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Suresh Sagadevan, Is Fatimah, Jayasingh Anita Lett, Md Zillur Rahman,  
Won-Chun Oh, Estelle Léonard

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## Review Article

Suresh Sagadevan\*, Is Fatimah, Jayasingh Anita Lett, Md Zillur Rahman, Estelle Leonard, Won-Chun Oh\*

# Eco-friendly green approach of nickel oxide nanoparticles for biomedical applications

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**Abstract:** The two most prominent areas of nanotechnology and nanoscience are environmental remediation and biomedical applications, which has a strong need to develop cleaner and more eco-friendly methods for preparing functional nanomaterials. This involves incorporating non-toxic chemicals and reagents for converting metal cations into metal or metal oxide nanoparticles (NPs), using readily available plant reagents and microbes as redox mediators. The extracts of these plants and microbes contain varying amounts of phytochemicals and metabolites that act as redox mediators and capping agents to stabilize biosynthesized NPs. Considering these natural reagents for forming metal/metal oxide NPs, the present work aims to provide a complete review of the green fabrication of nickel oxide (NiO) NPs using extracts from various plant and microbial sources. In addition, the performance of various biosynthesized NiO NPs and their potential uses in biological applications are discussed.

**Keywords:** nickel oxide nanoparticles, green synthesis, biomedical applications

\* **Corresponding author: Suresh Sagadevan**, Nanotechnology & Catalysis Research Centre, University of Malaya, Kuala Lumpur 50603, Malaysia; Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Islam Indonesia, Kampus Terpadu UII, Jl. Kaliurang Km 14, Sleman, Yogyakarta, Indonesia, e-mail: drsureshnano@gmail.com

\* **Corresponding author: Won-Chun Oh**, Department of Advanced Materials Science and Engineering, Hanseo University, Seosan-si, Chungnam 356-706, Korea, e-mail: wc\_oh@hanseo.ac.kr

**Is Fatimah:** Department of Chemistry, Faculty of Mathematics and Natural Sciences, Universitas Islam Indonesia, Kampus Terpadu UII, Jl. Kaliurang Km 14, Sleman, Yogyakarta, Indonesia

**Jayasingh Anita Lett:** Department of Physics, Sathyabama Institute of Science and Technology, Chennai, Tamil Nadu, India

**Md Zillur Rahman:** Department of Mechanical Engineering, Ahsanullah University of Science and Technology, Dhaka 1208, Bangladesh

**Estelle Leonard:** Laboratoire TIMR UTC-ESCOM, Centre de recherche de Royallieu, rue du docteur Schweitzer, CS 60319, F-60203 Compiègne Cedex, France

## 1 Introduction

Nanotechnology has enabled scientists to develop advanced materials with various nanoscale morphologies, including nanomaterials with unprecedented physical, chemical, and optical properties in the size range of 1–100 nm [1]. Nanomaterials produced by various conventional processes have many advantages and disadvantages, depending on the application in which they are employed [2–4]. The mechanical and chemical synthesis of nanomaterials is typically costly, labor-intensive, and potentially hazardous to the natural environment [5]. In addition, conventional chemical techniques rely largely on specialized lab-scale reactors and may produce toxins that pose significant health and safety issues to humans, ecosystems, and the environment [6]. From this perspective, green synthesis techniques are attracting the attention of researchers to produce safer materials, and many small production units have recently increased their investments in sustainable technologies [7–11]. Nanomaterials mainly produced by chemical and physical processes are used in many areas today. In addition to their inexpensive and modern synthesis methods, it is necessary to have more environmentally friendly substances (such as natural solvents, non-toxic reducing agents, and stabilizers) so that their applications can be expanded to the life science and healthcare sectors [12,13]. Therefore, research organizations are interested in developing cost-effective and environmentally benign nanoparticle (NP) synthesis processes that decrease or avoid hazardous chemicals to prevent the production of redundant and hazardous byproducts.

In general, the synthesis methods for forming NPs are divided into three categories: chemical, physical, and biological. Chemical and physical approaches are usually costly, time-consuming, and impact the environment, whereas biological methods are non-toxic, environmentally friendly, have control over size and shape, at mild reaction conditions, reduce agglomeration, and serve as cheaper alternatives for NP production [14,15]. Biological approaches can be divided into two categories: microorganism-mediated and plant extract-mediated. Plant-mediated synthesis of metal

NPs (MNPs) is preferred over microorganism-mediated synthesis [16]. Plant extracts contain many secondary metabolites that play essential roles in converting metal precursors into MNPs during the synthesis process [17–20]. Numerous alternative methods have been developed to synthesize biocompatible NPs, which have the benefits of avoiding chemical risks, reducing waste, and preventing pollution. Owing to the growing environmental concerns, various efforts have been made to produce NPs using plant extracts. Synthetic approaches based on naturally occurring biomaterials offer an alternative method for generating NPs, which are commonly required in the industrial sector. Green chemistry principles have motivated researchers to develop synthetic techniques, and enzymes [21], microorganisms [22], and plant extracts [23,24], all of which play an important role in the manufacturing of NPs. Compared to other biological and traditional methods, plant extract-based synthesis strategies are more environmentally friendly for alternative nanomaterial synthesis.

Among the many different kinds of MNPs, nickel oxide (NiO) is an inorganic black substance, insoluble in all solvents and susceptible to base and acid attacks [25,26]. The simplest and most practical method for obtaining NiO NPs is heating nickel(II)-based compounds, including hydroxides, nitrates, and carbonates [27,28]. High levels of Ni in soils harm plants, while the same high levels reduce algal growth in water [29]. A minimal amount of Ni must be present in animal feed; however, exceeding the recommended value can be dangerous. For example, animals living near factories are at risk of various cancer types due to nickel levels in the water and soil [30]. However, high levels of Ni at a localized level do not impact the food chain, as Ni is not accumulated in animals or plants [31]. This review article reports recent studies on NiO NPs obtained via plant- and microbe-mediated green synthesis. The biomedical applications of NiO NPs prepared using these methods are also discussed.

## 2 Green synthesis and characterization of NPs

Due to the unique characteristics of metal oxide NPs, including surface functionality and modifying capacity, small size and high reactivity, an enriched surface-area-to-volume ratio, good magnetic properties, and high biocompatibility, these NPs have gained a lot of interest. Economically viable, environmentally sustainable, and socially accessible production of NPs is highly sought after in line with a global aspiration toward green engineering solutions [32]. In recent

years, an extensive study on living organisms, such as bacteria, fungi, yeast, and plants, has used biological intermediates for the transition of inorganic metal ions into MNPs. The availability of polyphenols in naturally derived biomaterials is primarily responsible for the degradation of organic compounds using a green approach (plant extracts). Various plant extracts and their chemical constituents have been extensively studied for their utility in green synthesis, and the polyphenols present in plant extracts are responsible for certain characteristics of NPs [33–35].

### 2.1 Green synthesis

The 12 key principles of green chemistry can be used to establish green synthesis processes [36]; a common example is the biogenic production of NPs. In this approach, naturally occurring chemicals generate NPs with different characteristics. Green chemistry concepts integrate reducing hazardous reagents and increasing chemical process efficiency [37]. Compared with chemically produced NPs, NPs formed by green routes have fewer adverse effects on nature and humans. This method leads to numerous applications of NPs in various disciplines [38]. Plant extracts, plants, and microbes are examples of naturally occurring resources for biogenic synthesis, including the synthesis of metal oxide NPs [38,39]. Other biodegradable natural compounds that can be used as reagents for NP synthesis include enzymes, vitamins, and proteins. Plant extraction techniques offer advantages over others in terms of scaling up for industrial production because of their ease of use and greener processes [40]. Metal oxide NPs have emerged as next-generation, cost-effective disinfectants with enormous potential in the biomedical field, pollutant removal, and other industrial applications owing to their novel properties such as antimicrobial, photocatalytic, UV filtering, and high catalytic activity [41,42]. Figure 1 shows the green synthesis approach for forming MNPs and their applications.

### 2.2 Plant-mediated synthesis

Green synthesis has become an ideal alternative to the currently available chemical and physical synthesis methods because it is cheaper, safer, and more environmentally friendly [43–45]. During green synthesis, metal ions are reduced through putative metabolic activity, which requires relatively minimal activation energy. Much research on metal oxides has been performed using microorganisms and plants, which take

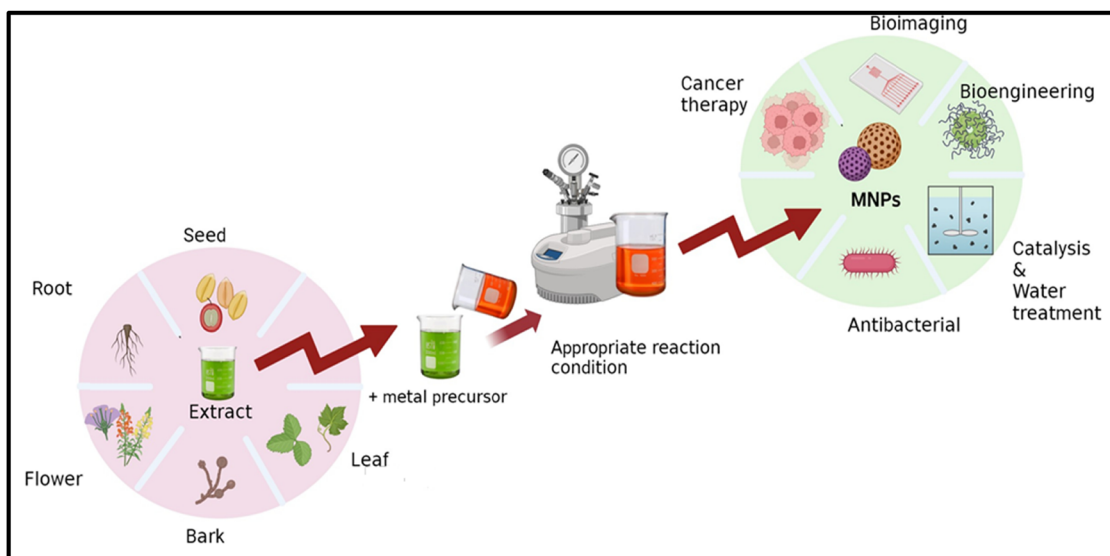


Figure 1: Green synthesis and applications of MNPs.

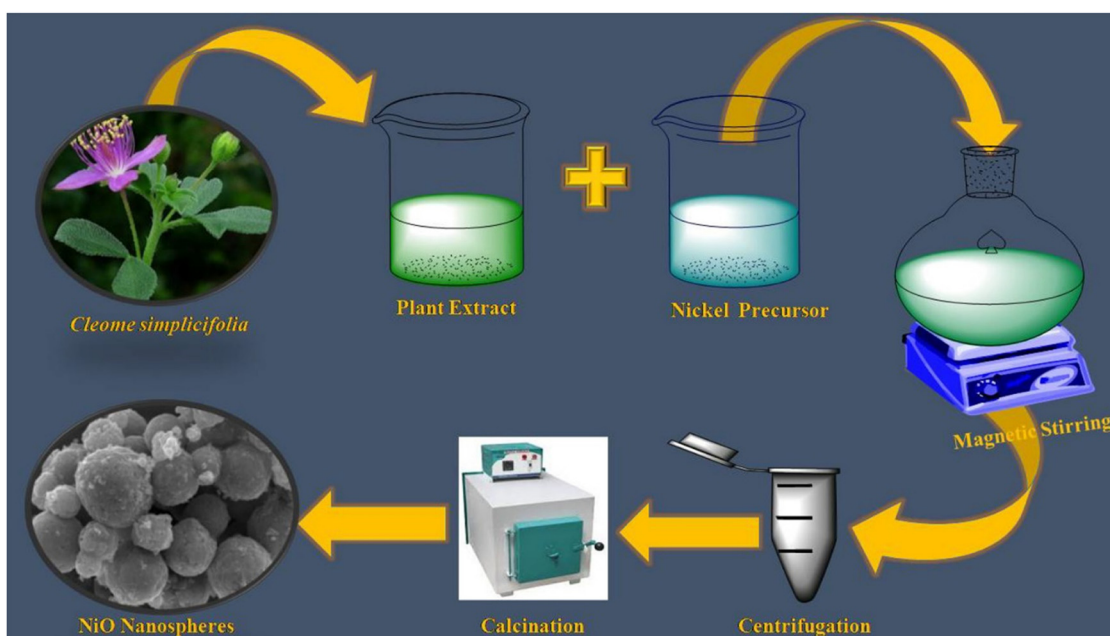
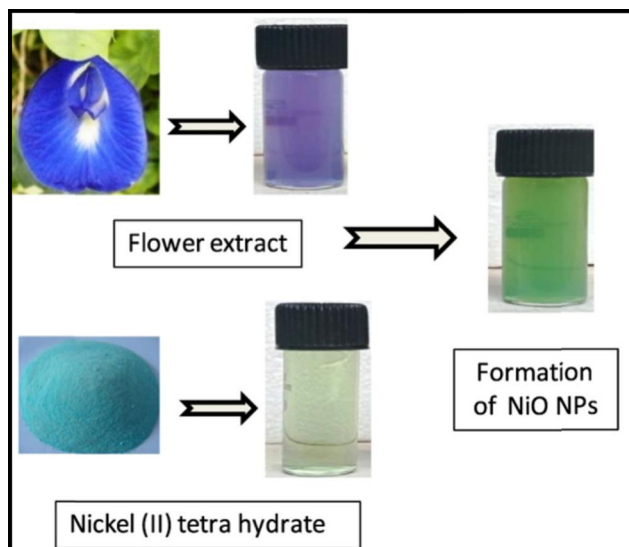


Figure 2: Schematic representation of the *Cleome simplicifolia*-mediated synthesis of NiO NPs [52].

advantage of their ability to mediate precursor redox processes, generate metal/metal oxide NPs, and stabilize the resulting NPs [45–47]. For example, bacteria have been reported to be effectively reducing agents for metal ions, and bacterial cells are easy to culture, making them ideal for producing nanomaterials [48]. Owing to the reductive ability of its proteins and intracellular enzymes, the fungus has been used to produce NPs [49]. NPs can be synthesized on purely green principles by utilizing an eco-friendly solvent solution and stabilizing and reducing

components [50]. Chouke et al. [51] demonstrated a novel *Cleome simplicifolia*-mediated green fabrication of NiO NPs to explore *in vitro* toxicity in Bm-17 and Labeo rohita liver cells (Figure 2).

NiO nanostructures were prepared using the flower extract from *Clitoria ternatea*, as depicted in Figure 3 [52]. Additionally, the antibacterial activity of NiO NPs was tested against Gram-positive *S. aureus* and Gram-negative *E. coli*. Figure 4(a and b) displays high-resolution

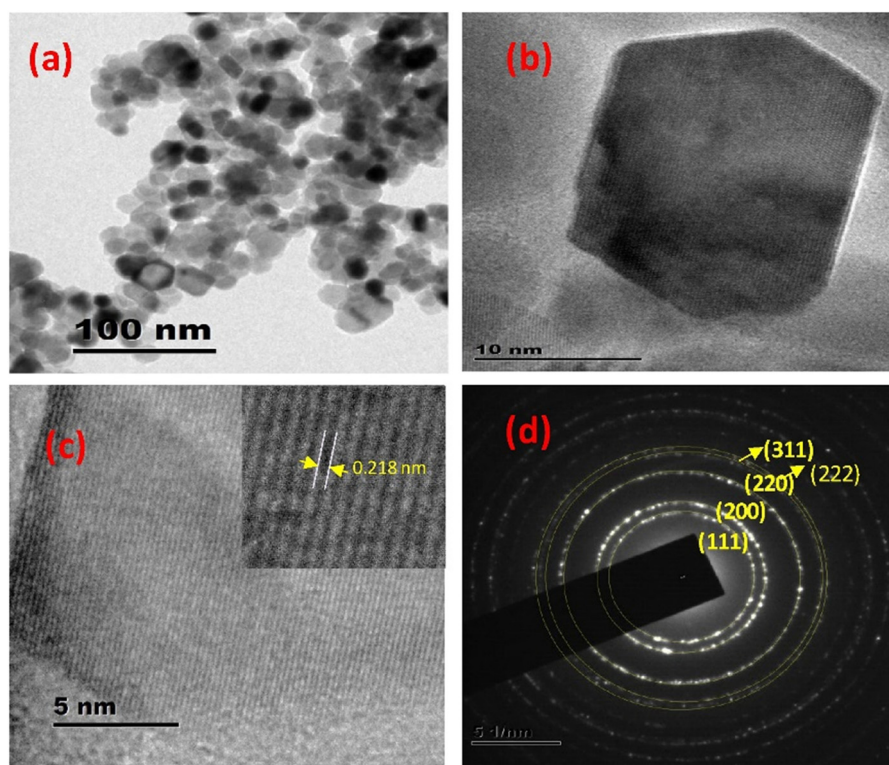


**Figure 3:** Green synthesis of NiO nanostructures using the *Clitoria ternatea* flower extract [52].

transmission electron microscopy (HRTEM) images of the NiO NPs at two different magnifications (100 and 10 nm). The hexagonal shape and lack of agglomeration of the NPs were observed at a magnification of 10 nm. The (2 0 0) plane of NiO was found to have a  $d$ -spacing of 0.218 nm

between the planes (Figure 4(c)). This result demonstrates the pristine crystalline character of the synthesized NPs. Figure 4(d) shows the diffraction rings with concentric circles.

Energy dispersive X-ray (EDX) spectroscopy is a powerful analytical technique that offers precise elemental analysis with exceptional spatial resolution. The fundamental principle of EDX spectroscopy involves directing a highly focused electron beam onto a thin sample and measuring the energy of the resulting emitted X-rays. This energy information allows for identifying atomic species present in the material under investigation. Determining elemental distributions within individual NPs is particularly valuable as it enables the characterization of their optical, catalytic, and magnetic properties [53]. The EDX elemental analysis of co-precipitated NiO indicates that the Ni content is 73.83 wt% and the O content is 12.48 wt%, as shown in Table 1 [54], and the remaining carbon comes from the acetate precursor. Zorkipli *et al.* [55] synthesized NiO NPs using a sol-gel approach, and the NPs were spherical and porous. Another study [56] also showed that NiO NPs synthesized by the biological method have a composition of atomic percentages as determined from the EDX spectrum (Figure 5). In particular, the composition consists of Ni (73.31%) and O (26.69%). Consequently, the atomic ratio of nickel/oxygen is 2.74. The



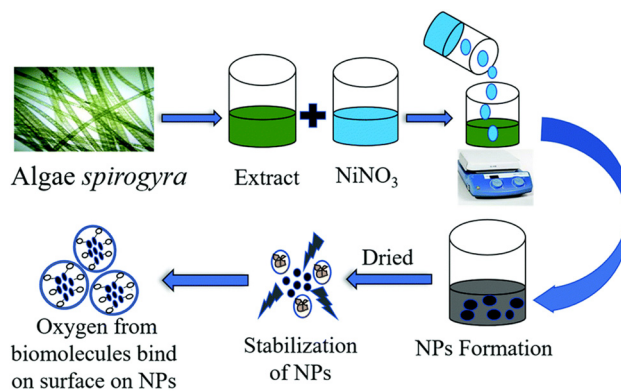
**Figure 4:** HRTEM images of NiO NPs at different magnifications: (a) 100 nm, (b) 10 nm, (c) 5 nm, and (d) selected area electron diffraction (SAED) pattern [52].

**Table 1:** Elemental compositions of the synthesized NiO particles [54]

Element	Weight (%)	Atom (%)
C	13.69	35.87
O	12.48	24.55
Ni	73.83	39.58

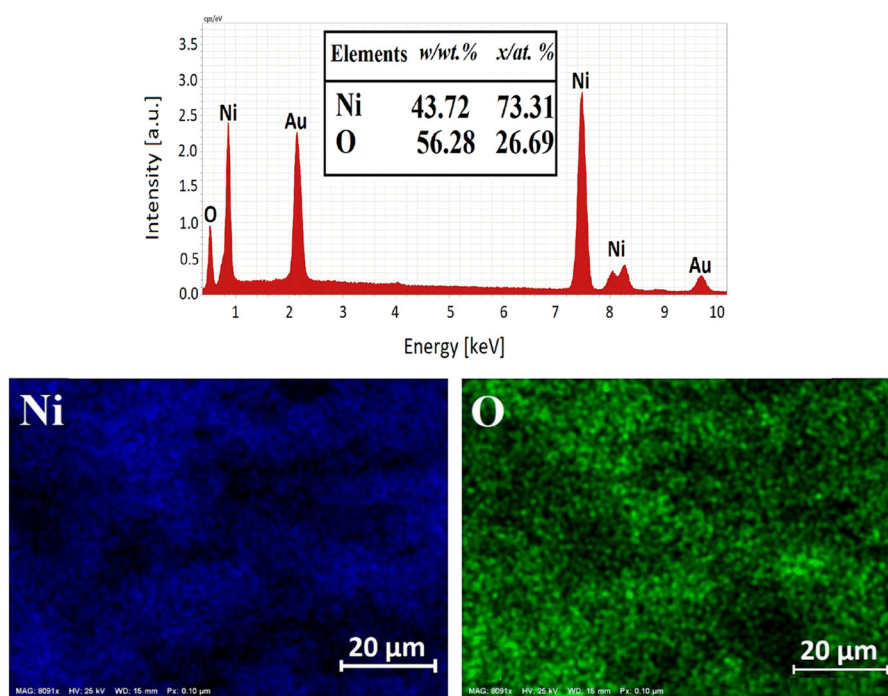
presence of gold (Au) in the EDX spectrum may be attributed to apply a thin layer of gold to the surface of NiO NPs. This coating improves the visual clarity and overall quality of the scanning electron microscopy (SEM) images. The elevated atomic percentage ratio of Ni/O may be associated with the progression of formation during the nucleation of NiO and nickel hydroxide ( $\text{Ni}(\text{OH})_2$ ) during combustion at  $600^\circ\text{C}$ . Notably, when heated at  $600^\circ\text{C}$  for 40 min,  $\text{Ni}(\text{OH})_2$  undergoes full conversion to NiO within the high atomic percentage ratio of Ni/O.

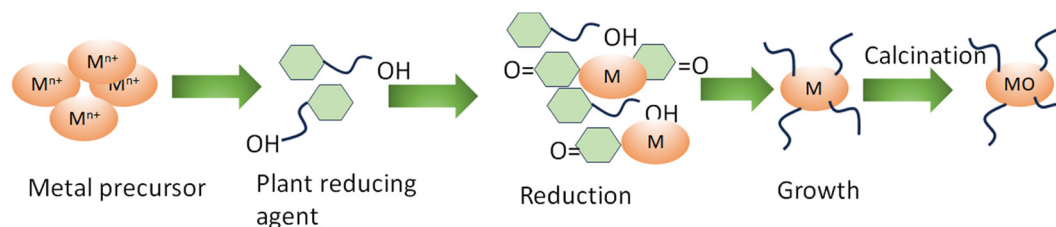
Recently, researchers found that MNPs synthesized using medicinal plants have excellent anticancer effects. Indeed, green-made MNPs have received considerable attention in several medical disciplines [57,58]. Recent discoveries in phytochemicals and NPs have enabled the production of customized NPs using eco-friendly processes [59]. The production of phyto-nano-mixtures was previously achieved by adding bioactive compounds to prefabricated NPs [60], which enabled the loading of bioactive phytochemicals onto

**Figure 6:** Schematic for the step-wise synthesis of NiO NPs [64].

NPs to produce functionalized NPs using a straightforward one-pot synthesis technique [61]. However, as plant extracts typically comprise a complex blend of phytochemicals such as lignans, sugars, flavonoids, polyphenols, xanthenes, aromatic acids, proteins, terpenes, alkaloids, and quinones, it is difficult to identify the specific component that catalyzes the intended NP production [62]. Another issue is that climate change and location can affect phytochemical levels in plants [63]. The probable mechanism for synthesizing NiO NPs is shown in Figure 6 [64].

As a result, the properties of plant extracts are likely to vary between batches, making NP production difficult

**Figure 5:** EDX analysis with elemental mapping of biosynthesized NiO NPs [56].



**Figure 7:** Mechanisms of plant-mediated metal oxide NP synthesis.

with this method. However, there are limitations to this approach, such as the simple and inexpensive process of skipping purification steps to obtain higher-quality chemicals. The plant extracts are used as renewable and environmentally favorable resources, so they are sustainable [63,64]. Recent advances in bio-inspired materials science have increased interest in studying the interaction between materials science and biological systems. In addition to plants, there are also examples of microbes that synthesize

inorganic compounds; for example, magnetotactic bacteria are useful for synthesizing magnetite NPs [65,66]. However, microbial synthesis was found to be more expensive than synthesis using plant extracts. The screening and cultivation of microorganisms usually take a long time. The mechanism of metal oxide NP synthesis using plant extracts is shown in Figure 7. The various plant extracts used to synthesize the NiO NPs are listed in Table 2.

**Table 2:** Different plant extracts obtained from various plant parts are useful for the synthesis of NiO NPs

Plant name	Precursor	Size (nm)	Morphology	Reference
<i>Avicennia Marina</i> leaf extract	$NiCl_2$	30–50	Flacks	[67]
Olive leaves	$Ni(NO_3)_2$	30–65	Spherical	[68]
Aloe vera	$Ni(NO_3)_2 \cdot 6H_2O$	—	—	[69]
<i>Lactuca serriola</i> seeds	$NiCl_2 \cdot 6H_2O$	—	Spherical	[70]
<i>Calendula officinalis</i> (leaf)	$NiSO_4 \cdot 6H_2O$	60.39	Spherical	[71]
<i>Abutilon indicum</i> (leaf)	$Ni(NO_3)_2 \cdot 6H_2O$	—	Cubic	[72]
<i>Capparis decidua</i> (leaf)	$Ni(NO_3)_2 \cdot 6H_2O$	—	Flower	[73]
<i>Areca catechu</i> (leaf)	$Ni(NO_3)_2 \cdot 6H_2O$	5–15	Hexagonal	[74]
<i>Nigella sativa</i> (seed)	$Ni(NO_3)_2 \cdot 6H_2O$	10–50	Spherical	[75]
<i>Lantana camara</i> linn (leaf)	$NiCl_2 \cdot 6H_2O$	21	Hexagonal	[76]
<i>Berberis balochistani</i> (stem)	$Ni(NO_3)_2 \cdot 6H_2O$	31.44	Rhombohedral	[77]
<i>Rosemarinus officinalis</i> (leaf)	$Ni(NO_3)_2 \cdot 6H_2O$	8.09	Quasi-spherical	[78]
<i>Opuntia ficus indica</i> (leaf)	$Ni(NO_3)_2 \cdot 6H_2O$	20–35	Spherical	[79]
<i>Limonia acidissima</i> (fruit)	$Ni(NO_3)_2 \cdot 6H_2O$	23	Spherical	[80]
<i>Raphanus sativus</i> (root)	$Ni(CH_3COOH)_2 \cdot 4H_2O$	34.89	—	[81]
Arabic gum (gum)	$Ni(NO_3)_2 \cdot 6H_2O$	59	Spherical	[82]
<i>Eichhornia crassipes</i> (leaf)	$NiCl_2$	9.1	Spherical	[83]
<i>Limonia acidissima</i> natural fruit juice	$(NO_3)_2 \cdot 6H_2O$	23	Spherical	[84]
<i>Euphorbia heterophylla</i> (L.)	$Ni(NO_3)_2 \cdot 6H_2O$	12–15	Rhombohedral	[85]
<i>Rhamnus triquetra</i> (leaf)	$Ni(NO_3)_2 \cdot 6H_2O$	65	Spherical	[86]
<i>Vernonia amygdalina</i> (leaf)	$NiCl_2 \cdot 6H_2O$	—	Octahedral	[87]
<i>Phoenix dactylifera</i> (Dates)	$Ni(NO_3)_2$	—	Rod	[88]
<i>Plectranthus amboinicus</i> (leaf)	$Ni(NO_3)_2$	100	Spherical	[89]
<i>Ananas comosus</i> leaf	$NiCl_2 \cdot 6H_2O$	—	—	[90]
Stevia (leaf)	$Ni(CH_3COOH)_2 \cdot 4H_2O$	10–40	Spherical	[91]
<i>Solanum trilobatum</i> leaf	$Ni(NO_3)_2$	25–30	Cylindrical and rod	[92]
<i>Leucas aspera</i> (leaf)	$NiCl_2 \cdot 6H_2O$	—	Spherical	[93]
<i>Allium jesdianum</i> (leaf)	$Ni(NO_3)_2 \cdot 6H_2O$	—	Spherical	[94]
<i>Cydonia oblonga</i>	$Ni(NO_3)_2 \cdot 6H_2O$	74.5	—	[28]
<i>Zingiber officinale</i> and <i>allium sativum</i> (roots)	$Ni(NO_3)_2$	<50	The cubical and more spherical shape	[95]

### 2.3 Microbe-mediated synthesis

The essential mechanism for forming NP biogenesis involves the reduction of metal ions by the biomolecules present in living things. This process creates a large number of NPs with well-defined sizes and morphologies that can be isolated from the contaminants. Many researchers applied various techniques for the synthesis of NPs by using bacteria, actinobacteria, viruses, fungi, yeast, and microalgae, as these microorganisms have the innate capability to multiply in various environments [96–102]. Bacteria and microalgae can produce unique nanomaterials such as exopolysaccharides, nanocellulose, and nanowires [103–105]. The production of NPs using microorganisms is far safer than chemical and physical processes [96–102]. Bacteria are preferred over other microorganisms for NP production because they can be cultured in a laboratory setting and their growth rate can be regulated. Microorganisms can adapt to environments with higher metal concentrations and can reduce inorganic elements to NPs via extracellular or intracellular pathways [96]. Microbes take up metal ions from their environment/media and the microorganisms ingest metal ions from the culture media and enzymatically reduce them into their elemental form [106]. During the extracellular synthesis of NPs, the extracellular microbial enzymes, especially the reductase-containing supernatant, are extracted from the microbial culture by centrifugation and allowed to react with the metal ions to synthesize NPs [107–109]. Metal ions are bio-reduced in a cell-free supernatant, resulting in the production of NPs [110]. For microbial

intracellular manufacturing, the cellular mechanism of the microbe is exploited for NP production. Initially, sufficient microbial biomass is obtained by following an appropriate culture protocol [111]. Then, the microbes are supplemented with metal ions and cultured further under optimal conditions for the reduction process, which will be observed by specific chromatic changes. Microbes synthesize NPs as a part of their defense mechanism, as high reactive ion concentrations in their environment are detrimental to their sustainability. To prevent cell death, the microbes use their cellular machinery to convert the reactive ions into a stable form of the respective NPs of reduced ions. Cell damage can occur when the NPs are generated in excessive concentrations. The microbes can tolerate a range of environmental parameters such as ionic strength, pH, temperature, and pressure, but the tolerable range is often limited, and any further change beyond this range due to a longer reaction time can be detrimental to the microbes [42].

## 3 Biological applications

### 3.1 Antibacterial and antifungal activity

The NiO NPs are synthesized with *aloe vera* gel and heated at 300–500°C to study their antibacterial properties, as the free radical nature of NiO NPs can impair microbial cell proliferation [69]. Figure 8(a) shows the zone of inhibition

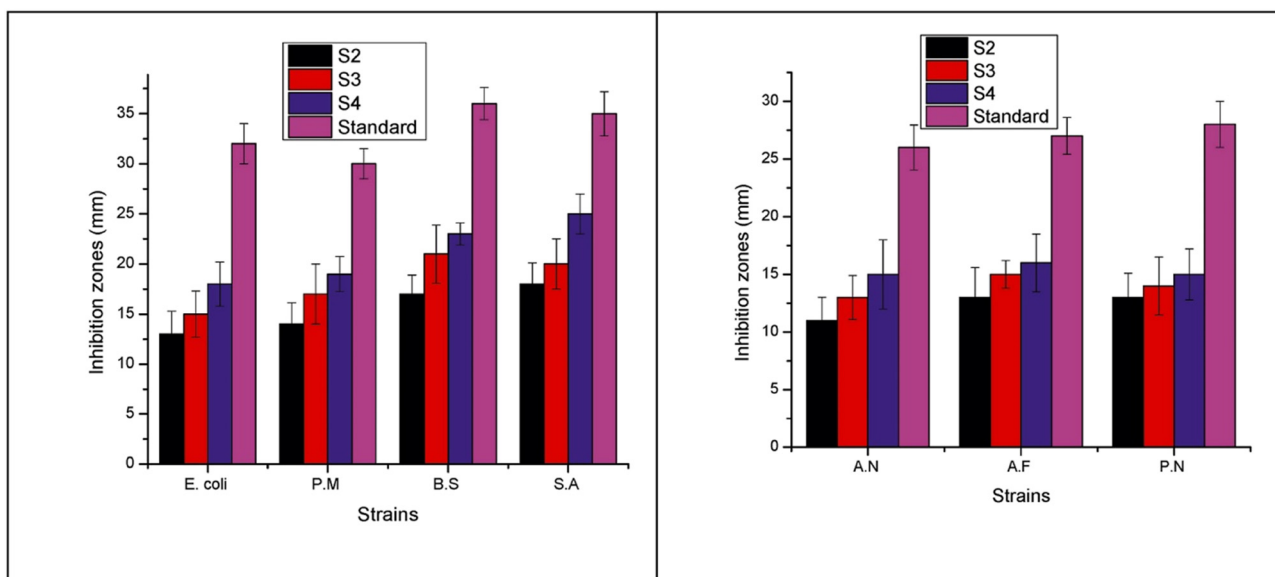


Figure 8: ZoI of NiO NPs against (a) bacterial and (b) fungal strains [69].

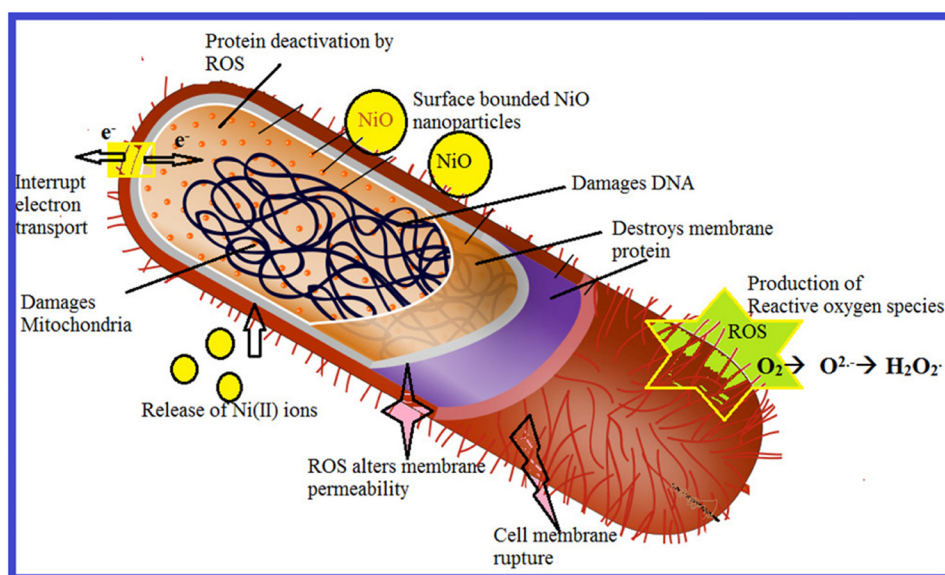


(Zol) for the antibacterial activity of *Bacillus subtilis*, *Pasteurella multocida*, *Staphylococcus aureus*, and *Escherichia coli*, where the NPs showed significant antibacterial activity against all the tested bacteria. Among all tests, the NiO NPs made from *aloe vera* gel and annealed at 500°C have excellent antibacterial activity. In this, regard the NiO NPs have stronger antibacterial activity toward Gram-negative bacteria than Gram-positive bacteria due to a single layer of peptidoglycan in the Gram-negative bacteria's cell wall, while Gram-positive bacteria have a multi-layered solid peptidoglycan. According to Arokiyaraj *et al.* [112], the NiO NPs are more effective against Gram-positive bacterial strains. Similarly, the NiO NPs synthesized were tested for antifungal activity against the fungal strains *Aspergillus niger*, *Aspergillus flavus*, and *Penicillium notatum*. The analysis indicated the observation of significant antifungal activity as well. However, this activity is lower than the antibacterial activity due to the increased resistance of fungal strains compared to bacterial strains (Figure 8b).

The particle size of NiO NPs is attributed to its antimicrobial activity, as it improves the NPs' dispersibility and causes cell damage due to the binding of the extracellular  $\text{Ni}^{2+}$  to the intracellular  $\text{Ca}^{2+}$  metabolism. The electrostatic interaction between Ni ions and the membrane of a microbial cell is stronger in NPs, resulting in significant activity [113]. The activity is also influenced by the consistency, shape, and size of the NPs [114]. According to a study, NPs change bacteria and fungi's membrane shapes by interacting with them and inhibiting their growth. It disrupts normal mobility during the development of the

plasma membrane, resulting in cell death [115]. Since the prepared NiO NPs have a smaller particle size than micro-sized particles and a high surface area to volume ratio, the NPs react with phosphorus or sulfur in the DNA, stopping protein production and causing cell death [116]. The reactive oxygen species (ROS) structure promotes antimicrobial effects that are part of normal metabolism in living organisms [117]. The onset of ROS destroys cells, which defines the formation of extremely reactive radicals that destroy cell membranes, proteins, the intracellular system, and DNA [118]. The mechanism for the various damages due to the cell lines is shown in Figure 9 [119].

Various mechanisms are proposed for the action mode of MNPs against microbiological organisms, which include (1) cell wall/membrane degradation, (2) MNP-generated oxidative stress, and (3) deterioration/damaging of intracellular proteins due to NP penetration. Because of their nano size, NPs penetrate the intracellular cell matrix, disrupting intracellular absorption and causing cell injury. Electrostatic interactions cause NiO NPs to disrupt cell membranes. Due to electrostatic attraction, the  $\text{Ni}^{2+}$  ions produced by the NiO NPs interacted with the bacterial cell surfaces of opposite charge and disrupted the cell membrane and its normal physiology and functions. Also, the NPs are so narrow that they can easily pass through the cell wall/membrane and disrupt the cellular components by several routes, which include [120] (1) DNA damage/dysfunction by the interaction of NiO NPs, rendering them unable to perform the regular functions; (2) breaking of hydrogen, oxygen, and phosphate bonds that denature the



**Figure 9:** Schematic mechanism of the toxicity effect of NiO NPs against bacteria [119].

proteins and associated alteration of protein structure; and (3) oxidative stress-mediated damage of mitochondria. Furthermore, these results are consistent with previous research results that indicate the highly active antibacterial activity of NiO NPs against multiple strains of bacteria [121–124]. Since NiO NPs have promising bioactivity in addition to antibacterial activity, they have potential as medicinal antibacterial agents in the medical sector. Furthermore, eco-friendly routes for synthetic purposes must be developed and used to ensure the environmental safety of green synthetic routes and avoid environmental pollution. The routes using biological agents are one of the best solutions to avoid problems associated with conventional synthetic techniques [125,126]. Ali et al. [70] described the environmentally friendly production of Ni<sup>0</sup>/NiO NPs using the *Lactuca serriola* seed extract with bactericidal activity against human pathogenic microorganisms. The surface morphology of the Ni<sup>0</sup>/NiO NPs is shown in Figure 10. The spherical morphology of the Ni<sup>0</sup>/NiO NPs with a small agglomeration can be attributed to the induced magnetic interaction and polymeric adhesion among the NiO/NiO NPs, as evident from the field emission scanning electron microscopy (FESEM) images. The antibacterial effect of MNPs is strongly dependent on size and surface charges and thus causes changes to the cell membrane and blocks

transport channels. When nano-sized metallic ions reach the cell, they generate ionization that can disrupt intracellular structures and trigger cell death [127,128]. Multifunctional ROS are formed by the combination of short-lived oxidants, including superoxide radicals (O<sup>2-</sup>), hydroxyl radicals (OH<sup>-</sup>), singlet oxygen (O<sup>2-</sup>), and hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) (Figure 11) [129,130]. Due to their extremely high reactivity, such oxidants produce ROS with the strong ability to destroy cell membranes, DNA, mRNA, proteins, ribosomes, and peptidoglycans [131]. In that view, the traditional disk diffusion method was used to evaluate the antibacterial activity of Ni<sup>0</sup>/NiO NPs against different cultures of *E. coli*, *S. aureus*, *Staphylococcus epidermidis*, *Bacillus pumilus*, *B. subtilis*, *Pseudomonas aeruginosa*, and *Bordetella bronchiseptica* bacteria. From the analysis, the Ni<sup>0</sup>/NiO NPs at a 20 g/mL concentration showed outstanding antibacterial efficacy (as compared to the ciprofloxacin drug) against 7 out of 8 harmful bacteria included in this study, where a ZoI of 6.05–15.04 mm was observed [127–130]. Also, the antibacterial activity of Ni<sup>0</sup>/NiO NPs was investigated against serially diluted bacterial strains with varying concentrations of Ni<sup>0</sup>/NiO NPs (10 and 20 µg/mL). The results showed that bacterial growth was significantly reduced at both concentrations of Ni<sup>0</sup>/NiO NPs, and such an inhibitory effect on pathogenic bacterial growth by the

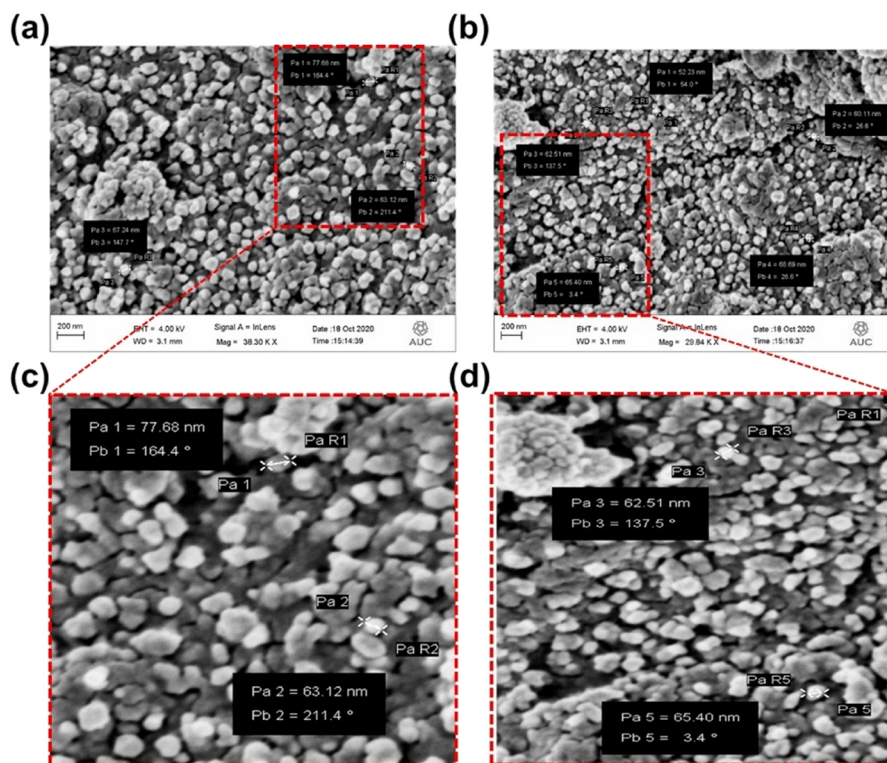
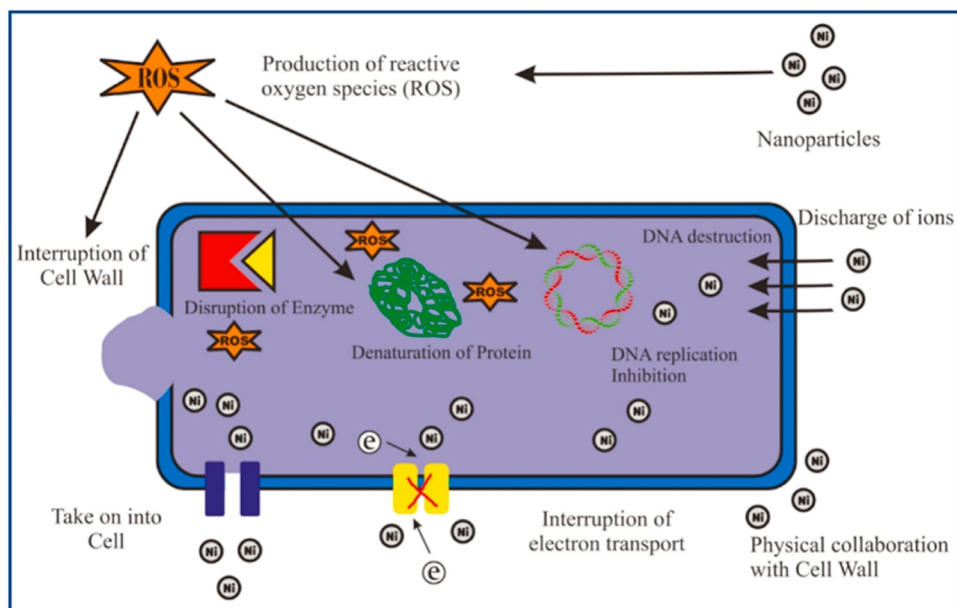


Figure 10: (a–d) FESEM images of Ni<sup>0</sup>/NiO NPs [70].



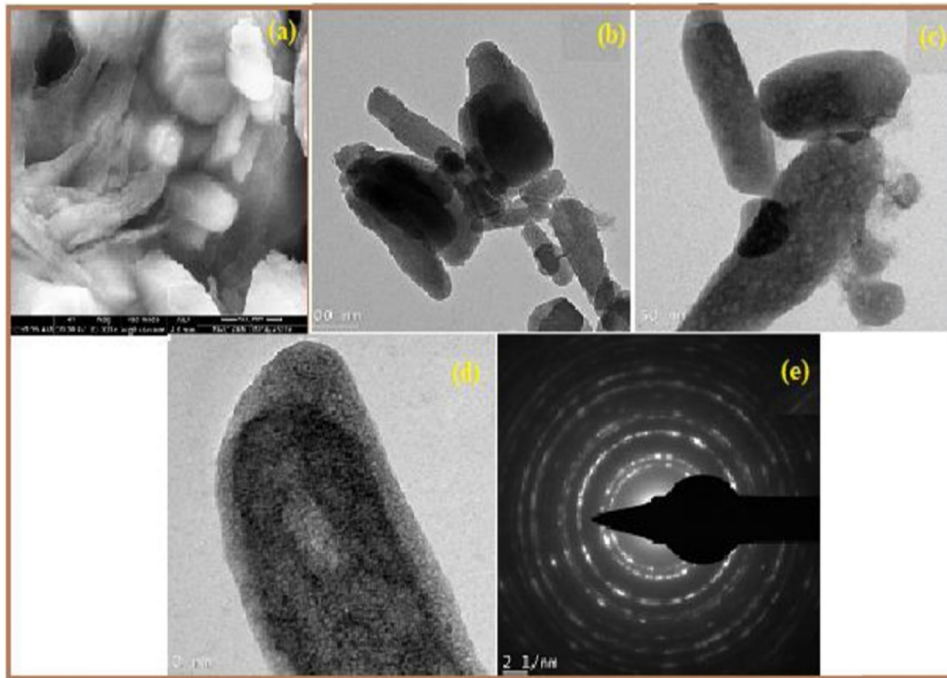
**Figure 11:** Different possible mechanisms associated with the antimicrobial activity of  $\text{Ni}^0/\text{NiO}$  NPs [70].

biologically synthesized  $\text{Ni}^0/\text{NiO}$  NPs was most likely responsible for the inclusive activity. As a result,  $\text{Ni}^0/\text{NiO}$  NPs were observed for bacteriostatic activity at low concentrations and bactericidal activity at high concentrations.

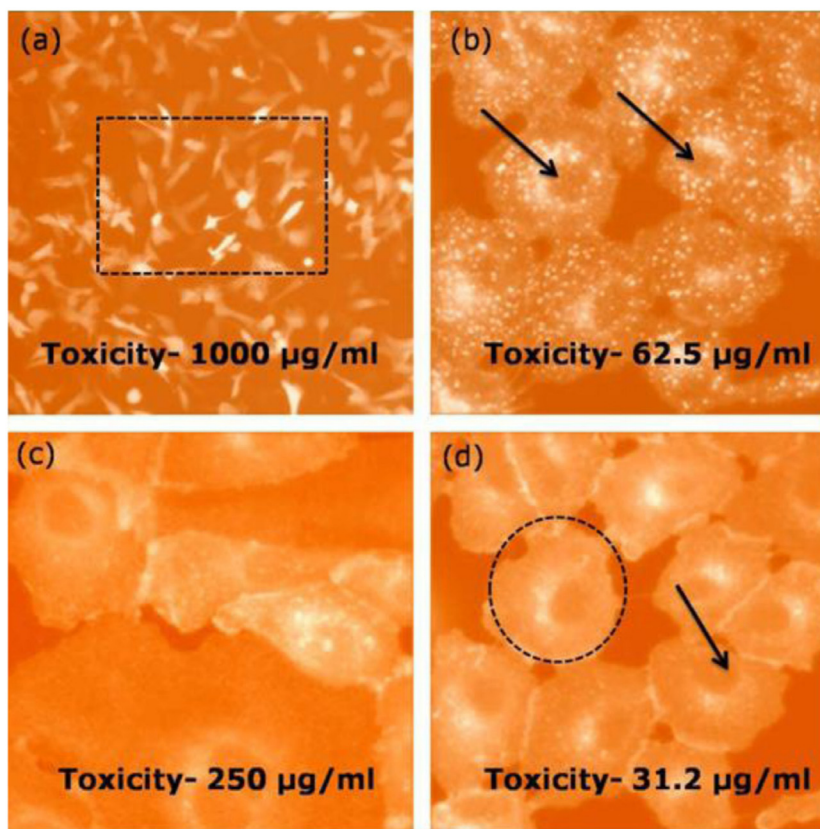
Another study used the hot plate combustion method to synthesize NiO NPs, utilizing the *Solanum trilobatum* leaf extract as the fuel and nickel nitrate as the precursor [92]. The high-resolution scanning electron microscopy (HR-SEM) images support the shape of the NiO NPs, as shown in Figure 12. The surface does not have a cylindrical or rod-like form. Some of the elements that influence the morphology attained are the preference of the solvents, capping agents, and experimental parameters such as temperature and time, which affect the reaction mechanism. As a result, the approach used nickel nitrate, and the fuel, an extract of *Solanum trilobatum* leaves, favored the synthesis of NiO NPs with cylindrical and rod-like morphologies. Therefore, it was concluded that the synthesis of NiO NPs with a large surface area and small particle size has made possible by the *Solanum trilobatum* leaf extract, making them suitable for biological applications [92].

Similar to any other cell viability test, the cytotoxicity of NiO NPs prepared using the *Solanum trilobatum* leaf extract was also tested using the 3-(4,5-dimethyl-2-thiazolyl)-2,5-diphenyltetrazolium bromide (MTT) assay, where the analysis is based on the reduction of the MTT dye to formazan crystals. For example, in a previous study [92], the cell viability of A549 cells was tested using varying concentrations of NiO NPs (up to 1,000  $\mu\text{g}/\text{mL}$ ), and the results

indicated negligible cell viability losses up to 31.2  $\mu\text{g}/\text{mL}$  and a significant reduction above that concentration, meaning that the cell viability is dose-dependent. The fluctuation in percent cell viability in response to NiO NPs at their change of concentrations was observed at change in absorbance which has directly influenced by the number of viable cells [92]. The observed absorbance for the control cells was 0.481 OD (optical dispersion) and 0.083 OD for the cells that reacted with 1,000  $\mu\text{g}/\text{mL}$  NiO NPs, indicating that the cells' metabolic activity reduced at the NPs' maximum concentration. Furthermore, to understand the physiological changes occurring to the cells due to NiO NP treatment, morphological studies are performed against the A549 cells at varying concentrations of NiO, as shown in Figure 13(a–d). The regulated cells have a normal, smooth, and uniform morphology, but the cells exposed to NiO NPs have an uneven morphology due to cell division and swelling following death. The extent of cell damage is dose-dependent, and the cell nuclei changed dramatically, indicating that the NiO NPs impact the cell nuclei and their morphology to interrupt regular biochemical functions. The NiO NPs generated ROS and associated oxidative stress, which could decrease the cell's biological activity [132]. For example, following the treatment of A549 cells were observed to have ROS damage. In general, ROS induces DNA damage, a basic site, cell wall damage, oxidized base lesions, breaks single and double strands, and oxidizes proteins and lipids, resulting in the formation of dangerous electrophilic species that alter cellular signal transduction pathways, and lead to cell



**Figure 12:** (a) HR-SEM image of NiO NPs, (b–d) HR-TEM images of NiO NPs, and (e) SAED pattern of NiO NPs [92].



**Figure 13:** (a–d) Morphological changes due to the treatment of varying concentrations of NiO NPs formed using *Solanum trilobatum* leaf extract [92].

death [133]. In addition, oxidative stress is generated due to electron transfer from ROS such as  $\cdot\text{OH}$ ,  $\text{H}_2\text{O}_2$ , and  $\text{O}_2^{\cdot-}$  [134]. Several studies have also indicated that the metal ions released from the MNPs are a significant component of cytotoxicity [135]. For instance, the  $\text{Ni}^{2+}$  ions released by the NiO NPs following the treatment of A549 cells were found to induce oxidative stress induction both directly and indirectly, eventually dysfunctioning the mitochondria [136]. Also, the release extent of  $\text{Ni}^{2+}$  ions is determined by the intrinsic properties of bulk materials, particle size, surface properties, and crystallinity of NiO. Hedberg *et al.* [137] suggested that the increased metal ion release is associated with ligand-induced metal release processes. They also showed that the  $\text{Ni}^{2+}$  ions released into the cell culture medium by the NiO particles were absorbed by the A549 cells and further tightly bound to the cell membrane to eventually form stable complexes with various ligands, such as proteins and amino acids. Moreover, the toxicity associated with NiO NPs and the released Ni ions is significantly higher in the nano-sized particles than in the corresponding micro-sized ones [138]. In the nano-sized NiO NPs, considerable cytotoxic effects were observed due to the specific surface area, metal ion-releasing ability, strong physicochemical activities, high crystalline effects, etc. As a result, the NiO nanomaterials thus synthesized by the green synthesis routes serve as promising biomaterials for cytotoxic induction in cancer cell lines (e.g., A549 cells) through oxidative damage by the production of ROS.

### 3.2 Cytotoxicity activity

The NP's research for cancer diagnosis and treatment is increasing nowadays. Sabouri *et al.* [82] studied the cytotoxic effects of NiO NPs on normal CN cell lines and cancer U87MG cell lines using gum arabic polymer. The analysis results indicated that NiO NPs have contributed to a 50% cancer cell reduction at only 16  $\mu\text{g}/\text{mL}$  concentration, thereby confirming this value as the half-maximal inhibitory concentration ( $\text{IC}_{50}$ ). Also, a steep increase in cell viability loss with increased NiO NP concentration was observed, implying that the cytotoxicity is dose-dependent, which can severely impair cancer cell survival. According to the results of this study, the lethal effect of NiO NPs formed by the green synthesis routes is greater in cancer cells than in normal cells, thus supporting the potential role of NiO NPs in cancer treatment. Ghazal *et al.* [28] used the *Cydonia oblonga* extract to carry out the biosynthesis of NiO NPs in an environmentally friendly and cost-effective manner,

using the same MTT test to understand cell viability and bioavailability [139]. Figure 14 shows FESEM/PSA images of NiO-NPs prepared using an extract of *Cydonia oblonga* at 400°C [28]. According to the SEM results, the sample's morphology, with an average particle size of roughly 74.5 nm, was investigated.

Figure 15 provides the *in vitro* cell viability studies following NiO NP treatment in the concentration range of 0–400 mg/mL, where the results have indicated no significant cytotoxicity up to 400 mg/mL concentration. This suggests that the L929 cells can tolerate the synthesized NPs, thereby indicating their biocompatibility.

Chouke *et al.* [51] investigated the *in vitro* toxicity of bioinspired NiO NPs on the growth of the *B. mori* cell line (Bm-17 cells) and the liver cells of *L. rohita* fish, as illustrated in Figure 16. Agar gel electrophoresis was used to assess cell viability, necrotic cell morphology, and DNA damage. NiO NPs promote significant vacuolization in an insect cell line (Bm-17 cells).

### 3.3 Anticancer activity

Kganyago *et al.* [140] reported the preparation of NiO NPs using the *Monsonia burkeana* plant extract and studied their potential antibacterial activity against numerous bacterial strains and anticancer activity. As shown in Figure 17, the cell viability results analyzed using both MUSE and MTT assays indicated that the treatment of A549 cells with different concentrations of NiO NPs does not affect the viability (>95% of cells are viable) up to a 24 h incubation period. The analysis showed that the plant extract-mediated formation of NiO NPs was ineffective against the lung cancer cells even at high concentrations during the first 24 h period. However, these results contradicted the recent findings and demonstrated that NiO NPs formed with *Moringa olifera* continued to exhibit antiproliferative activity against the HT-29 colon cancer cells. This disparity can be attributed to the changes in phytochemicals in plants such as *Moringa olifera* versus *Monsonia burkeana*, specificity, and incubation time. Also, the kind of cell line matters, as the plant extract used for the formation of NPs has previously been shown to serve as a blood purifier, and it is not surprising that the same plant-derived NPs are effective against bacterial strains. In addition, light microscopy provided morphological analysis of A549 cells, indicating that the plant-derived NiO NPs had no lethal effects on the cells even after 24 h. However, there was a significant effect on the cell growth. Plant-made NiO NPs significantly reduced the development of A549 cells. The

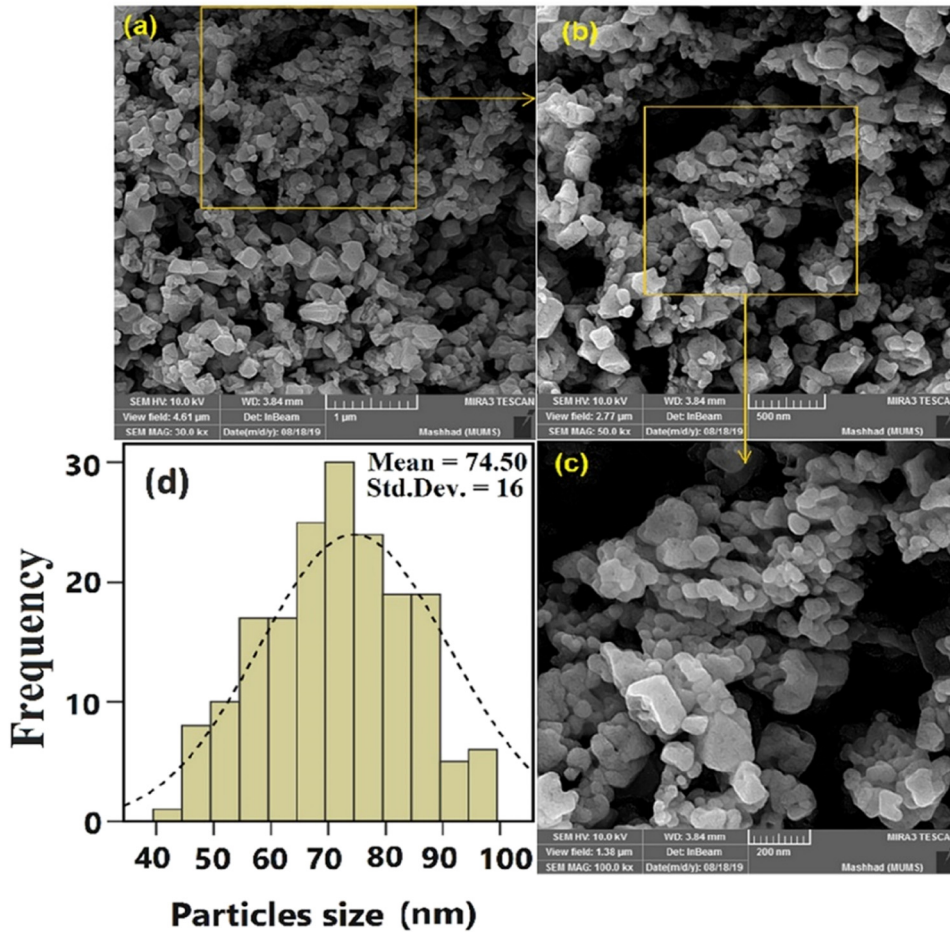


Figure 14: (a–c) FESEM images and (d) PSA of NiO-NPs [28].

morphological form of untreated and treated A549 cells is shown in Figure 18(a–d). The green circles indicate that both groups retained the usual epithelial cell shape. The NiO NPs do not affect the morphology of A549 cells and show no

cytotoxicity toward A549 in both treatments, as confirmed by the viability profile data. However, treated cells have more space than the corresponding cells without any treatment. Observing some cells with classic apoptotic features (e.g., red circles) can be linked to the natural cell death associated with cell cycles. NiO NPs produced from *Monsonia burkeana* do not affect the viability of non-cancerous HEK 293 cells of the embryonic kidney, thereby supporting the fact that the particles have the potential for the sustainable treatment of cancer and are non-harmful even if consumed.

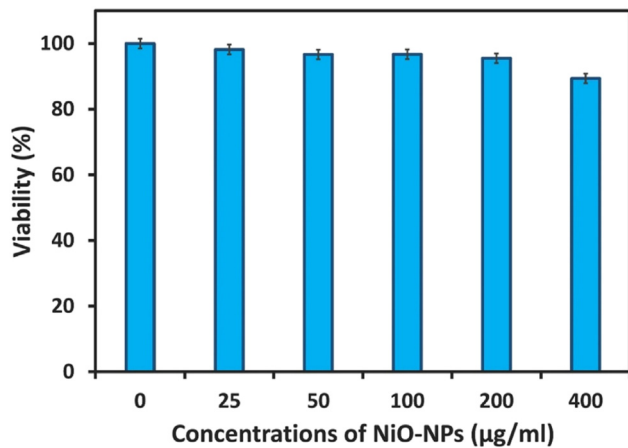
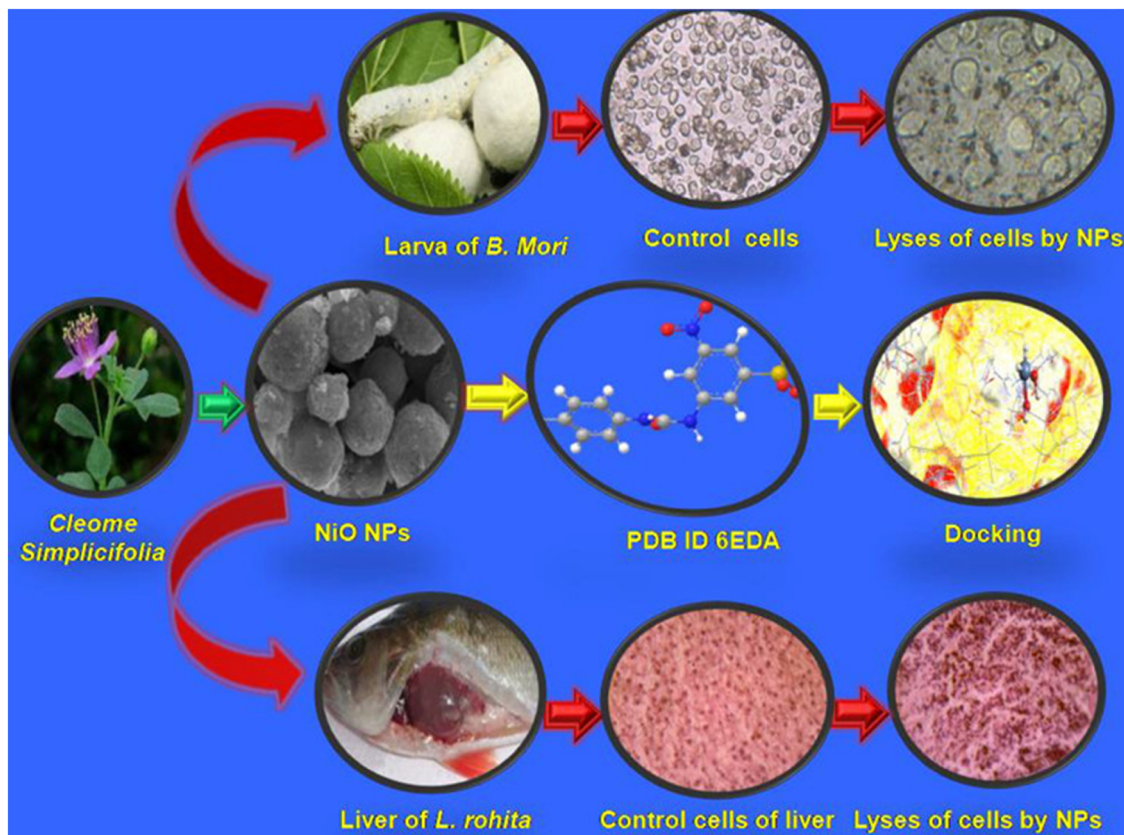


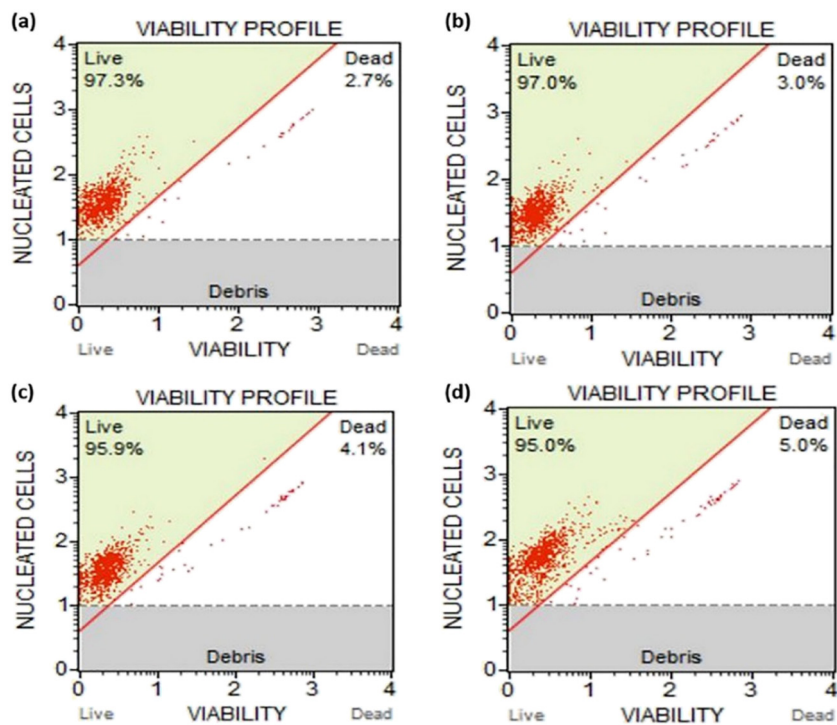
Figure 15: Cytotoxicity studies of varying concentrations of NiO NPs (up to 400 µg/mL) by MTT assay [28].

### 3.4 Antioxidant properties of NiO NPs against DPPH

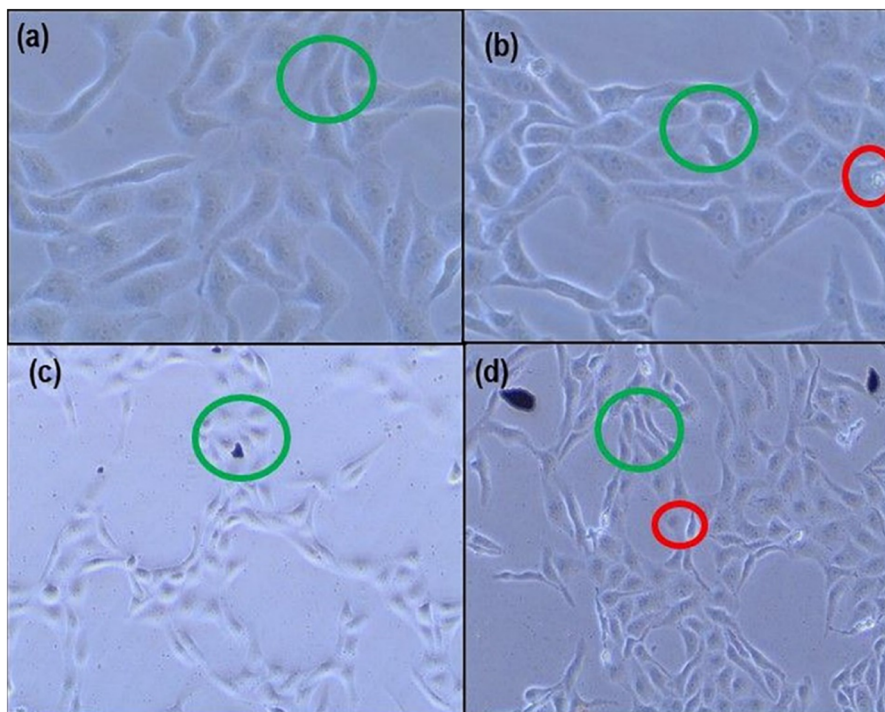
Zhang et al. [71] effectively prepared NiO NPs in an aqueous medium using the *Calendula officinalis* leaf extract. They also tested the DPPH radical scavenging potentials of particles coated with the leaf extract by comparing them with BHT as a typical antioxidant. In general, free radicals are species that do not have a complete electron shell and



**Figure 16:** Schematic representation of *in vitro* toxicity of bioinspired NiO NPs [51].



**Figure 17:** Flow cytometry studies of A549 cells following the treatment of NiO NPs at different profiles of (a) untreated, (b) 125 µg/mL, (c) 250 µg/mL, and (d) 500 µg/mL [140].



**Figure 18:** Morphological observation of A549 cells: (a) untreated, (b) 125  $\mu\text{g/mL}$ , (c) 250  $\mu\text{g/mL}$ , and (d) 500  $\mu\text{g/mL}$  NiO NP treatment [140].

can speed up chemical reactions more than others. They develop when the human body is exposed to cigarette smoke and radiation. The main human free radical is oxygen. When an oxygen ( $\text{O}_2$ ) molecule is exposed to radiation, it steals an electron from other molecules, destroying DNA and other molecules. These changes can lead to chronic diseases such as heart disease, muscle failure, diabetes, and cancer [141]. Antioxidants, which act like a broom against free radicals, are recognized as effective treatments for destroying free radicals and regenerating damaged cells. More importantly, laboratory evidence suggests that antioxidants can significantly reduce cancer risk [57,142–144]. Aqueous leaf extracts of *C. officinalis*, BHT, and NiO NPs have  $\text{IC}_{50}$  of 328, 204, and 192  $\text{mg/mL}$ , respectively (Figure 19). The MNPs have high potential for DPPH inhibition. The results of our investigation are consistent with many other studies examining the mutual effects of herbs and metal salts on anti-oxidant capacity against DPPH [57,142–144]. In general, MNPs have outstanding antioxidant properties, with the antioxidant properties of NiO NPs being well documented. When NiO NPs are made from medicinal plants, the Ni element forms a powerful compound with phenolic and flavonoid chemicals, resulting in unique antioxidant properties.

### 3.4.1 DPPH radical scavenging assay

Kumar et al. [84] demonstrated a facile green synthesis of NiO NPs using the natural *Limonia acidissima* fruit juice via a solution combustion technique. Antioxidants are characterized by their ability to scavenge free radicals. Another important characteristic of antioxidants is their ability to donate hydrogen or electrons to oxidizing agents. DPPH is a stable free radical with an unpaired electron on the nitrogen atom and an absorbance of 517 nm (a deep violet color). The color changed to yellow when the odd electron was connected to the DPPH [145]. The ability of antioxidant molecules to donate hydrogen is required for scavenging free radicals [146]. The radical scavenging activity of NiO NPs against DPPH is significant (Figure 20a). In addition, as NiO NPs were prepared by combustion using the *Limonia acidissima* fruit juice, with a possibility of phytochemical adsorption on their surface. Compared to the reference substance, BHT, NiO NPs proved to be more effective. The antioxidant activity of NiO NPs is comparable (2.73  $\mu\text{g/mL}$ ) to that of the reference chemical BHT (2.21  $\mu\text{g/mL}$ ). NiO NPs have significant hydroxyl radical scavenging activity (Figure 20b).



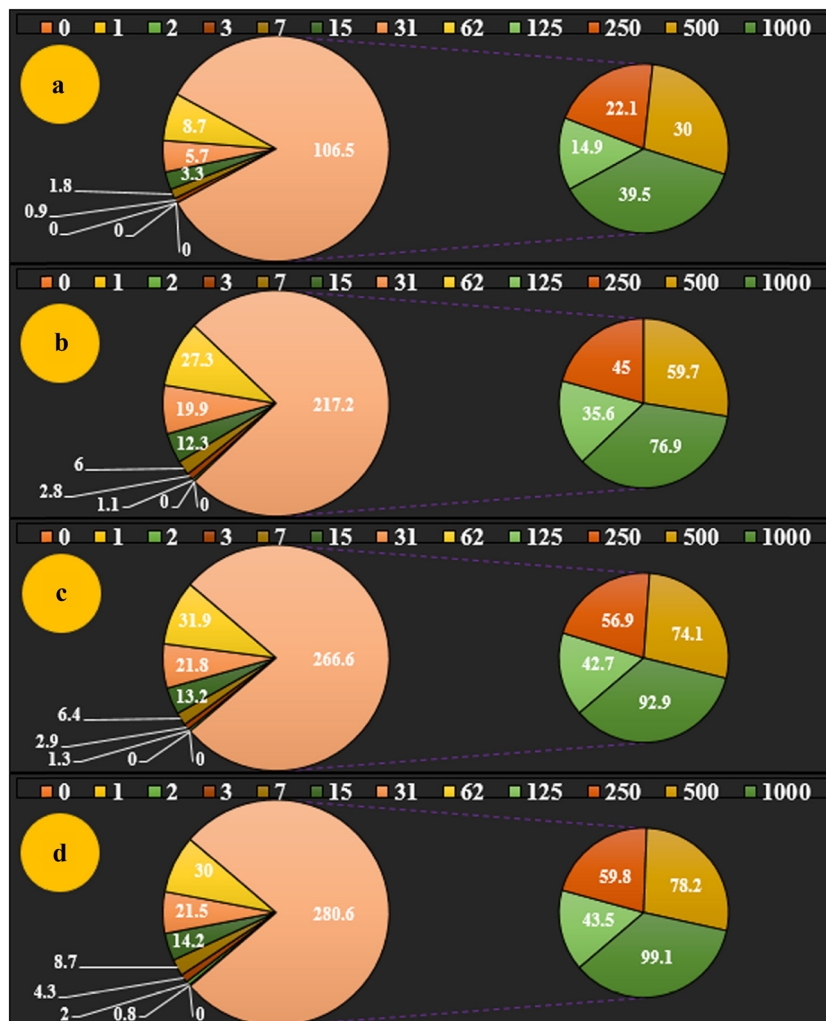


Figure 19: (a) Comparison of the antioxidant nature of NiSO<sub>4</sub>, (b) aqueous extract of *C. officinalis*, (c) NiO NPs, and (d) BHT against DPPH [71].

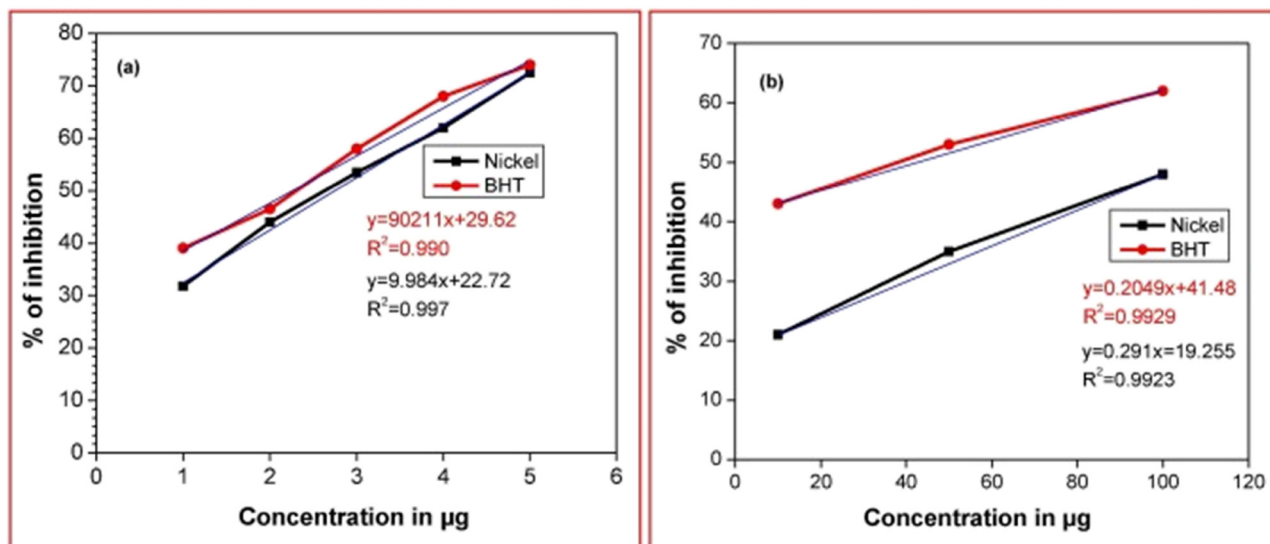


Figure 20: Comparison of antioxidation effects of NiO NPs by (a) DPPH radicals and (b) hydroxyl radicals [84].

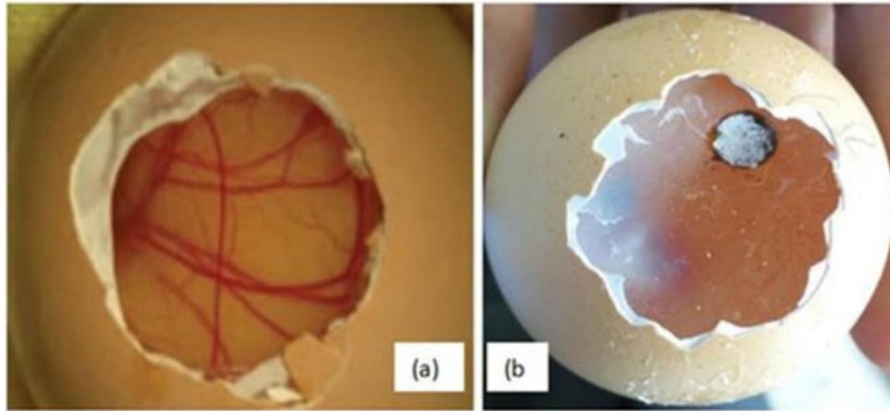


Figure 21: (a and b) CAM model assay provided suppression of *in vivo* angiogenesis by NiO NPs [84].

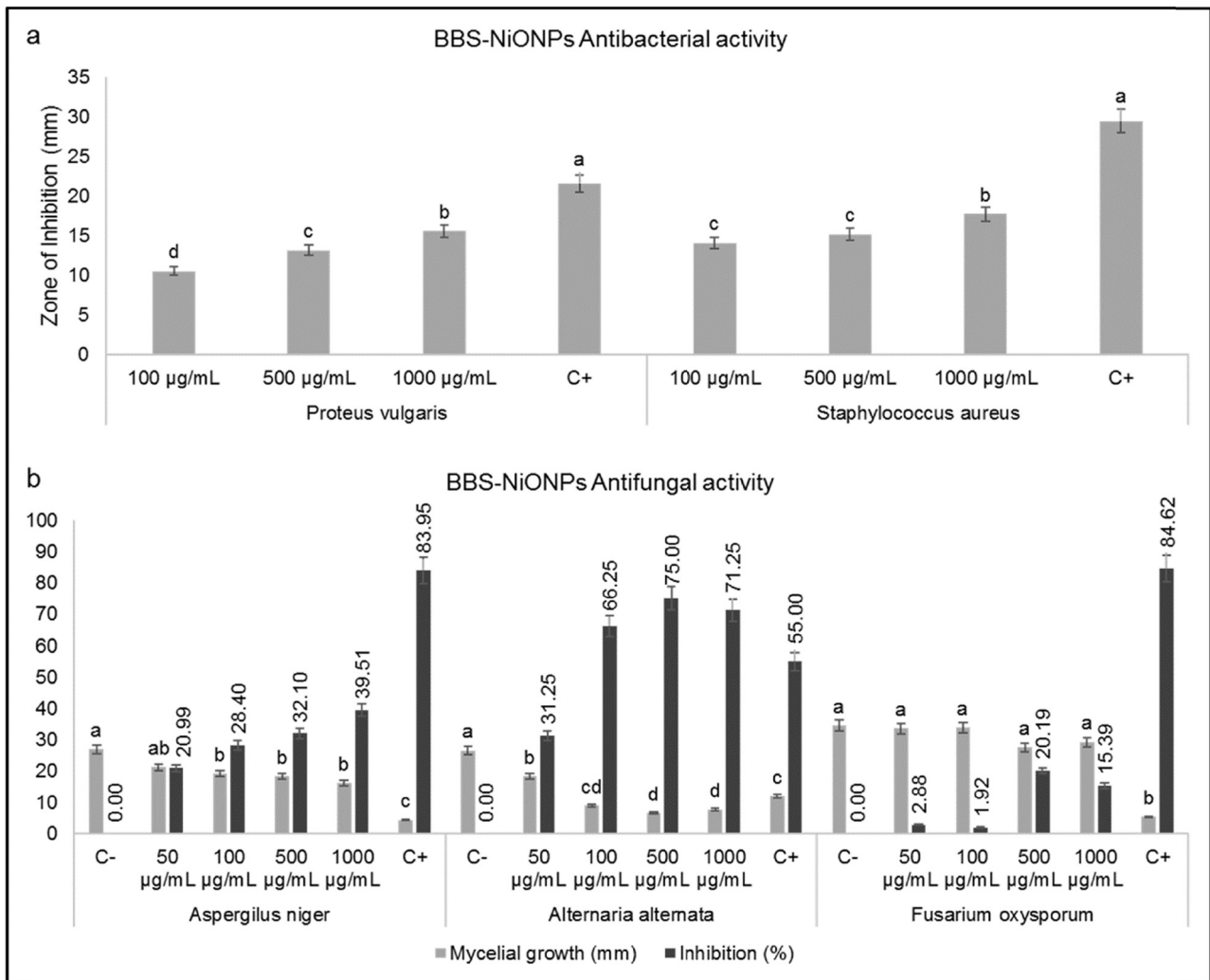


Figure 22: (a and b) Comparison of antimicrobial potentials of various NiO NP-based composites [77].

### 3.4.2 Angioinhibitory effect by NiO NPs

Figure 21 shows the autoinhibitory effect of NiO NPs, where the analysis showed a significantly progressive result in the chorioallantoic membrane (CAM) test model of growing embryos. The data show the results of six eggs in one batch. The anti-angiogenic effect of NiO NPs was examined and shown to have excellently slowed the proliferation of capillaries near the area of disks containing NiO NPs compared to controls (Figure 21).

## 3.5 Antifungal activity of phytofabricated NiO NPs

Uddin *et al.* [77] developed a green biogenic approach for the green production of NiO NPs using the phytochemical-rich strain extract of *Berberis balochistanica* (BBS). The antibacterial activity of phytofabricated BBS-NiO NPs (100, 500, and 1,000 g/mL) against the bacterial strains *Proteus vulgaris* and *Staphylococcus aureus* is shown in Figure 22a. BBS-NiO NPs showed a dose-dependent response to both bacterial strains tested. In addition, for antibacterial activities, it was found that 10 g of ciprofloxacin (a positive control) was more reactive than any BBS-NiO NPs used. BBS-NiO NPs were tested for antifungal activity against *Fusarium oxysporum*, *Aspergillus niger*, and *Alternaria alternata* at different doses (50, 100, 500, and 1,000 µg/mL). There were dose-dependent responses against all three fungal strains studied (Figure 22b). *F. oxysporum* showed less susceptibility at high concentrations (1,000 µg/mL), while *A. alternata* showed the highest level of susceptibility (71.25% inhibition), followed by *A. niger* (39.51% inhibition).

## 4 Conclusions and future perspectives

Green synthesis is by far the most environmentally friendly method for producing NPs, using plant sources and microbes as redox mediators to convert metal cations into metal/metal oxide NPs. Plant and microbial extracts contain a variety of phytochemicals and metabolites that act as stabilizers for biosynthesized NPs by acting as capping agents. The advantages of green synthesis over standard synthetic methods include low cost, safety, and environmental friendliness, justifying the growing interest in green synthesis over the past few decades. Many recent investigations on the preparation of NiO NPs by plant-mediated green synthesis are discussed

and covered in this review. Many of these are medicinal plants with established therapeutic uses. Synthetic techniques using plant and microbial extracts and the characterization and performance of the bio-synthesized NiO NPs are briefly described, highlighting their promise in photocatalysis and biomedical applications. The main advantages of more environmentally friendly approaches are low cost and the use of antimicrobial NP combinations, allowing natural plant extracts where the synthesis approach does not require toxic chemicals as reducing agents, as well as new uses such as antibacterial bandages. A thorough understanding of the wide range of microbial/biochemical constituents is required, as well as the various routes of laboratory synthesis, including the isolation and tracing of components used in the precise reduction of multiple metal salts to the required materials. Future challenges and achievements related to green prospects for manufacturing nanomaterials need to be addressed by expanding laboratory-based compliance to a feasible industrial level by considering current and past health and environmental impacts. On the other hand, a more environmentally friendly approach based on bio-derived materials or nanomaterials is needed and will be widely used in the field of environmental remediation as well as in other broad fields such as the food, cosmetics, and pharmaceutical industries. In addition, biomaterials from marine plants and algae isolated from specific regions have yet to be discovered. As a result, there are several potential avenues for developing novel green techniques based on biogenic synthesis. A significant amount of scientific research is required to enable the industrial production of green nanomaterials. The eventual release of such nanomaterials into the environment could result in unusual behavior, which is a concern that requires further research.

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**Conflict of interest:** The authors declare no conflict of interest.

**Ethical approval:** The conducted research is not related to either human or animals use.

**Data availability statement:** The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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