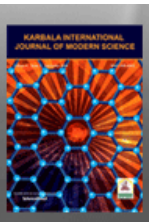

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Green Approach for Iron Oxide Nanoparticles Synthesis: Application in Antimicrobial and Anticancer- an Updated Review

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Keywords

Iron oxide nanoparticles; Biological synthesis; Anticancer activity; Antimicrobial activity

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REVIEW ARTICLE

Green Approach for Iron Oxide Nanoparticles Synthesis: Application in Antimicrobial and Anticancer- an Updated Review

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Abstract

Cancer and microbial infections create numerous challenges nowadays. Chemotherapy agents cause severe side effects, while microbial infections, especially multidrug-resistant bacterial strains hard to treat with available antibiotics. Therefore, this review provides an overview of the green synthesis of Iron oxide nanoparticles (IONPs) with their physicochemical properties and mechanism of action. The IONPs causes cytotoxicity and antimicrobial activity by causing oxidative distress through the production of Reactive Oxygen Species (ROS). The IONPs as an anticancer and antimicrobial agent may help to overcome the limitation of conventional treatments but needs toxicity evaluation before usage in clinical applications.

Keywords: Iron oxide nanoparticles, Biological synthesis, Anticancer activity, Antimicrobial activity

1. Introduction

Cancer is a dreadful disease that causes mortality worldwide, with an expected 10 million deaths in 2020 [1]. According to WHO, by 2040, it is likely that more than 27.5 million new cancer cases will occur and 16.3 million deaths [2]. The most endangering factors for unmodifiable factors include gender, age and family history [3], and modifiable factors include obesity, tobacco use, imbalanced diet, sedentary lifestyle, and alcohol intake [4]. Cancer occurs due to abnormal accumulation of cells arising from an imbalance of cell proliferation and programmed cell death (apoptosis) [5]. Cancer cells can survive longer due to mutation, abnormal cell proliferation, and differentiation leading to tumour progression, angiogenesis, and metastasis development [6]. Chemotherapy and radiation therapy, which are currently used to treat cancer, can inhibit uncontrolled cell proliferation [7,8]. The primary goal of the treatment is to cure the disease and improve the quality of the patient's life. However, the administration of the therapy may cause significant side effects to patients, such as hair loss, nausea and vomiting, anaemia, leukopenia, and thrombocytopenia during the treatment [9]. In addition, some reports showed that cancer cells are resistant to the chemotherapy drug's action [10]. Therefore, the need to discover an effective treatment to overcome the limitations of conventional treatment must be addressed.

Microbial agents such as fungi, bacteria, parasites, and viruses cause various infectious diseases and can be treated with antimicrobial agents. Antibiotics have been preferred as a treatment strategy for bacterial infection as their effective action in killing the bacteria [11]. The main concern in treating infectious diseases is that many pathogenic microorganisms have developed resistance toward antimicrobial agents, for example, antibiotics. The result of antibiotic resistance is due to the inappropriate use of antibiotics in community, clinical, and agricultural settings may result in antibiotic-resistance [12]. It causes the multidrug-resistant bacterial problem has become a

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global health threat [13,14]. Therefore, there is an urgent need to find new effective agents to overcome drug resistance. In this regard, nanotechnology reveals new opportunities for the biosynthesis of nanoparticles with promising anticancer and antibacterial characteristics to solve these challenges.

Nanotechnology is one of the most crucial technology in this century. The development of novel nanomaterials with diverse applications has become a significant contribution in the field of nanotechnology. Nanoparticles or nanomaterials are synthesized through the approach of top-down and bottom-up [15,16]. Metal nanoparticles are produced in the top-down method by breaking the amplitude material using various mechanical procedures to produce nanoscale size. Metal nanoparticles in a bottom-up method are produced from atoms or molecules to molecular structures of nanoscale size using various chemical or biological processes [17,18]. These nanoparticles, which range in size from 1 to 100 nm and have a broad surface area to volume ratio, are applicable in various disciplines, including optics, mechanics, biotechnology, engineering, remediation, microbiology, environmental medicine, and electronics [19]. Interestingly the nano-sized particles have immense applications due to their non-toxicity, non-immunogenicity, and ability to get modified to target specific applications [20].

In recent years, bio-nanotechnology approaches have become the primary interest in the various research areas to synthesize safe nanomaterials that can be applied in many fields, especially biomedical and pharmaceutical applications [21–23]. It is an approach or method to overcome the limitation of conventional methods in synthesizing nanoparticles [24]. Traditional approaches such as chemical and physical methods have shown many drawbacks (Fig. 1). For example, physical methods utilize a vast amount of energy, pressure, and temperature. On the other hand, chemical methods use hazardous solvents in their process that produce dangerous by-products harmful to nature and life that cause usage limitations of their products [25–27].

Thus, biological approaches have been established in which green synthesis provides more advantages than conventional methods. Many researchers have reported metal nanoparticles synthesized through green approaches as easy, fast, cost-effective, non-toxic, environmental-friendly, and readily scaled for large-scale synthesis [26,28–30]. Biological methods that apply the bottom-up approaches synthesize metal nanoparticles from the atoms or molecules to nanoscale molecular structure via different chemical processes. This method employs natural sources such as plants and microorganisms (fungi, bacteria, yeast, actinomycetes, and algae) in the synthesis of nanoparticles process.

Bioactive compounds from biological sources, plants and microorganisms have a pivotal role in the production of nanoparticles. In plants, metabolites include flavonoids, phenolic acids, alkaloids, terpenoids, carbohydrates and amino acids [31–33]. Metabolite products from microorganisms, including enzymes, protein, carbohydrates, vitamins, and fats,

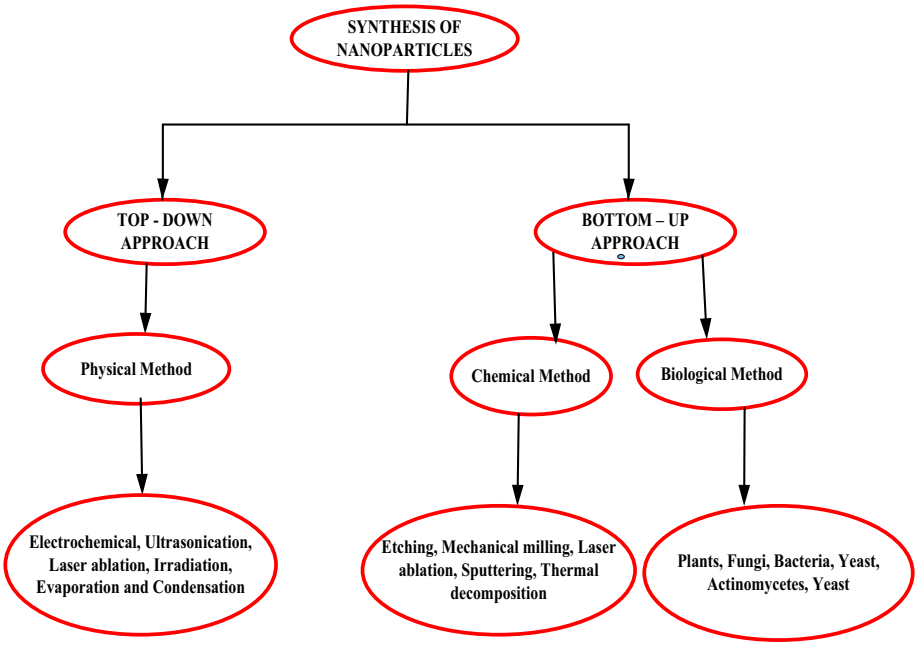

Fig. 1. Various approaches for the synthesis of nanoparticles.

are produced through extracellular and intracellular synthesis [34,35]. The biosynthesis process of metal nanoparticles embroilment the bio-reduction of metal salts, then capping and stabilizing the metal nanoparticles by active compounds [36]. Furthermore, the products produced through this approach are more compatible with biological systems and more applicable for health applications.

Iron oxide nanoparticles are metal nanoparticles that emerge as promising in various applications. Biomedical applications are mainly employed in hyperthermia Magnetic Resonance Imaging (MRI), hyperthermia, and targeted drug delivery (Fig. 2). MRI is a non-invasive diagnostic medical imaging technique with the potential to detect and diagnose cancer earlier than existing imaging methods. Using superparamagnetic iron oxide nanoparticles as contrast agents can improve MRI imaging sensitivity. Hyperthermia, localized heating within a tumour or closeness of tumour cells, can be induced by iron oxide magnetic nanoparticles with heat generation through relaxation in an alternating magnetic field. Targeted drug delivery use nanoparticles to deliver drugs to the targeted tumour. The drugs are encapsulated in the nanoparticles to avoid interaction with normal cells in order to avoid side effects. The surface functionalization of nanoparticles with biomolecules helps in targeting drug delivery to tumour cells [37–39].

Several studies have indicated that the IONPs serve as promising anticancer and antimicrobial agents as their action with biomolecules in cancer and microbial cells [38,40–42]. Superparamagnetic iron nanoparticles' magnetic, optical, photochemical, electrical, and chemical features are particularly useful in biomedical applications [43]. The advantages of IONPs include non-toxic, biodegradable, non-immunogenic, and biocompatible [44]; hence the interest of researchers in iron oxide nanoparticles keeps growing due to their unique characteristics applicable for various applications [45]. Their biological activities are determined by nanoparticles' physiochemical, such as shape, size, concentration, and surface charge [39].

This current review provides an overview of iron oxide nanoaprticles green synthesis using microorganisms and plants. Their potential applications and proposed mechanisms as anticancer and antimicrobial activities have been discussed as cancer and microbial resistance have become significant health problems.

2. Green synthesis of IONPs

Green nanotechnology has caught attention nowadays to overcome the limitation of conventional methods, physical and chemical methods in synthesizing metal nanoparticles. Conventional methods were reported with disadvantages such as using energy, temperature, and toxic chemicals. Green nanotechnology was established to produce safe and eco-friendly products, cost-efficacy and easy fabrication. The synthesized products are also safe for the environment and health applications. The green synthesis of IONPs using biological sources from plants and microbes (bacteria, fungus, algae) was reported by researchers [31,46].

Green synthesis approaches using biological precursors can be optimized with various reaction

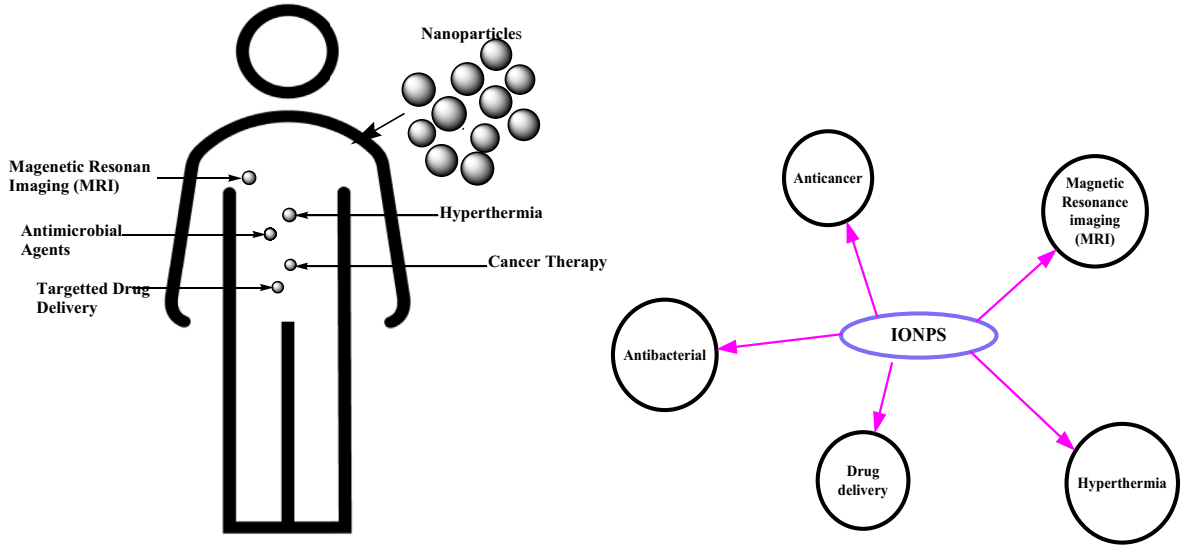

Fig. 2. Biomedical employments of IONPs.

parameters to obtain high production rate and the coveted morphology of nanoparticles. The parameters include the extract concentration, metals concentration, pH, temperature conditions, and incubation time [21]. Most studies have found that greater temperatures result in faster synthesis rates, but it is crucial to evaluate the quality of nanoparticles, which can affect nanoparticle size and stability. The value of pH of the reaction mixture can be manipulated to obtain the desired size and shape of nanoparticles. It also may affect either deactivation or activation of the activity of biomolecules from biological sources to synthesize nanoparticles [47]. A study by Adeleye et al. [47] demonstrated the optimum biosynthesis of iron nanoparticles from *Rhizopus stolonifer* at pH 4.5 and 6 while the temperature was 35 °C. The fungal oxidoreductase enzymes were found to be sensitive to pH. Fatemi et al. [110] investigated the production of iron oxide nanoparticles from *Bacillus cereus* strain HMH1 at various pH values of 3.5, 5.5, 7.4, 8.5, and 11. It was found that the optimum pH in synthesizing nanoparticles is 11. At this pH, it may induce nitrate reductase activity for nanoparticle synthesis.

2.1. Biosynthesis of IONPs using plants

Numerous plants that have been applied for the synthesis of IONPs are *Punica granatum, Garcinia mangostana, Psoralea corylifolia, Carica papaya, Sageretia thea, Eucalyptus, Rhamnella gilgitica, Papaver somniferum, Rhamnus virgata* (Roxb.), *Rhamnus triquetra*, *Rhus punjabensis* and *Brassica oleracea* var *capitata sub var rubra*, *Laurus nobilis, Phyllanthus Niruri, Artemisia vulgaris, Tridax procumbens, Platanus orientalis, Leucas aspera, Withania coagulans, R. gilgitica, P. somniferum* and *Pleurotus florid*.

The biological synthesis of IONPs from plants poses many advantages, such as being easy, fast, cost-effective, eco-friendly, and non-toxic to the environment and biological system [48]. Different plant parts such as flowers, stems, roots, and leaves are used in the green synthesis of nanoparticles. Plant constituents contain various phytochemicals such as polyphenols, flavonoids, alkaloids, phenolic acids, terpenoids, carbohydrates and amino acids which are responsible for stabilizating, capping, and reducing the synthesis of nanoparticles [49–52]. For example, the phytochemicals present in *Artemisia leave* extracts [51], *Lagenaria siceraria* leaves extract [53], and *Punica Granatum* Fruit Peel Extracts [54], *Azadirachta indica* leaf extracts [55] were found to play the role of reducing, capping and stabilizing agents responsible for the synthesis of IONPs. The phytochemicals from the plant extracts cause the abatement of iron ions to form iron oxide nanoparticles. The functions of phytochemicals as the stabilizing and capping agents result in stable nanoparticle formation to decrease particle interactions and agglomeration [56,57].

The plant metabolites also reported could enhance the biological application of nanoparticles [58,59]. On the other hand, plant metabolites also allow better control of the shape and size of the biosynthesized nanoparticles [60]. Furthermore, compared to conventional methods, IONPs stabilized with plant extracts may have higher water permeability, biocompatibility, antioxidant activity, acceptable toxicity, and biodegradability for numerous biomedical applications [49,58,61]. Plant extract-derived nanoparticles have many uses, including catalytic activities, antibacterial activities, biomedical fields, environmental remediation and drug delivery systems [20].

Interestingly, plants can produce more stable metal nanoparticles in a short time compared to microorganisms and be the ideal candidates for large-scale and rapid nanoparticle synthesis [24,62]. Characteristics of synthesized nanoparticles depend on the parameter's modification during their synthesis. Types of plant extracts, the concentration of extracts, metal salts, and environmental conditions such as pH, incubation time, and temperature have significant roles in obtaining the desired size and morphology of nanoparticles [28,63–66]. Ullah et al. [65] investigated the optimum condition for nanoparticles with various parameters such as the effect of salt concentration, extract and salt ratios, temperature, and duration of time for synthesis of metal nanoparticles at different time intervals. The results found that from the various conditions for the synthesis of metal nanoparticles, the optimum conditions for synthesizing stable AgNPs from *Fagonia indica* leaf extract at 1 mM $AgNO_3$ with 5 mg/ml extract in a ratio of 1:10 (extract to $AgNO_3$) at 60 °C for 2 h. Vijukumar & Prem found the optimum synthesis IONPs by adding the leaf extract to an iron salts mixture in a 1:2 ratio for 30 min at 30 °C, under stirring compared to 1:3, 1:5, and 2:3 ratios. The presence of phytochemical compounds such as flavonoids, alkaloids, terpenoids, lignans, polyphenols, tannins, coumarins, and saponins may help the reducing iron ions in its nanoparticles [63].

2.2. Green synthesis of IONPs from microorganisms

Microorganisms such as bacteria, fungi, and algae have been explored for their ability to synthesize nanoparticles. They have a promising role for

various applications, especially in the medical and health fields. Among the microorganisms that have been studied are *B. cereus strain HMH1, Proteus vulgaris, Sargassum muticum, Alternaria alternata, Trichoderma asperellum, Phialemoniopsis ocularis, Fusarium incarnatum, Aspergillus flavus, Colpomenia sinuosa and Pterocladia capillacea*.

Fungi, eukaryotic cells produce certain biomolecules such as NADH-nitrate reductase enzymes, anthraquinones, and protein that act as the capping and reducing agents to reduce metallic irons into metal nanoparticles [67–69]. Zomorodian et al. [69] reported that *Aspergillus fumigatus* secreted NADH-nitrate reductase higher than *Aspergillus niger* and *A. flavus,* which is probably responsible for the formation of nanoparticles. The metal reduction can occur through intracellular and extracellular mechanisms [70]. In the intracellular mechanism, the metal ions diffused into the cell wall through electrostatic attraction. Then, the metal ions are converted into metal nanoparticles using enzymes present in the cell walls. While in the extracellular mechanism, metal ions are breakdown to metallic nanoparticles by enzymes and other metabolites present in the medium [71]. The advantages of using the extracellular method are straightforward in obtaining pure nanoparticles, free from cellular components, and simple downstream processing [72,73]. In addition, fungi have an advantage in the biosynthesis of nanoparticles because their mycelia have a greater surface area of interaction and can produce more protein than bacteria, allowing for a quick change of metal salts to metal nanoparticles [73,74].

Bacteria, the prokaryote cells, have been employed to synthesize metal nanoparticles. The ability of bacteria to detoxify and accumulate metals using nitrate reductase enzymes; hence they utilized this activity for synthesizing metallic nanoparticles [75,76]. Singh et al. [75] found that the nitrate reductase enzyme in *Bacillus licheniformis* was responsible for metal nanoparticle synthesis. In another study, nitrate reductase is secreted by *B. cereus* strain HMH1 to reduce iron ions to iron nanoparticles [110]. Bacteria can reduce the metal ions through extracellular and intracellular methods to form metal nanoparticle synthesis [77–80]. The enzymes present in the cell wall are essential for reducing metal ions in the intracellular mechanism. In the extracellular mechanism, metal ion reduction occurs by the enzymes present on the cell wall and in the medium secreted by bacteria. The extracellular method is more cost-effective and simple than the intracellular method due to the easy extraction [81,82].

Another biological source used for the biosynthesis of nanoparticles is algae. Algae such as macroalgae, microalgae (unicellular) and seaweeds (multicellular) contain a wide range of bioactive substances like polysaccharides, minerals, lipids, vitamins, proteins, soluble fibres, alkaloids, terpenes, glycoproteins, and enzymes act as a reductant agent, capping and stabilizer in the fabrication of nanoparticles [83–85]. In addition, seaweed contains several phytochemical functional groups such as hydroxyl, amino, and carboxyl groups involved in metal nanoparticle fabrication [83]. For example, El-Kassas et al. [86] found that sulphated polysaccharides in seaweed water extract play a role in nanoparticle stabilization, increasing nanoparticles' compatibility for biomedical applications. The possible active compounds involved in the synthesis of nanoparticles are shown in Table 1.

The biosynthesis process of nanoparticles can be optimized by parameter adjustments such as pH, temperature, the strain of microorganism, biomass amounts, incubation time, growth medium, and concentration of salts [43,70,87–89]. Furthermore, these parameters affect nanoparticles' physiochemical, including size, shape, composition, surface charge, and stability [47,90]. Elamawi et al. [89] investigated the different physical parameters such as fungal biomass concentration (1, 5, 10, 15, and 20 g), temperature (25, 28, and 33 °C), incubation time (0–120 h), and agitation (shaken or not shaken) to determine the optimal conditions for nanoparticle biosynthesis. It was found that the optimum condition for the synthesis of the metal nanoparticles was 10 g fungal biomass, a reaction temperature of 28 °C, a 72-h incubation time, and without shaking. The synthesized nanoparticles were monodispersed spherical shape with a size of 10 nm. Mahanty et al. [71] found that synthesis of IONPs from *T. asperellum* and *P. ocularis* at low pH (3.2) and high temperature (30 °C) in the presence of extracellular protein in fungal cell filtrate. Therefore, these modification parameters are essential for obtaining the desired size and monodisperse nanoparticles for

Table 1. Different biological sources used for nanoparticle synthesis and their proposed active compounds.

Biological Sources	Actives compounds
Plants	Polyphenols, alkaloids, flavonoids, terpenoids, phenolic acids, amino acids, carbohydrates
Fungus	Reducing enzymes such as NADH-dependant nitrate reductase, protein, nitrate reductase, hydroquinone
Bacteria	Reducing enzymes like or nitrate reductase or NADH-dependent reductase
Algae	Proteins, polysaccharides, lipid, vitamins, minerals, soluble fibres, alkaloids, terpenes, glycoproteins, and enzymes

biological application. The proposed mechanism of IONPS using biological factories like plants, fungi, bacteria, algae were shown in Fig. 3.

3. Applications of IONPs in anticancer and antimicrobial agents

3.1. Plants

3.1.1. Anticancer activity

Various research has been carried out to explore the anticancer activity of IONPs synthesized from plants. A study by Yusefi et al. [54] found that IONPs synthesized from *P. granatum* fruit peel extract exhibited anticancer activities against HONE1,nasopharyngeal carcinoma (NPC) cell line. However, no cytotoxicity effects of IONPs were observed against breast (MCF7), colon (HCT116), lung (A549), and cervical (HeLa) cancer cell lines and two healthy human colon and kidney (CCD112 and HEK293) cell lines. The study proposed the possible killing mechanism induced by IONPs on cancer cells due to the production of reactive oxygen species (ROS), damage of DNA, cell apoptosis, cell cycle arrest, and disturbance of membrane integrity [54]. Another study, Yusefi et al. [91] reported the effects of IONPs synthesized from fruit peel extract of *G. mangostana* as the anticancer effect against HCT-116 colon cancer cells and hyperthermia. They reported that synthesized IONPs ($Fe3O_4$ NPs) showed higher killing effects on HTC116 compared to the CCD112 colon normal cell line. The active compounds in *G. mangostana* fruit peels (xanthone and α-mangostin) act as capping and stabilizing agent to enhance the physicochemical properties and colloidal stability of IONPs. The iron ions released from IONPs leads to oxidative stress (via Fenton reaction) causes impaired mitochondrial function, damage to DNA and protein, and lipid peroxidation, results in cell death. In addition, the increased temperature in cancer cells causes the release of phenolic compounds in IONPs, which also can act as anticancer [91].

Iron oxide nanoparticles (α-Fe_2O_3 (hematite)) synthesized from *P. corylifolia* seeds through aqueous extract as a reducing agent was investigated. The results showed anticancer activity IONPs caused by apoptosis which induces caspase-3 (executer caspase) expression in renal carcinoma cells (Caki-2 cells). The expression of caspase-3 in renal cancer cells increased concentration-dependent [92]. Another study of anticancer activity of IONPs synthesized from *C. papaya* found that cytotoxic effects of IONPs against BHK-21, HeLa, and Vero cell line at maximum doses. It was observed that DNA damage caused by ROS-mediated oxidative stress increases with nanoparticle concentration. The results showed cancer cells were more keen to ROS as compared to healthy cells [93].

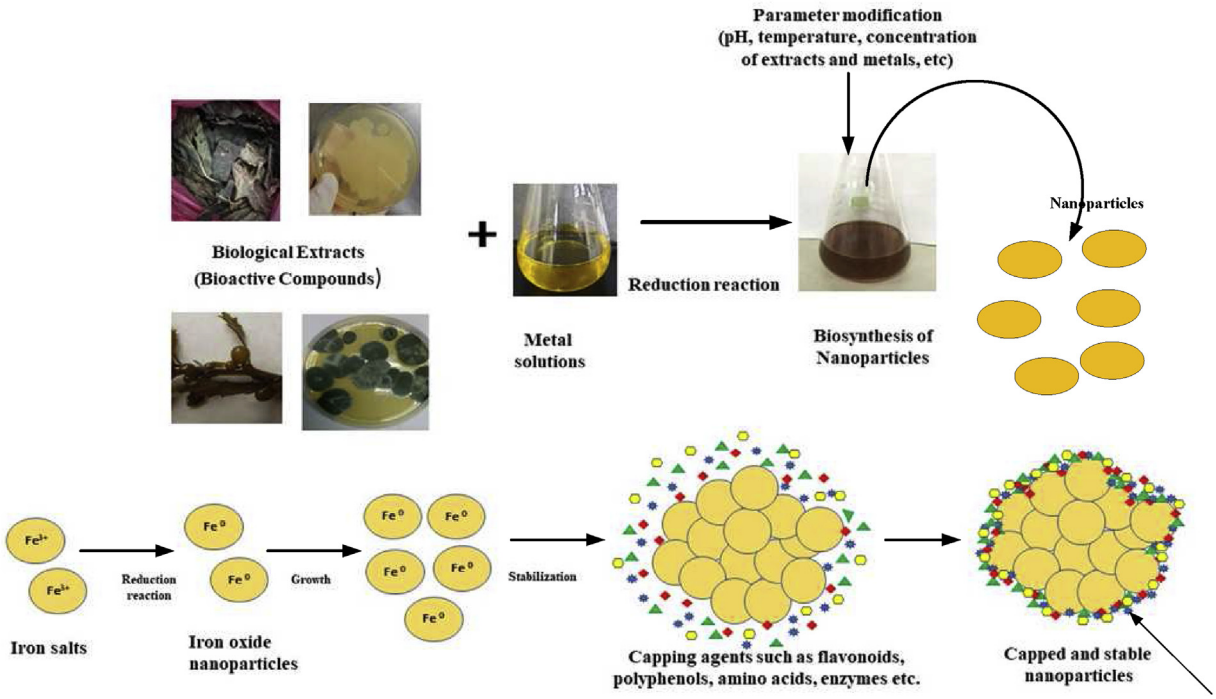

Fig. 3. Schematic representation of the mechanism of IONPs using biological sources (Plants, fungi, bacteria, algae).

Khalil et al. [94] investigated the anticancer activity of the biosynthesized IONPs from *S. thea (Osbeck.)* extract against brine shrimps. The authors discovered that IONPs have the potential cytotoxicity by the generation of ROS. ROS interferes with the genetic materials leading to genotoxicity. The dissociation of iron ions from IONPs disrupts the protein's function and initiates mitochondria to generate further ROS. IONPs also significantly inhibit protein kinase enzymes. The inhibition of these enzymes is associated with the inhibition signalling cascade for the proliferation and division of cells. Furthermore, the compatibility test of IONP on red blood cells (RBC) and macrophages demonstrated the non-toxicity of IONPs at a lower concentration (1 μg/ml), indicating the safety of IONPs [94]. The anticancer potential of IONPs derived from Rosemary leaf extract was evaluated against C26 murine colon cancer and 4T1 breast cancer cell lines by Farshchi et al. [95]. In comparison to rosemary extract, the cytotoxic effect of IONPs from Rosemary leaf extract was substantially more significant in both cancer cell lines. The polyphenol component in the extract is believed to be responsible for the anticancer action since it successfully induces apoptosis and suppresses the cell cycle [95].

Anticancer activity of IONPs synthesized from *R. gilgitica* leaves extract was investigated by Iqbal et al. [96] IONPs demonstrated strong anticancer activity against HepG2 cancer cells. IONP also successfully inhibits protein kinase enzyme; therefore, it can halt cancer progression by inhibiting cell proliferation and inducing apoptosis [96]. Abbas et al. [58] achieved similar results when they synthesized IONP from *R. virgata* (Roxb.) leaves extract. IONPs have demonstrated potential anticancer activity in HepG2 cells, with dose-dependent cytotoxicity and protein kinase inhibition. The biocompatibility test confirms the biosafe of IONPs [58]. Abbasi et al. [97] also found that IONP from *R. triquetra* (RT) leaves extract exhibited cytotoxic effect against HepG2 cancer cells (IC50: 11.2 μg ml^{-1}). The biocompatibility tests against human RBCs and macrophages confirmed the biocompatibility and non-toxic behaviour of IONPs [97].

IONPs synthesized from *R. punjabensis* extract exhibited significant anticancer and protein kinase inhibition activities compared with the corresponding plant extract. IONPs demonstrated a cytotoxic effect against DU-145 prostate cancer and HL-60 leukemic cell lines with ED50 values of 11.9 and 12.79 mg/ml, respectively. Inhibition of Nuclear factor-kB (NF-kB) by IONPs on cancerous cells is associated with inhibiting cell proliferation, migration and invasion, angiogenesis and causes apoptosis [98]. Yoonus et al. [99] investigated the anticancer activity of IONPs exploited *Piper betel* leaves extract against A549 cells. The results showed that IONPs cause cytotoxicity in A549 lung cancer cells on a concentration-dependent manner. Cancer cell proliferation was inhibited by cell shrinkage, condensed, and fragmented nuclei. Furthermore, the interaction of IONPs with NADPH oxides from the plasma membrane and mitochondria generates reactive oxygen species (ROS) in the cells; then, it triggers signalling cascades resulting in cytotoxicity [99].

MCF-7 cells treated with IONPs synthesized from *Brassica o.* var *capitata sub var rubra* (red cabbage) aqueous peel extract inhibited the proliferation and sign of apoptosis. The cells showed blebbing of the plasma membrane and shrinkage after being treated with 100–1000 μg/ml IONPs. The membrane asymmetry was lost in the apoptotic cells, which caused phosphatidylserine to be exposed on the membrane surface [100]. However, synthesized IONP from mango leaves extracts showed no cytotoxicity effects on breast cancer cells (MCF7) which do not reach IC50 even at higher concentrations (200 μg/ml) [101]. Another study employed *Eucalyptus* leaf extract in synthesizing IONPs, and its anticancer activity was evaluated. In this study, the authors reported that cisplatin-chitosan-IONPs induce effective apoptosis in MDA-MB-231 breast cancer cells compared to cisplatin-IONPs and cisplatin. The activation of apoptosis was indicated by the downregulation of BCL2 protein (antiapoptotic) and overexpression of BAX (proapoptotic) [102]. The proposed mechanism of anticancer activity of IONPS was shown in Fig. 4.

3.1.2. Antimicrobial activity

Kanagasubbulakshmi & Kadirvelu [53] synthesized IONPs from *L. siceraria* leaves extract to evaluate the antimicrobial activity against *Staphylococcus aureus* and *Escherichia coli*. The result showed the moderate antibacterial activity of IONPs due to the small size of NPs (30–100 nm), which aids NP penetration into the cell wall, resulting in cell death. The authors suggested that the plant components responsible for producing IONPs should be isolated and purified to avoid plant contaminants influencing the IONPs properties [53]. *T. procumbens* weed extracts also were used to synthesis IONPs. The finding showed the significant inhibition of the fungal growth *S. rolfsii*. It occurs due to the destruction of membrane cells inducing the reactive oxygen, eventually causing cell death. It concluded that IONPs could manage fungal diseases in agriculture as antifungal agents [103].

A comparative study between synthesis IONPs from *Phyllanthus niruri* leaf extract dan chemical

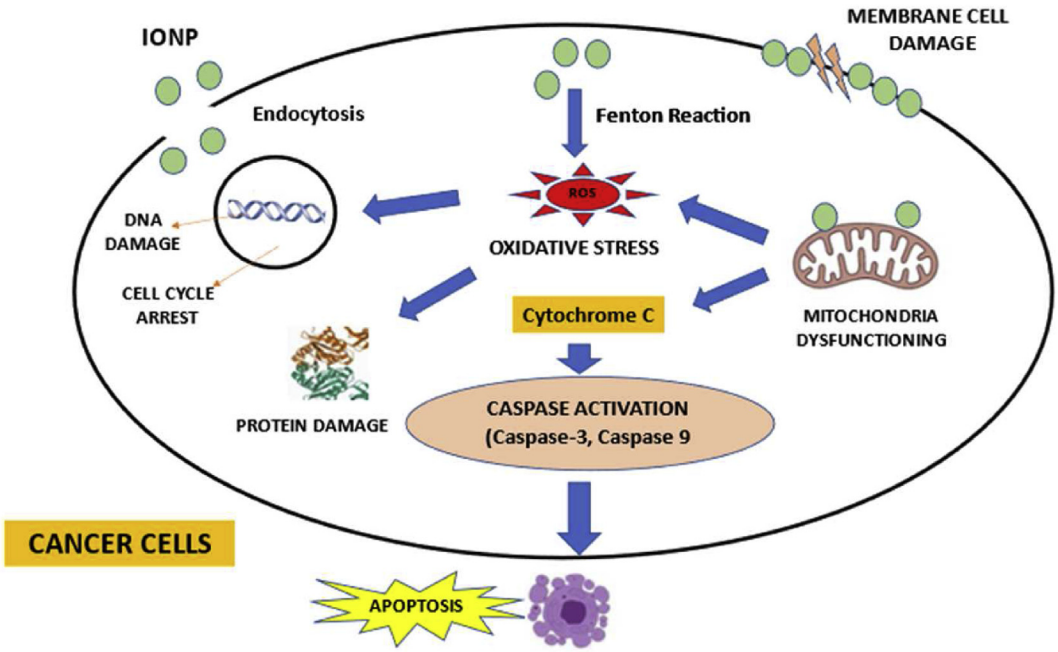

Fig. 4. Proposed mechanism of anticancer activity of biosynthesized iron oxide nanoparticles.

method synthesis was conducted by Viju Kumar & Prem [63]. The study found that the biosynthesis of IONPs is more advantageous than toxic chemicals as it is more cost-effective, energy-efficient, low-cost, and environmentally benign. Furthermore, the antibacterial activity of the green synthesized iron oxide nanoparticles was significant against *Pseudomonas aeruginosa* and *E. coli* through agar well diffusion method at various concentrations. The antibacterial activity of IONPs is due to the generation of ROS generated by the nanoparticles and the chemical interaction between IONPs and the outer bilayer of bacteria [63]. A study on the antimicrobial activity of IONPs synthesized from the aqueous extract of *L. nobilis* leaves showed potential antifungal (*A. flavus* and *Penicillium spinulosum*) and antibacterial (*Listeria monocytogenes*) agents. Reactive oxygen species (ROS) destroy macromolecules of bacteria and fungi [104].

Bhuiyan et al. [93] evaluated the antibacterial activity of IONPs synthesized from *C. papaya* leaves extract on some pathogenic bacteria. According to their finding, IONPs showed a more significant inhibition zone in gram-positive bacteria (*S.aureus*) than gram-negative bacteria (*Klebsiella* spp., *E. Coli, Pseudomonas* spp.). They proposed that the extra outer layer of peptidoglycan and lipopolysaccharide in gram-ve bacteria might protect the bacteria from nanoparticles activity [93]. Another study of antibacterial and antifungal effects of biosynthesized IONPs from *S. thea* (Osbeck.) was reported by Khalil et al. [94]. *P. aeruginosa* was found as the most sensitive strain to biosynthesized IONPs. Antifungal activity was investigated against *A. niger, Mucor racemosus, A. flavus, R. solanai,* and *A. fumigatus* showed susceptibility to the IONPs. The authors have proposed the bioactive compounds, phenols that stabilize and caps IONPs play a significant role in antimicrobial actions. The proposed mechanism of antimicrobial activities is an oxidant and non-oxidant factors. The cellular oxidative damage occurs due to the generation of ROS. The binding of nanoparticles to the surface of the cell membrane leads to cellular injury. Another factor is that non-symmetry nanoparticles surface can also contribute to the cause of cell injury [94].

Qasim et al. [105] found that IONPs synthesized with *W. coagulans* extract exhibited more significant antibacterial activity against *S. aureus* and *P. aureginosa* than IONPs synthesized with the chemical method. The antibacterial activity was contributed with the concentration, surface area, morphology, and crystalline structure of IONPs. The presence of biomolecules from the plant for synthesing IONPs enhances the antibacterial activity [105]. *Ruellia tuberosa* (RT) leaf aqueous extract was employed to synthesis IONPs by Vasantharaj et al. [106]. The finding found that IONPs incorporated cotton fabrics demonstrated better bactericidal activity against *E. coli* than *Klebsiella pneumonia* and *S. aureus*. Furthermore, the penetration of IONPs into bacteria's cell walls causes cell membrane damage and lysis of the membrane due to oxidative stress [106]. According to Devi et al. [107], the antifungal activity of IONP employed

from *P. orientalis* extract was associated with small size and the large surface-to-volume ratio of the nanoparticle that altered the permeability of cell membrane that led to penetration of IONPs and caused oxidative stress [107].

Goma [108] found that incorporating IONPs synthesized from aqueous leaf extract *Corchorus olitorius* into chitosan-nanoparticles (NP) synthesized from shells of *Penaeus semisulcatus* improves the function of IONPs biocompatible antimicrobial agents compared to IONPs and chitosan NP alone. The prevention of aggregation of IONPs by chitosan NP may result in increased surface area and enhanced contact with microbial cells [108]. Da'na et al. [109] successfully synthesized IONPs using *Acacia nilotica* seedless pods extract. According to their finding, the better antimicrobial activity of IONPs is attributed to changing in the accessible surface functional groups and surface potential. These modifications would alter IONP's interaction with the bacterial surface and play a crucial role in defining IONP's antibacterial potential [109].

The *Pleurotus florida* mushroom extracts were explored in the synthesis of IONPs as antimicrobial agents. The highest zone of inhibition was reported against *Candida glabrata* and lower activity against *S. aureus*. Cinnabarine, an active pigment found in mushrooms showed antimicrobial activity [31]. Antibacterial activity of IONPs synthesized from *R. triquetra* showed the IONPs were more potent against *S. aureus* and *Bacillus subtilis* (MIC: 37.5 μg/ml) and least effective towards *K. pneumoniae* and *E. coli* (MIC: 75 μg/ml). ROS production, defects the surface symmetry of IONPs, and IONPs causes membrane injury due to adsorption to the surface of microbes that cause microbial cell damage. Furthermore, the attached biomolecules to the surface of nanoparticles may attribute a potential role in inhibiting the growth of bacteria. The antifungal potency of IONPs synthesized from *R. triquetra* was studied by Abbasi et al. [97]. Among the fungal strains, *Candida albicans* and *A. flavus* were the least sensitive strains (MIC: 75 μg/ml), while *A. niger* was the most sensitive (MIC:37.5 μg/ml). The fungal growth inhibition is due to the production of ROS and restriction of IONPs to fungal spores/hype [97]. The proposed mechanism of antimicrobial activity of IONPs was shown in Fig. 5.

3.2. Microorganisms

3.2.1. Anticancer activity

Fatemi et al. [110] reported the magnetic IONPs synthesis using *B. cereus* strain HMH1 bacterial supernatant, which provides a cost-effective, fast, eco-friendly and simple method for synthesizing useful nanomaterials in nanomedicine. The study's results revealed that the nitrate reductase enzyme is responsible for nanoparticle synthesis. This enzyme reduces the metal ions by providing the electron source in the solution. The synthesized IONPs may recommend as an option for drug administration and targeting of cancer cells as they showed the cytotoxicity effects on MCF-7 and low toxicity to normal cells. In addition, it has indicated a significant benefit for decreasing the side effects of treatment [110].

Majeed et al. [111] evaluated the anticancer activity of IONPs synthesized from *Proteus Vulgaris*

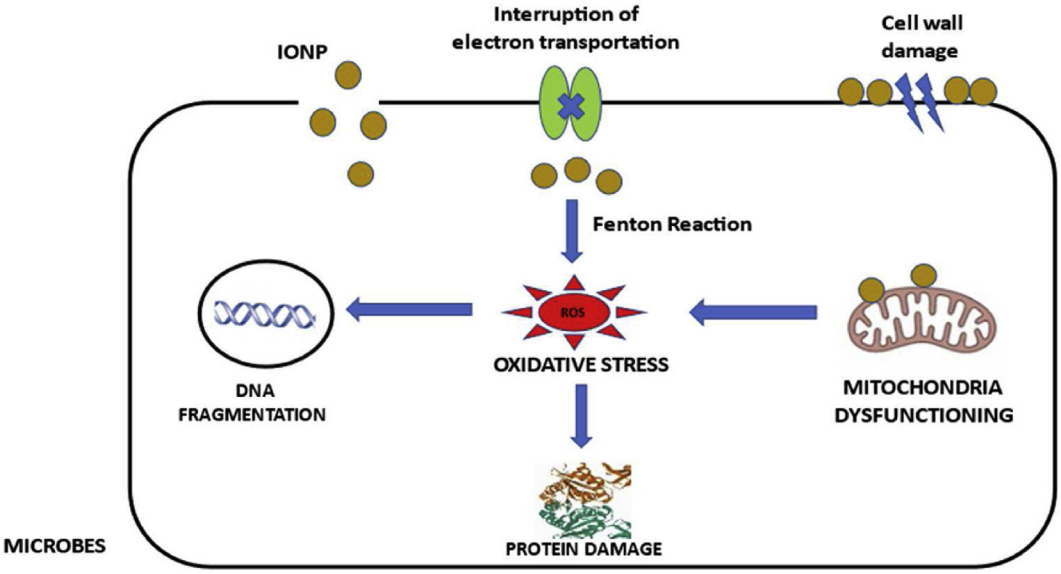

Fig. 5. Proposed mechanism of antibacterial activity of biosynthesized iron oxide nanoparticles.

Table 2. Application of biosynthesized IONP in anticancer activity.

Sources	Shape	Size (nm)	Applications	Cell lines/ Cells	IC_{50}/ ED_{50}	References
Plants						
Punica granatum fruit peel	Spherical and cubical	10.32 ± 2.87	Anticancer activity	Colon (HCT116), breast (MCF7), cervical (HeLa) and lung (A549) cancer cells Nasopharyngeal carcinoma (NPC) cell line, HONE1 (2% & 4%wt.% of peel extract)	> 250 μg/ml 197.46 and 85.06 μg/ml	[54]
Rhamnus virgata (Roxb.) leaves	Spherical	~20	Anticancer activity	HepG2 cancer cells	13.47 μg/ml	[58]
Garcinia mangostana fruit peel	Spherical	13.42 ± 1.58	Anticancer activity	HTC116 colon cancer cells	99.80 μg/ml	[91]
Psoralea corylifolia seeds	Spherical, rod-like and uneven shapes	~39	Anticancer activity	Renal carcinoma cells (Caki-2 cells)	-	[92]
Carica papaya	Not uniform	21.59	Anticancer activity	Hela, BHK-21	30 mg/ml (almost 95% inhibition)	[93]
Rhamnella gilgitica leaves	Spherical	~ 20	Anticancer activity	HepG2 cancer cells	14.30 mg/ml	[96]
Rhamnus triquetra (RT) leaves	Spherical	~ 21	Anticancer activity	HepG2 cancer cells	11.2 μg/ml	[97]
Rhus punjabensis	Rhombohedral crystal	41.5 ± 5	Anticancer activity	HL-60 leukemic and DU-145 prostate cancer cell lines	11.9 and 12.79 mg/ml	[98]
Piper betel leaves	Cubic	25.17	Anticancer activity	A549 (lung cancer) cells	104.6 μg/ml	[99]
Brassica oleracea var *capitata sub var rubra* (red cabbage)	-	675 ± 25	Anticancer activity	MCF-7 cancer cells	1000 μg/ml (27.5% inhibition)	[100]
Mango leaves	Spherical	1 to 12	Anticancer activity	breast cancer cell type (MCF7) to	> 200 μg/ml	[101]
Eucalyptus leaves	Spherical	352.1 ± 222.7 nm	Anticancer activity	MDA-MB-231 breast cancer cells	30 μM (45.8% inhibitory)	[102]
Sageretia thea (Osbeck.)	Tetragonal crystalline	~30	Anticancer activity	Brine shrimps	16.46 μg/ml	[94]
Rosemary leaves	Spherical	20 to 80	Anticancer activity	C26 colon cancer and 4T1 breast cancer cell lines	20.98 μg/ml and 44 μg/ml	[95]
Papaver somniferum L.	Elliptical or spherical	38 ± 13	Anticancer activity	HepG2 cancer cells	200 μg/ml 61.51% (Inhibition)	[117]
Isolated *proanthocyanidin* (PAC) from grape seed	-	50–100	Anticancer activity	Colon cancer cell lines HT29 and COLO320DM	59.39 ± 1.84% (Inhibition)	[116]

Sources	Approach	Shape	Size	Application	Cell lines	IC_{50}	References
Bacteria							
Bacillus cereus strain HMH1	Extracellular	Spherical	18.8−28.3	Anticancer activity	MCF-7	> 5 mg/ml	[110]
Proteus vulgaris	Extracellular	Spherical	19.23−30.51	Anticancer activity	U87 MG-glioblastoma cancer cells	250 μg/ml	[111]
Algae							
Brown seaweed (*Sargassum muticum*)	-	*Cubic*	18 ± 4	Anticancer activity	Leukemia (Jurkat cells), breast cancer (MCF-7 cells), cervical cancer (HeLa cells), and liver cancer (HepG2 cells)	6.4 ± 2.3 μg/ml (Jurkat), 18.75 ± 2.1 μg/ml (MCF-7), 12.5 ± 1.7 μg/ml (HeLa), 23.83 ± 1.1 μg/ml (HepG2)	[112]

against U87 glioblastoma brain cancer. The results showed that an IC50 value of IONPs at 250ug/ml caused morphological changes in cancer cells. In addition, the IONPs showed high toxicity effects on cancer cells compared to healthy cells (L132 cells). The IONPs also prevent l migration of HT-29 cancer cells and delay scratch closure [111]. In another study, Namvar et al. [112] investigated the toxicity of IONPs synthesized from brown seaweed (*S. muticum*) aqueous extract in human leukaemia (Jurkat) cells. The results showed significant cytotoxicity in Jurkat cells after exposure to IONPs presenting an apoptotic response. Chromatin condensation, nuclear margination, membrane blebbing and DNA fragmentation and apoptotic body formation were observed in the treated cells. Inhibition of cell proliferation, cell cycle, and activation of caspase-3 and caspase-9 results in apoptosis induction. Interestingly, IONPs do not cause toxicity to the normal Chang liver cell line, indicating the safe delivery of IONPs and application in anticancer therapy [112].

3.2.2. Antimicrobial activity

The biosynthesis of IONPs employing *A. alternata* fungus exhibited antibacterial activities against *B. subtilis*, *S. aureus P. aeruginosa* and *E. coli*. In addition, IONPs may initiate oxidative stress via the production of reactive oxygen species and Fenton reaction. Oxidative stress can occur due to the disruption of the ionic transport chain due to strong binding nanoparticles to membrane cells. In another mechanism, iron ions may cause decomposition of proteins and lipopolysaccharide in the membrane occurs due to the great affinity of the nanoparticles to cell membrane, result in cell death [113]. Gouda et al. [114] discovered that IONPs produced from *A. flavus* have superior bactericidal efficacy against *S. aureus* than *K. pneumonia*. In addition, IONPs was also found to have antifungal properties against *A. fumigatus* and *C. albicans*. The authors proposed that the mechanism of IONPs in antimicrobial activity is due to oxidative stress generated by ROS. ROS such as superoxide radicals (O2−), hydrogen peroxide (H2O2), singlet oxygen (1O2), and hydroxyl radicals (−OH), that lead to protein and DNA damage in bacteria. Direct interaction between IONPs and cell surfaces of microbes causes changes in the permeability of membrane cells. IONPs easily penetrate the cells and trigger oxidative stress in microbial cells that cause inhibiting cell growth, finally leading to cell death [114].

Salem et al. [115] have synthesized IONPs from *C. sinuosa* (brown seaweed) and *P. capillacea* (red seaweed) aqueous extracts. The antibacterial efficacy of IONPs was proven superior against Gram-

Table 3. Application of IONPs in antimicrobial activity.

Biological Sources	Shape	Size (nm)	Applications	Bacteria/ Fungi	References
Plants					
Pleurotus florid (mushroom)	Spherical	100	Antibacterial and antifungal activity	*Bacillus cereus, Staphylococcus aureus and Micrococcus mucilaginosus, Klebsiella pneumoniae, K. terrigena, Pseudomonas aeruginosa, Escherichia coli and Fungi; Candida albicans, C. glabrata and Candida* sp.	[31]
Leucas aspera leaves	Irregular rhombic	117 μm -1.29	Antibacterial activity	*Bacillus cereus Staphylococcus aureus, Listeria monocytogens Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, Salmonella enterica, Shigella flexneri, Vibrio cholera, Pseudomonas aeruginosa*	[50]
Lagenaria siceraria leaves	Cubical	30–100	Antibacterial activity	*E. coli, S.aureus*	[53]
Phyllanthus Niruri	Nearly square	10	Antibacterial activity	*E. coli* and *P. aeruginosa*	[63]
Carica papaya leaves	Not uniform	21.59	Antibacterial activity	*Klebsiella* spp., *E.Coli, Pseudomonas* spp., *S.aureus*	[93]
Sageretia thea (Osbeck.) leaves	Tetragonal crystalline	~30	Antibacterial activity Antifungal activity	*E. coli, B. subtilis,* *S. epidermidis, K. pneumoniae and P.aeruginosa);* *M. racemosus, A. niger, A. flavus, A. fumigatus and R. solanai.*	[94]
Rhamnella gilgitica leaves	Spherical	~ 20	Antibacterial and antifungal activity	*B. subtilis, S. aureus, E. coli, P. aeruginosa, K. pneumoniae Aspergillus flavus, Fusarium solani, A. niger, Candida albicans, Mucor racemosus*	[96]
Rhamnus triquetra (RT) leaves extract	Spherical	~ 21 nm	Antibacterial and antifungal activity	*Bacillus subtilis, Staphylococcus aureus, E. coli, Pseudomonas aeruginosa Klebsiella pneumoniae; Aspergillus flavus, Fusarium solani, Aspergillus niger, Candida albicans, Mucor racemosus*	[97]
Piper betel leaves extract	Cubic	25.17	Antibacterial activity	*Escherichia coli, Pseudomonas aeruginosa, Staphylococcus aureus and Streptococcus mutans*	[99]
Tridax procumbens weed	Spherical	26 ± 5	Antifungal activity	*S. rolfsii* and *F. oxysporum*	[103]
Laurus nobilis L. leaves	Almost spherical like and partly as a hexagonal	8.03 ± 8.99	Antifungal and antibacterial activity	*Listeria monocytogenes, Aspergillus flavus* and *Penicillium spinulosum*	[104]
Withania coagulans (Berries)	Nanorod	16 ± 2	Antibacterial activity	*S.aureus and P. aeuroginosa*	[105]
Ruellia tuberosa (RT) leaves	Hexagonal nanorods	52.78	Antibacterial activity	*Escherichia coli, Klebsiella pneumoniae Staphylococcus aureus*	[106]
Platanus orientalis leaves	Spherical	38	Antifungal activity	*Aspergillus niger* and *Mucor piriformis*	[107]
Papaver somniferum L.	Elliptical or spherical	38 ± 13	Antibacterial and antifungal activity	*B. subtilis, Staphylococcus epidermidis, Klebsiella pneumonia, and Pseudomonas aeruginosa,* *Fusarium solani, Aspergillus flavus, Aspergillus fumigates, Aspergillus niger and* Mucormycosis	[117]
Iraqi grapes	Cubic	49 to 50	Antibacterial activity	*Escherichia coli, Staphylococcus aureus*	[118]
Tannic acid (polyphenol from plants)	Circular	10 and 30	Antifungal activity	*Trichothecium roseum, Cladosporium herbarum, Penicillium chrysogenum, Alternaria alternata and Aspergillus niger*	[119]
Sida cordifolia	Spherical	10–22	Antibacterial activity	*B. subtilis, S. aureus, E. coli, and K. pneumonia*	[120]

Sources	Approaches	Shape	Size (nm)	Applications	Bacteria/ Fungi	References
Fungi						
Trichoderma asperellum, *Phialemoniopsis ocularis*, *Fusarium incarnatum*	Extracellular	Spherical	25 ± 3.94 13.13 ± 4.32 30.56 ± 8.68	-	-	[71]
Alternaria alternata	Extracellular	Cubic	9 ± 3	Antibacterial activity	*Escherichia coli, Proteus mirabilis, Bacillus subtilis, and Pseudomonas aeruginosa*	[113]
Aspergillus flavus isolate D05	Extracellular	Spherical and irregular	28–33	Antibacterial activity antifungal activity	*Staphylococcus aureus, Escherichia coli, Candida albicans* *Aspergillus Fumigatus*	[114]
Bacteria						
Proteus vulgaris	Extracellular	Spherical	19.23–30.51	Antibacterial activity	*Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli, Salmonella typhi,* *Vibrio cholera, and Methicillin-resistant Staphylococcus aureus (MRSA)*	[111]
Algae						
Colpomenia sinuosa (Brown seaweed) and *Pterocladia capillacea* (red seaweed) aqueous extracts		Spherical	11.24–33.71 16.85–22.47	Antibacterial & Antifungal activity	*Escherichia coli, Pseudomonas aeruginosa, Salmonella typhi and* *Vibrio cholera, Bacillus subtilis and Staphylococcus aureus;* *Aspergillus flavus and Fusarium oxysporum*	[115]

negative (*P. aeruginosa, E. coli, Vibrio cholera*) than Gram-positive bacteria (*Salmonella typhi, B. subtilis, S. aureus*). It may be due to cell wall composition. The gram-positive outer cell wall has thicker peptidoglycan than gram-negative, which act as a resisting layer and lead to difficult permeation of nanoparticles. In addition, the small size of nanoparticles contributes to antibacterial capability as the high surface area to volume ratio [115]. Majeed et al. [111] found that IONPs synthesized from *P. vulgaris* displayed antibacterial activity. The highest zone was indicated in *E. coli,* followed by *S. aureusus, V. cholera. S. typhi* and *Staphylococcus epidermidis*. In addition, IONPs showed good antibacterial activity at 40 μg/ml against MRSA (Methicillin-resistant *S. aureusus*) [111].

Information on the biological sources used, physiochemical, and application of IONPs in anticancer and antimicrobial activities are summarized in Table 2 and Table 3.

4. Conclusion and future scope of work

Green synthesis of IOPNs has been shown to have potential anticancer and antimicrobial properties. The bioactive compounds from biological sources such as plants, fungi, bacteria, and algae have a pivotal role in reducing, capping, and stabilizing nanoparticles. Hence, nanoparticles synthesized from this process are considered safe, eco-friendly, and do not cause harm to health compared to physical and chemical methods. The biological action of IONPs against cancer cells and microorganisms is strongly linked to their physiochemical characteristics such as size, shape, stability, and composition. In-vitro studies reveal that IONPs exhibited various mechanisms as anticancer and antimicrobial therapies. IONPs have disrupted cell proliferation, induced apoptosis, and damaged DNA, mitochondrial, macromolecules, cell wall, and membrane through ROS-mediated oxidative stress. Their activities against cancer cells and microorganisms exhibit the potential development of biosynthesis IONPs to overcome the limitation faced by conventional treatment. However, the main challenge of nanoparticle biosynthesis is obtaining the desired size and monodisperse nanoparticles, as these characteristics determine their efficiency. Therefore, the adjustment parameters during the biosynthesis of nanoparticles are significant. In addition, must evaluate the toxicity and compatibility of IONPs to assure their use's safety. Therefore, the in-vivo study needs to be conducted before IONPs can be employed in therapeutic application.

Conflicts of interest

No conflict of interest among authors.

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