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Original Article

Application of Nanotechnology in Antimicrobial and Antitumor

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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: Nanotechnology , Application, Antimicrobial, Antitumor

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Introduction:

Cancer is a dreadful disease that causes mortality worldwide, with an expected 10 million deaths in 2020 [H. Sung and et al 2020]. According to WHO, by 2040, it is likely that more than 27.5 million new cancer cases will occur and 16.3 million deaths [J. Ferlay, et al 2019]. The most endangering factors for unmodifiable factors include gender, age and family history [H.J. Youn, et al 2020], and modifiable factors include obesity, tobacco use, imbalanced diet, sedentary lifestyle, and alcohol intake [F. Islami, et al 2018]. Cancer occurs due to abnormal accumulation of cells arising from an imbalance of cell proliferation and programmed cell death (apoptosis) [A. Letai, 2015]. Cancer cells can survive longer due to mutation, abnormal cell proliferation, and differentiation leading to tumour progression, angiogenesis, and metastasis development [M. Hassan 2014]. Chemotherapy and radiation therapy, which are currently used to treat cancer, can inhibit uncontrolled cell proliferation [G. Baskar et al 2015 and , E. Dickens et al 2018]. 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 [J. Fernando, et al 2015]. In addition, some reports showed that cancer cells are resistant to the chemotherapy drug's action [Y. Zhao, et al 2013]. 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 [J.M. Stokes, et al 2019]. 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 [K.Bush,et al 2011]. It causes the multidrug-resistant bacterial problem has become a global health threat [F. Prestinaci,etal 2015and , E. Tacconelli,et al 2018]. Therefore, there is an urgent need to find new effective agents to overcome drug resistance. In this regard, nanotechnology revealsnew 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 [H. Barabadi, et al.2019,and A.K. Mittal et al 2013,]. 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 [K.B. Narayanan, et al 2010 and H.D. Yu, et al 2013]. 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 [I. Khan, et al 2019]. Interestingly the nano-sized particles have immense applications due to their non-toxicity, non-immunogenicity, and ability to get modified to target specific applications [L. Aakash et al 2020]. 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 [J.K. Patra, et al 2014 and S. Bayda, et al 2020]. It is an approach or method to overcome the limitation of conventional methods in synthesizing nanoparticles [N.N. Prabhu 2018].

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 byproducts harmful to nature and life that cause usage limitations of their products [P. Khandel, et al 2016 and H. Bahrulolum et al 2021]. 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, nontoxic, environmental-friendly, and readily scaled for large-scale synthesis [P. Khandel et al 2018 and , S. Patil et al (2020) and P.

Velusamy, et al 2016]. Biological methods that apply the bottom-up approaches synthesize metal nanoparticles from the atoms or molecules to nanoscale molecular structure via different chemical processes. Thismethodemploys 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 [G. Manikandan et al ,2021 and P.V. Rao, et al,2016]. Metabolite products from microorganisms, including enzymes, protein, carbohydrates, vitamins, and fats,

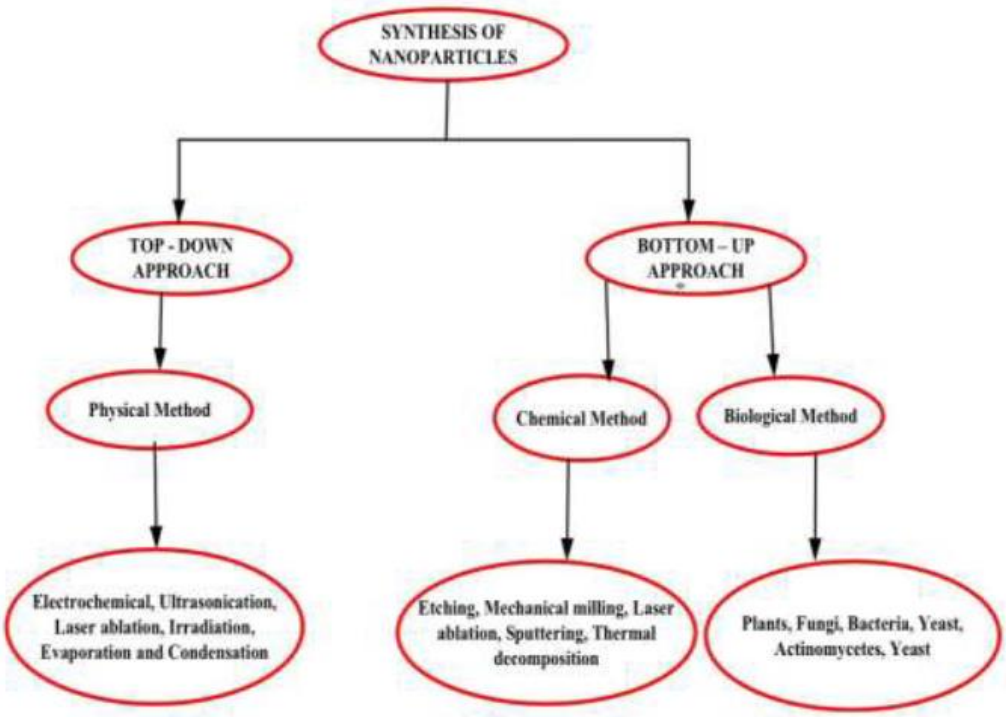

Fig. 1. Various approaches for the synthesis of nanoparticles.[K.B. Narayanan and, N. Sakthivel,2010].

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 [J. Kudr, et al 2017 andK.S. Siddiqi, et al 2016].

Several studies have indicated that the IONPs serve as promising anticancer and antimicrobial agents as their actionwith biomolecules in cancer and

microbial cells [A.A. Hern_andez-Hern_andez et al 2020 andP. Martinkova et al 2018 and M. Arakha et al 2015]. Superparamagnetic iron nanoparticles' magnetic, optical, photochemical, electrical, and chemical features are particularly useful in biomedical applications [N. Ajinkya,et al 2020]. The advantages of IONPs include non-toxic, biodegradable, non-immunogenic, and biocompatible [M.A. Gatoo,2014]; hence the interest of researchers in iron oxide nanoparticles keeps growing due to their unique characteristics applicable for various applications [H. Barabadi 2017]. Their biological activities are determined by nanoparticles' physiochemical, such as shape, size, concentration, and surface charge [K.S. Siddiqi 2016]. 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.

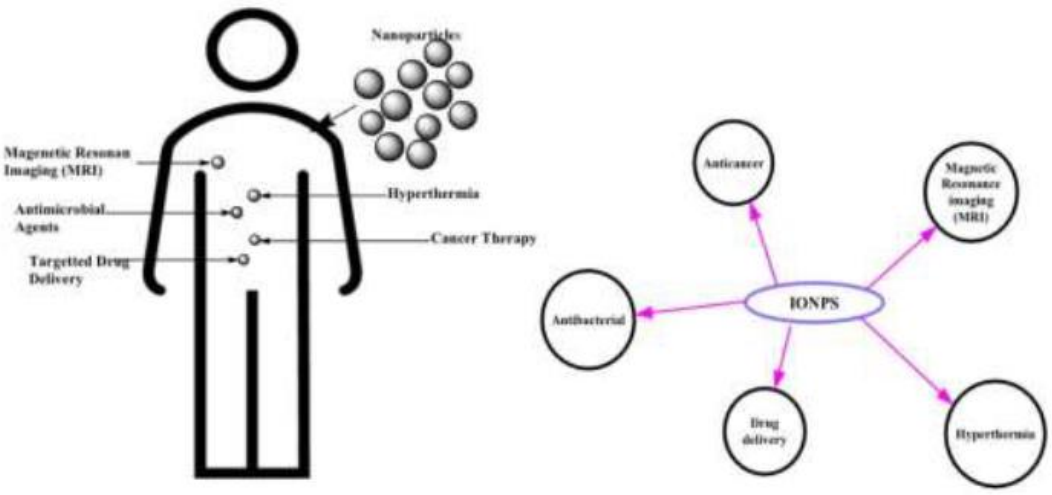

Fig. 2. Biomedical employments of IONPs.[J. Kudr, et al ,2017

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 [G. Manikandan, et al 2021, Naveen Priya et al,2021].

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 plantsposes many advantages,

such as being easy, fast, cost-effective, eco-friendly, and non-toxic to the environment

and biological system [E. Üstün, et al 2022].

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 forvarious 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 asNADH-nitrate reductase enzymes,

anthraquinones, and protein that act as the capping and reducing agents to reduce

metallic irons into metal nanoparticles [A. Yadav et al 2015 and K. Zomorodian, et al

2016

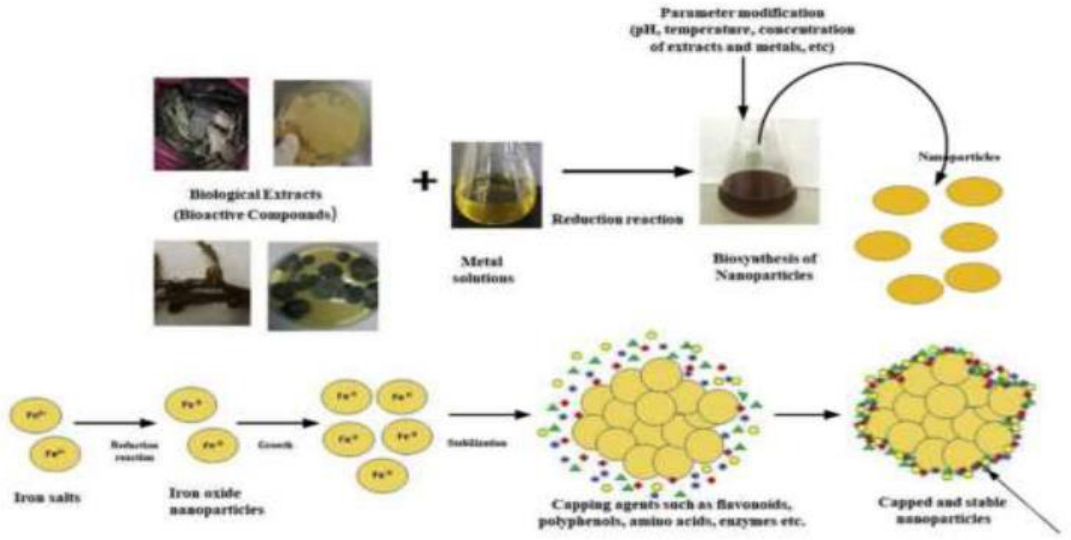

Fig. 3. Schematic representation of the mechanism of IONPs using biological sources (Plants, fungi, bacteria, algae).[N.N. Prabhu, 2018]

3. Applications of IONPs in antimicrobial agents

3.1.Antimicrobial activity From plants

[Kanagasubbulakshmi & Kadirvelu2017] 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 [Kanagasubbulakshmi & Kadirvelu2017]. 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 [M.K. Rachael and P. Rajiv 2020]. A comparative study between synthesis IONPs from Phyllanthus niruri leaf extract dan chemical method synthesis was conducted by [Viju Kumar & Prem 2018]. The study found that the biosynthesis of IONPs is more advantageous than toxic chemicals as it is more cost-effective, energy-efficient, lowcost, 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 [Viju Kumar & Prem 2018]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 [M. Jamzad and M. Kamari 2020]. [Bhuiyan et al.2020] 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 [Bhuiyan et al.2020]. Another study of antibacterial and antifungal effects of biosynthesized IONPs from S. thea (Osbeck.) was reported by [Khalil et al.2017]. 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 nonoxidant 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 nonsymmetry nanoparticles surface can also contribute to the cause of cell injury [Khalil et al.2017]. [Qasim et al.2020] 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 [Qasim et al.2020. Ruellia tuberosa (RT) leaf aqueous extract was employed to synthesis IONPs by [Vasantharaj et al.2019]. 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 [Vasantharaj et al.2019].

According to [Devi et al.2019], the antifungal activity of IONP employed fromP. orientalis extractwas 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 [Devi et al.2019]. [Goma 2018] 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 [Goma 2018].. [Da'na et al 2018] 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 interactionwith the bacterial surface and play a crucial role in defining IONP's antibacterial potential [Da'na et al 2018]. 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 [G. Manikandan,and R.

Ramasubbu, 2021]. Antibacterial activity of IONPs synthesized from R. triquetra showed the IONPs were more potent against S. aureus and Bacillus subtilis (MIC: 37.5 mg/ ml) and least effective towards K. pneumoniae and Ecoli (MIC: 75 mg/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 2020]. Among the fungal strains, Candida albicans and A. flavus were the least sensitive strains (MIC: 75 mg/ml), while A. niger was the most sensitive (MIC:37.5 mg/ml). The fungal growth inhibition is due to the production of ROS and restriction of IONPs to fungal spores/hype [Abbasi et al 2020]. The proposed mechanism of antimicrobial activity of IONPs was shown in Fig. 5

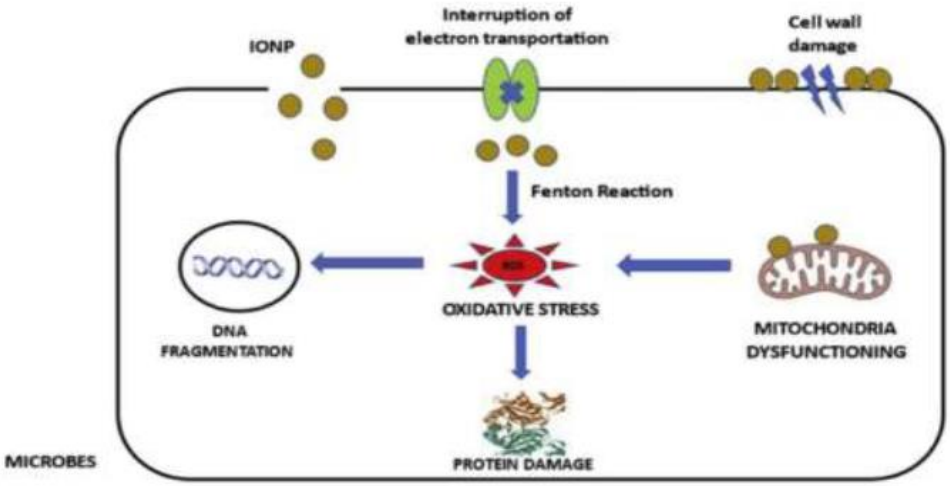

Fig. 4. Proposed mechanism of antibacterial activity of biosynthesized iron oxide nanoparticles.[B.A. Abbasi, et al 2020]

3.2.Antimicrobial activity From microorganism

Antimicrobial activity The biosynthesis of IONPs employing A. alternate 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 [Y.M. Mohamed, et al 2015]. [Gouda et al. 2020] 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 [Gouda et al. 2020] . [Salem et al. 2019] 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-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 [Salem et al 2019]. [Majeed et al.2021] 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 mg/ml against MRSA (Methicillin-resistant S.aureusus) [Majeed et al t al.2021

4. Applications of IONPs in anticancer

4.1. Anticancer activity from Plants

Various research has been carried out to explore the anticancer activity of IONPs synthesized from plants. A study by Yusefi et al. [M. Yusefi, et al 2020] 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 [M. Yusefi, et al 2020]. Another study, [Yusefi et al 2020.] 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 (Fe3O4 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 a-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 [M. Yusefi, et al 2021]. Iron oxide nanoparticles (a-Fe2O3 (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 [P.C. Nagajyothi, et al 2017]. 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 [M.S.H. Bhuiyan et al 2020].

[Khalil et al.2017] 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 mg/ml), indicating the safety of IONPs [Khalil et al.2017]. 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.2018]. 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 [Farshchi et al.2018].

Anticancer activity of IONPs synthesized from R. gilgitica leaves extract was investigated by [Iqbal et al.2020] 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 [Iqbal et al.2020]. [Abbas et al.2019] 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 [Abbas et al.2019].. [Abbasi et al2020] also found that IONP from R. triquetra (RT) leaves extract exhibited cytotoxic effect against HepG2 cancer cells (IC50:11.2 mg ml_1). The biocompatibility tests against human RBCs and macrophages confirmed the biocompatibility and non-toxic behaviour of IONPs [Abbasi et al2020]. 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 [S. Naz, 2019]. [Yoonus et al.2020] 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 signaling cascades resulting in cytotoxicity [Yoonus et al.2020]. 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 100e1000 mg/ml IONPs. The membrane asymmetry was lost in the apoptotic cells, which caused phosphatidylserine to be exposed on the membrane surface [O. Erdogan, et al 2021]. 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 mg/ml) [A. Bali Ogholbeyg, et al 2018]. Another study employed Eucalyptus leaf extract in synthesizing IONPs, and its anticancer activity was evaluated. In this study, the authors reported thatcisplatin-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) [A. Morovati, et al 2019]. The proposed mechanism of anticancer activity of IONPS was shown in Fig. 4

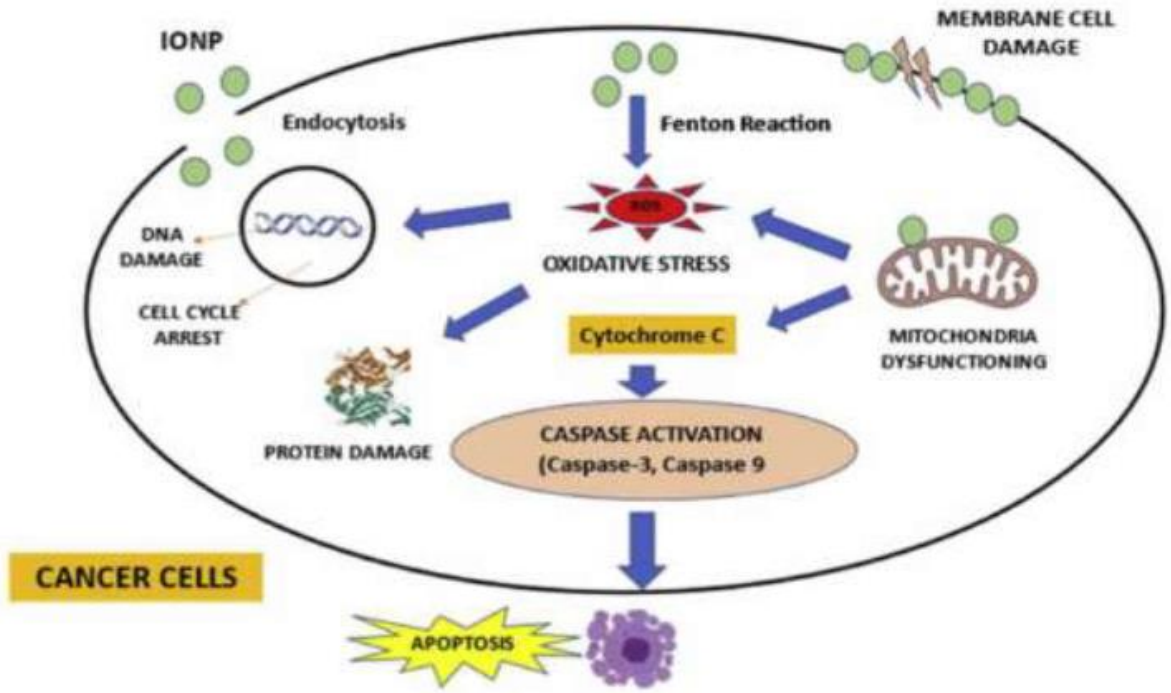

Fig. 5. Proposed mechanism of anticancer activity of biosynthesized iron oxide nanoparticles.[A. Morovati , et al 2019]

4.2.. Anticancer activity from Microorganisms

[Fatemi et al 2018] 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 [Fatemi et al 2018]. [Majeed et al.2021] evaluated the anticancer activity of IONPs synthesized from Proteus Vulgaris. 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 [Majeed et al.2021]. In another study [, Namvar et al.2014] 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 [, Namvar et al.2014]

5.Conclusion

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.

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