



Basic Nano Magnetic Particles and Essential Oils: Biological Applications

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Abstract

Essential oils (EOs) are complex mixtures of volatile compounds with different biological properties. Essential oils and their ability to resist the production of biofilms by pathogenic microorganisms have been linked to antimicrobial activity. After adherence of these pathogenic microorganisms to surfaces leads primarily to antibiotic resistance, it is vital to look for compounds or methodologies with this capacity. Essential oils have gained a lot of attention in recent years due to studies of their anti-bacterial, antiviral, anti-fungal, and insecticidal properties. Due to their low toxicity, biocompatibility, biodegradability, capability to precisely target tissue, and initial structures that enable various therapeutics to be attached, MNPs (magnetite nanoparticles) are one kind of nanocarrier that could be used to deliver EOs for antimicrobial therapies effectively.

Keywords: Magnetite Nanoparticles; Nano therapies; Antibiotic-resistant Bacteria; Nanoscaled Carriers; Anti-bacterial Essential oils

1 Introduction

Infections caused by bacteria, including those produced by drug-resistant bacteria, have posed a significant threat to human health worldwide. Antimicrobial resistance is estimated to kill 10 million deaths per year; early detection and treatment will significantly reduce the number of people who die due to bacterial infections. Given the epidemic's size, it is crucial to progress appropriate practical strategies for the early (detection, prevention, and treatment) of infections. Until now, various attempts to identify and kill pathogenic bacteria using nanoparticles have been made. While most microorganisms contribute to the survival of life on Earth and in Nature, a small number of infectious agents may trigger severe disease outbreaks and difficult-to-control pandemics. To get through the host's defensive mechanisms, pathogenic microorganisms use various tactics and virulence factors to infect the host. According to the (World Health Organization (WHO)) parasites, toxins, viruses, bacteria, and toxic as potentially lethal biohazards [1-3]. Pathogenic bacteria create extracellular polymeric matrices, known as glycocalyx, which are made up of lipids, nucleic acids, and polysaccharides [4-6]. Bacteria use these structures to bind to both biotic and abiotic substrates, forming biofilms linked to multicellular consortiums of cells with distinct constructions and modified phenotypes [5]. Biofilm formation is an important strategy for defending microorganisms against antimicrobial and environmental agents, dehydration, and starvation. There is also the immune system of the host, antibiotics, and biocides to remember. Corresponding to the (National Institutes of Health (NIH)), biofilm development with persistent infection persisting in 65-80% of instances is a significant factor in infection survival and recurrence [7-9].

Essential oils (EOs), as secondary oils extracted from plants, have become increasingly common. Metabolites are critical in defense mechanisms [10]. EOs have used a diverse combination of volatile organic compounds and odoriferous in

several medicinal uses, including herbal self-care products, cosmetics, and dermatology, since their inception. Many studies have shown that they can treat infections that are resistant or very difficult to treat. Antimicrobial (anti-bacterial, anti-fungal, antiviral, and antiparasitic) activity is becoming more widely recognized [11-14]. It is challenging to prescribe EOs to obtain the minimum inhibitory concentration against bacterial infections because of their lipophilic and reactive nature. In this case, nanotechnology and microencapsulation techniques can provide a possible solution [15-17]. Magnetic iron oxide nanoparticles are being studied for different uses, including theranostic, magnetic resonance imaging, and drug delivery, due to their extensive use and industrial formulations [18, 19]. The ability to use magnetic fields to guide nanoparticles to the desired position, resulting in increased heating and controlled drug release, is critical to their applicability. Magnetic properties have also been found to improve diagnostic precision by increasing imaging resolution and contrast. The two implementation pathways for both detection and treatment of theranostic alternatives are being combined in current trends. Iron oxide nanoparticles, especially magnetite, have biodegradability, biocompatibility, non-toxicity, and the ability to precisely primary structures and target tissue that enable different therapeutics to attach [18-24]. Thus, (EOs) and (MNPs) systems may represent a new and successful path in infectious disease executives [25].

2 Essential Oils as Antimicrobial Agents

Various extraction techniques use many plant segments, as well as flowers, barks, leaves, buds, seeds, and peels, based on the species and the type of segment, with extraction yields of solvent and solvent properties, for example, polarity, temperature, pH, concentration, and acidity [9, 26-28]. To avoid any potential significant changes in Eos' chemical composition, these approaches usually recommend a physical technique [26, 29]. Essential oils are extracted using various

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methods, including solvent extraction, cold pressing, steam or water distillation, and enfleurage. These approaches have many disadvantages, including heavy energy demand and carbon dioxide emissions [30]. A novel promising "green" technique has been developed to increase EO efficiency and extraction yield capable of generating EOs with similar and improved characteristics, sustainable, cost-effective, and non-thermal [13, 27, 30, 31]. These methods include immediate pressure drop processes, extraction, enzyme-assisted extraction, molecular distillation, steam diffusion, microwave steam distillation, ultrasound-assisted extraction, pressurized liquid extraction, extraction of pulsed electric fields, accelerated solvent extraction, microwave-assisted extraction, and

supercritical fluid extraction [32]. Table 1 reviews the advantages and disadvantages of required extraction methods.

Essential oils are a complex blend of terpenic hydrocarbons, especially monoterpenes and sesquiterpenes, as well as oxygenated derivatives like aldehydes (citronellal, sinensal), alcohols (geraniol, α -bisabolol), ketones (menthone, p-vetivone), phenols (thymol), and esters (γ -terpinyl acetate, cedryl acetate) [33]. Non-terpenic compounds known as phenylpropanoids are found in essential oils and give them a distinct flavor and odor. This collection of constituents contains eugenol and cinnamaldehyde Figure 1 [34, 35], which establishes the chemical structure of various components of essential oils [35].

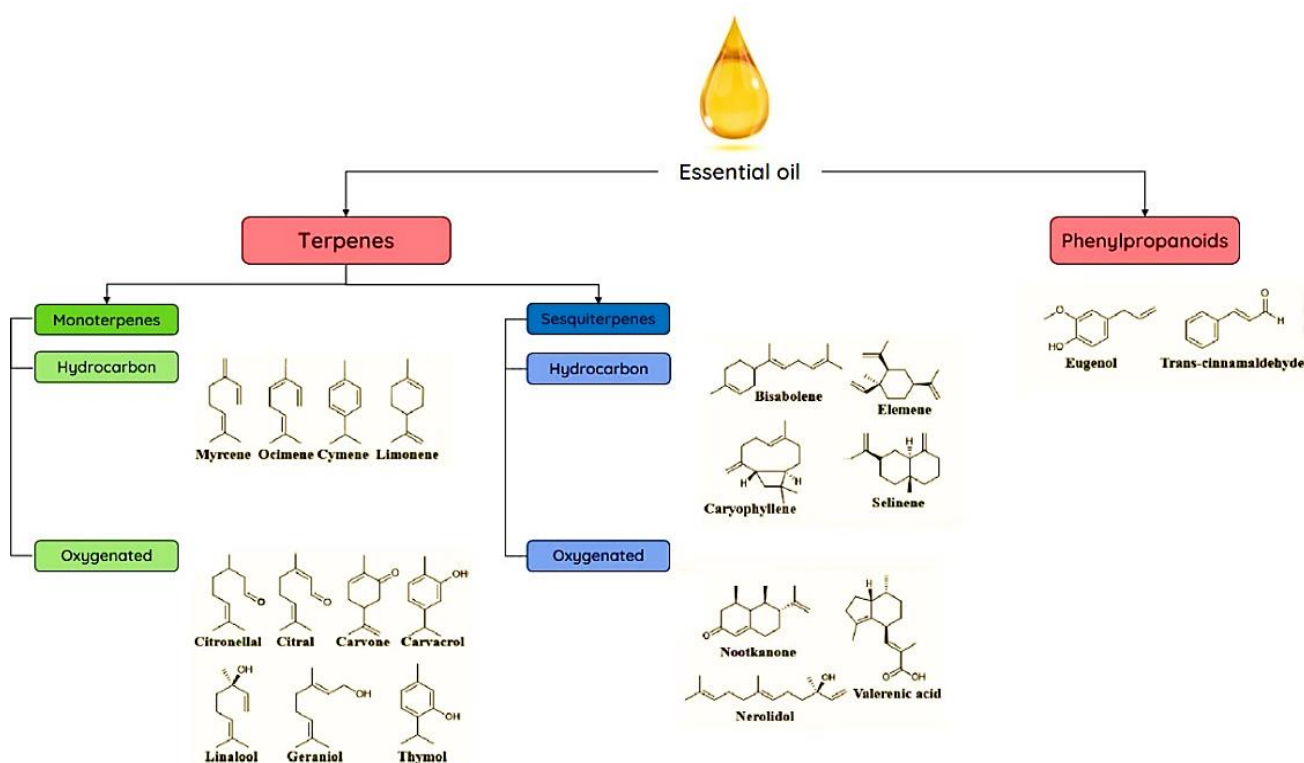


Figure 1: Chemical structures of some constituents of essential oils [35]

Table 1: The advantages and disadvantages of the principal EOs extraction methods [5, 30, 32]

Extraction Method	Advantages	Disadvantages
Enfleurage	Using lower temperatures	Time-Consuming; Labor-Intensive; Expensive
Cold Pressing	Using lower temperatures	Low Yield
Solvent Extraction	Inexpensive; Fast; Used During the Process; Lower Temperatures	Trace Amounts of Solvent, Compounds; Low Yield; Long Extraction Times; Loss of Volatile
Ultrasound-Assisted Extraction	High Yields; Avoidance/Reduction of Organic Solvents; Minimum Effects on Extractable Compounds; Shorter Extraction Times	Expensive
Supercritical Fluid Extraction	Environmentally Friendly; Fast; Low Energy Costs Analytically; Low Temperatures Used Throughout the Process and Industrially Scalable; High Selectivity	Lower EOs Quantities
Steam or Water Distillation	Straightforward Process	High temperatures can lead to chemical changes in compounds; Might Require Oil Rectification (Redistillation); Low Yield; Loss of Volatile Compounds
Microwave-Assisted Extraction	Shorter Extraction Times; Reasonable Costs; Higher Extraction Yields; Good Performance under Atmospheric Conditions;	Less Environmentally Friendly; Organic Solvent; Requires Higher Quantities of
Instantaneous Controlled Pressure Drop Process	Lower Energy Required; Higher Extraction Yields; Does Not Require the Use of Solvents; Enhanced Global Diffusivity; No Chemical Changes in the Compounds;	-

EOs are complex, volatile compound mixtures made up of two or three main components at relatively high concentrations, such as 20-60 components and 20-70% at different trace quantity concentrations. The major constituents of EOs are classified into two molecular families based on their hydrocarbon skeleton: terpenoids like thymol and carvacrol and phenylpropanoids like eugenol and cinnamaldehyde. Terpenoids based on the number of isoprene units are divided into monoterpenes, sesquiterpenes, and diterpenes. Monoterpenes are made up of two, three, or four units of 5-carbon building blocks. Based on ring complexes, oxygen incorporation, double bonds, and stereochemistry, over 3000 sesquiterpenes and 1000 monoterpenes. Even though both groups contain phenolic compounds, their biosynthesis pathways and metabolic precursors are distinct. Terpenoids are produced by the mevalonate and mevalonate separate pathways, while phenylpropanoids are produced by the shikimate pathways [15, 36, 37] {Tariq, 2019 #26; Omonijo, 2018 #27; Omonijo, 2018 #41}. Chemical groups may be used to classify the volatile compounds found in EOs, such as amides, phenols, aldehydes, alcohols, amines, ketones, and esters [10, 16]. The structure and concentration of essential oils (EOs) determine their therapeutic effects. As a result, a broad range of bioactive properties can be seen, as well as

neuroprotective, hepatoprotective, cardioprotective, antioxidant, anxiolytic, anti-cancer, anti-bacterial, anti-inflammatory, anti-diabetic, antiviral, anti-hyperpigmentation, antibiotic, and acaricidal Figure 2 [11, 36-38].

EOs including carvacrol, thymol, eugenol, citral, cinnamaldehyde, ketones, linaldehyde, or esters myrcene, alpha-thujone, or geranyl acetate has the most robust anti-bacterial activity. Terpene hydrocarbon-containing EOs usually are inactive [10]. Antimicrobial efficacy is improved or decreased due to interactions between these chemicals, which may take four different forms: additive, indifferent, synergistic, or antagonistic. The type of bacteria and their crude biochemical profile and the ratio influence EO anti-bacterial results [11, 31]. Owing to their hydrophobic nature, EOs can cross the lipids that structure bacterial cell membranes and disrupt cell wall structures, having both single and multiple target results. Electron flow, cell content coagulation, active transport changes, proton driving forces, ion, cellular material leakage, and cell death are all caused by increased membrane permeability Figure 3 [31] demonstrates the precise pathways involved in EOs anti-bacterial action. Besides, EO's anti-bacterial properties include aldehydes, phenols, and alcohols throughout their composition [39].

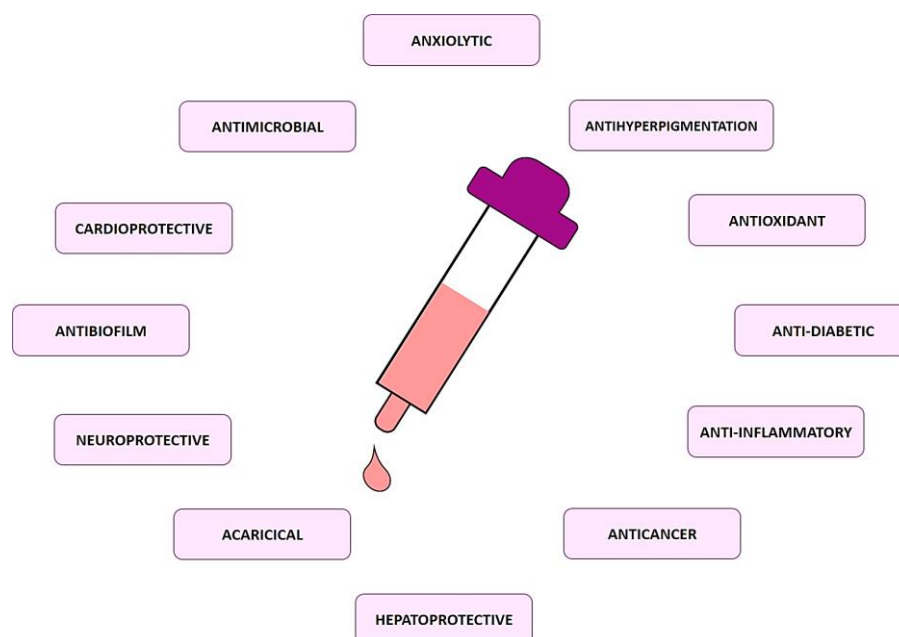


Figure 2: The foremost bioactive properties of Eos [5]

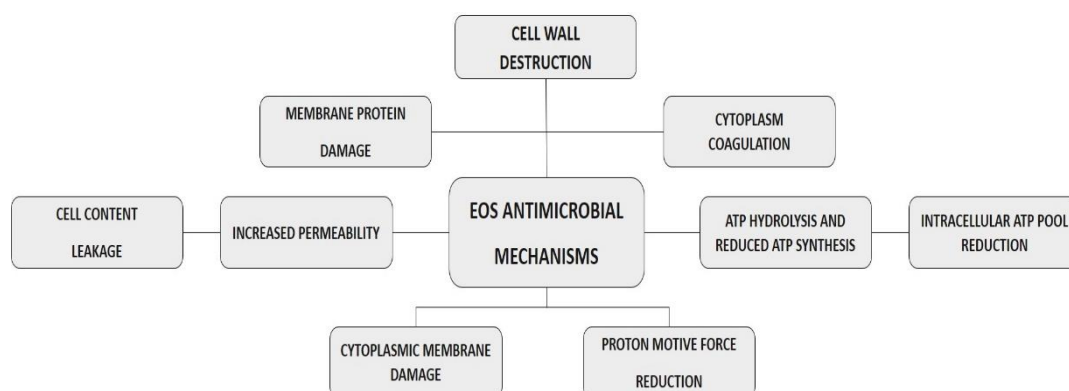


Figure 3: The key pathways that are involved in EOs' anti-bacterial activities. Adapted from Bhavaniramya et al., 2019, 'function of essential oils in food safety: antioxidant and antimicrobial applications' [10] ATP = the triphosphate of adenosine [5, 31]

Furthermore, 60% of EO derivatives could be beneficial in the food preservation industry because they have anti-fungal activity. EO's anti-fungal activity's underlying mechanisms are similar to the anti-bacterial activities previously mentioned, that is to say, membrane depolarization, ion channels and disruption of proton pumps, depletion of ATP pools, and consequent cell death via necrotic and apoptotic procedures. The presence of phenolic compounds, as well as alpha-terpinyl acetate, thymol, carvacrol, and terpenes, cymene, for instance, linalool and pinene, when conjugated with the CHO group of unsaturated aldehydes and carbon in the form of C = C [5, 40], is usually responsible for the anti-fungal bioactivity. The antiviral function of EOs is traditionally linked to interfering with virion envelopment processes, which prevent virion entry into the host cell. Despite this, the fundamental pathways remain unknown, necessitating further study in the field. In recent years, antimicrobial applications as carriers for EO distribution have sparked a lot of interest in nanometric systems [31, 41]. Nanomaterials benefit from increasing EO efficiency and providing protection against volatilization; they can penetrate membranes and biological barriers since they are absorbed by cells. Even though nanomaterial synthesis typically includes a step of heating or solvent evaporation, developing EOs and systems based on nanomaterials remains difficult. In developing such systems, MNPs have gained considerable interest; many studies have been conducted in recent years to investigate MNPs and EOs systems' antimicrobial activity.

3 Functionalization, and Magnetite Nanoparticles Synthesis

Concerning optical, electrical, and magnetic nanoparticles, they offer remarkable possibilities. Properties that can develop improved medical devices and therapeutics [42]. Inorganic nanoparticles have long been thought to be a viable tool for creating targeted drug delivery systems, medical imaging, and clinical diagnostics in this regard. Iron oxide, zinc oxide, silver, gold, and titanium are the most widely used inorganic nanoparticles for these purposes. Magnetic nanoparticles, in particular, have widened the potential for novel and practical biomedical uses due to their superparamagnetic properties, making them the first generation of clinically accepted nanomaterials, such as selective delivery of drugs and genomes, cancer detection and treatment, biosensors, magnetic resonance imaging, and diagnosis. The furthestmost common categories of iron oxide nanoparticles, which belong to the ferrimagnetic class of magnetic nanomaterials, are maghemite ($\gamma\text{-Fe}_2\text{O}_3$), mixed ferrites (MFe_2O_4 , where M = Co, Mn, Ni or Zn), hematite ($\alpha\text{-Fe}_2\text{O}_3$), and magnetite (Fe_3O_4) Figure 4 [43-47].

4 Synthesis Methods

Since their discovery, MNP synthesis approaches have been the right to investigate the subject because their scale, shape, and surface chemistry significantly affect how they behave. Furthermore, any modifications made during the planning phase would have a significant impact on the final product. Chemical, physical, and biological techniques are three important routes for MNP synthesis, depending on the desired characteristics and application area Figure 5 [48-52].

5 Physical Methods

MNPs are made using a top-down process, which involves physically separating large particles or bulk materials into nanoscale particles. These methods are suitable for large-scale nanoparticle growth, but they have severe advantages such as

inexpensive technologies, time-consuming, non-uniform size distribution, and particle size regulation [20, 53].

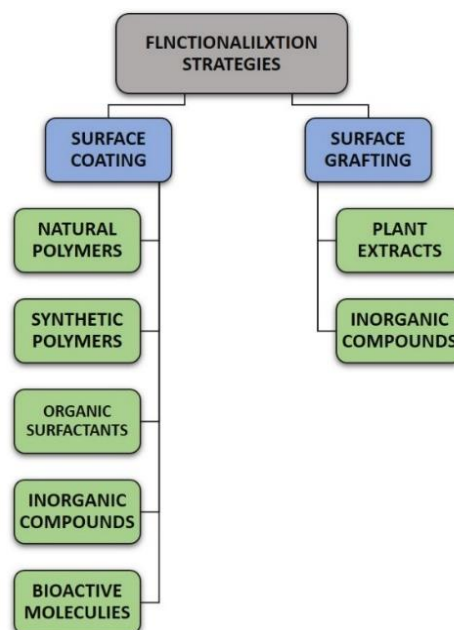


Figure 4: The main functionalization strategies for MNPs [5]

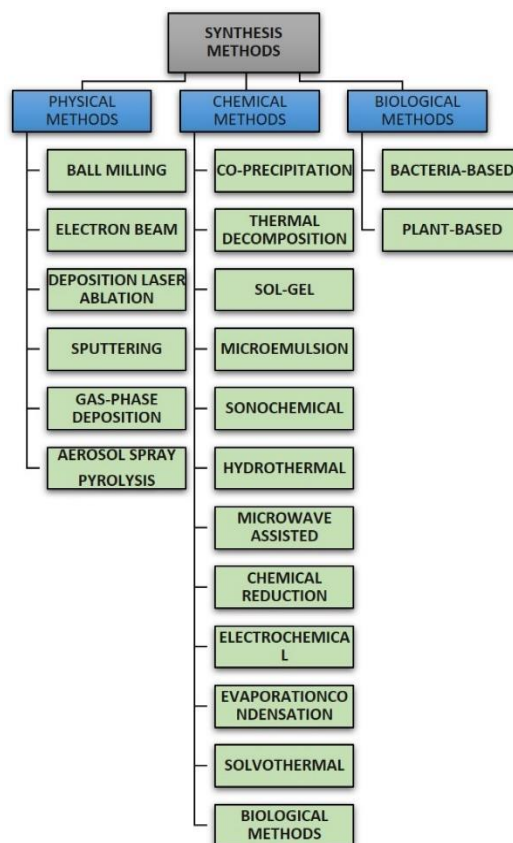


Figure 5: The furthermost standard techniques for making MNPs are as follows [5]

Among the various physical methods for synthesizing MNPs are sputtering, aerosol spray pyrolysis, gas-phase deposition, laser ablation, electron beam lithography, and ball milling [20, 53-55]. On the other hand, ball milling is a solid-state synthesis process that uses a collision between reactant

surfaces to generate frictional force, which raises the temperature, pressure, and internal energy [56]. Even though milling can be divided into high-energy and low-energy milling, the latter is greatly preferred to synthesize nanoparticles [57]. Electron beam lithography describes high-purity bulk iron materials or films' conversion into MNPs by emitting an electron beam through a high-purity bulk iron material or film deposited on a substrate. The interaction volume of the incident electrons is guided and accelerated towards the surfaces, resulting in electron-electron collisions and a change in the resistant substrate's chemical properties. After the initial iron precursors have evaporated, MNPs are formed [53, 58, 59].

6 Chemical Methods

Bottom-up methods are the most commonly used chemical methods because they are more cost-effective, time-efficient, easier to use, precise, and have a smaller particle delivery. Sol-gel, microemulsion, thermal decomposition, and co-precipitation are the furthestmost popular chemical synthesis methods [20]. Due to its cost-effectiveness, non-toxic composition, and mild reaction conditions, the co-precipitation process is one of the most widely used methods for synthesizing MNPs [5, 60-62]. It focuses on the nucleation and grain growth phenomenon. A combination of chlorides, perchlorates, sulfates, and iron Fe^{3+} and Fe^{2+} salts in nitrates, for instance, potassium hydroxide, sodium, or ammonia, precipitates when a base is added. To keep track of particle size [63], it is essential to use surfactants or polymers. Aside from that, the salts' form and concentration, the mixing rate, the ionic potency, and the medium's temperature and pH must all be considered [63] are affected by the shape, size, and magnetic properties of MNPs. However, as irregular large size distribution, forms, and low MNP crystallinity are obtained by co-precipitation, high-temperature synthesis techniques must prepare high-quality MNPs; thus, Thermochemical decomposition is becoming one of the most common methods for preparing MNP [16, 64, 65]. In high-boiling organic solvents, MNPs are produced by mixing iron precursors like acetates, acetylacetonates, and oleates with stabilizing and surfactants agents like oleylamine and oleic acid. To cause a nucleation reaction, the thermally unstable metal complexes are injected into the hot solution; this allows for modifications of the synthesis parameters for tuning the shape and size of the nanoparticles [5, 66].

A primary solution of precursors is used in the sol-gel process, usually metal-organic compounds or inorganic metal salts in a suitable solvent. A polymerization reaction happens when a surfactant is added, resulting in the "sol," a colloidal suspension of dispersed particles. Following that, a chemical reaction that disables the surfactant produces a broader network of entangled particles, forming the solution's gel. When a solvent evaporates, MNPs can form [67]. Because of its high homogeneity, low cost, and consistency of the nanoparticles obtained, the sol-gel approach is beneficial. To achieve a final crystalline state, further heat treatments are required. The microemulsion method includes preparing an aqueous phase microemulsion to be precipitated with ferrous ions and/or ferric acid by injecting organic precipitating agents, for example, oleylamine or cyclohexylamine. While it has the advantage of controlling the size and shape of the MNPs generated, it also has the disadvantage of aggregation and stability issues [68-70]. Solvothermal methods, electrochemical, hydrothermal, evaporation-condensation, microwave-assisted, and chemical reduction are other methods for the bottom-up synthesis MNPs [20, 71].

7 Biological Methods

Biological techniques use bottom-up approaches that include green biosynthesis processes. Metal precursors are used to making metal atoms, which are then formed into nanoparticles. Since the natural compounds in green substrates serve as both capping and reducing agents, the dispersibility, form, and concluding size can be organized by some parameters, for example, incubation time, temperature, pressure, and pH [53, 72]. As more metal ions are sequestered, the mechanism involves creating tiny nucleation centers that stretch around the nucleation site. Nanoparticle capping is needed to prevent and stabilize accumulation due to their high surface energy levels [73]. Higher plants, fungi, algae, and bacteria are included [53] in these processes. Although biological approaches are the greatest environmentally sustainable, cost-effective, and produce the most biocompatible nanoparticles [20, 74]. Strategies based on bacteria contain magnetotactic and iron, reducing the intracellular or extracellular production of MNPs by bacteria under anaerobic conditions. However, to remove the abundance of capping biomolecules, specific approaches typically include more therapies, such as calcination, sonication, and detergent use. On the other hand, plant-based methods necessitate various substrates, such as callus, fruit, leaf, or seed extracts. The utmost promising technique for large-scale growth in a short time is the synthesis of plant-mediated MNPs. Furthermore, since waste products also contain biomaterials from plants, they are easy to dispose of in the atmosphere [73, 75, 76].

8 Anti-bacterial activity of MNPs

8.1 Effect of shape

Studies of NP properties demonstrate particle shape's significance in deciding the desired antimicrobial and biological output [77-80]. It is also assumed that engineered NPs of various forms can be adapted to target specific cells [81]. Although the impact of particle form on the anti-bacterial possessions of AgNPs is apparent [82], MNPs' shape-dependent bacterial inhibition is still being researched. Apart from standard spherical NPs, the anti-bacterial properties of particles with other morphologies were investigated. Professional anti-bacterial activity against *Staphylococcus aureus*, *P. aeruginosa*, and *E. coli* showed an average diameter of 60 nm in synthesized NiO nanorods [83]. Ni-based anti-bacterial nanosystems include NiO/TiO₂ composite nanofibers [84] and NiO nanotubes [85], associated with traditional NiO and NiO nanoflowers, which would be effective in inhibiting the livability of a wide range of bacterial strains. Also, nanorods of Ni-doped zinc oxide (ZnO) have notable anti-bacterial potency and can fully eradicate the multi-drug-resistant bacteria described above [29, 86].

8.2 Effect of size

Since NPs with an average diameter greater than 40 nm are thought to be unable to penetrate the cell membrane, their size can be used to determine their ability to enter intracellular space [87] passively easily. Jose Ruben et al. [88] Size-dependent anti-bacterial activity has been observed in AgNPs synthesized in various diameters. Direct interaction with Gram-negative bacteria is more likely, with the size of NPs less than 10 nm. Furthermore, metal NPs' antimicrobial activity is considered a feature of their effective surface area. According to Digigow et al. [89], in the presence of superparamagnetic iron-oxide NPs (SPIONs) made silica-coated MNPs by tetra-ethyl orthosilicate (TEOS) and co-condensing 3-aminopropyltriethoxysilane (APTES). They observed that silica layer thickness directly

affects MNP magnetization. Kralj et al. [90] have also obtained an equivalent finding, where the inclusion of thicker silica shells results in reduced magnetization. In the synthesis of MFe_2O_4 NPs ($M = Co, Ni, Li, \text{ or } Mn$), growth, nucleation, and coarsening kinetics have been recognized as the main contributing factors in achieving uniform NPs size and shape [91, 92]. Assume that these processes occur at different times. In that case, the best results appear to be obtained, i.e., only after the nucleation process is completed, nuclei growth must begin. The nuclei coarsening must occur after the nucleation process is completed. The solution's homogeneity is also a determinative factor [29, 93, 94].

9 Functionalisation of MNPs

Bacterial multidrug resistance is caused by anti-bacterial agents' repeated use, which requires more effective strategies to combat bacterial infections. MNPs have enhanced their efficacy against pathogenic microbes through surface functionalization to target specific cells in this way. MNPs play a key role in cancer care and are among the most common uses of targeted drug delivery approaches. In a new study, the anti-cancer iron oxide nanoparticles were combined with the drug doxorubicin to create beneficial cytotoxicity in cells [14, 93]. Tryptophan, a necessary amino acid, was loaded onto Fe_3O_4 NPs as an anti-bacterial application to induce improved efficiency against bacteria [95, 96].

10 Anti-bacterial mechanisms of MNPs

Research on the possessions of MNPs on different Gram-negative bacteria and Gram-positive has recently been published (see results in Tables 2 and 3). However, whether used in vitro or in vivo, their anti-bacterial functions are still unknown. The cell wall and the cytoplasmic membrane are the two main components of the bacterial cell membrane. The cytoplasmic membrane's primary cellular function is selective permeability, which allows for the control of waste disposal and nutrient intake [97]. A cytoplasmic membrane is a phospholipid bilayer that forms an intracellular space gate about 10 nm thick and contains proteins. In a bacterial phospholipid molecule, an ester bonded fatty acids to a glycerol molecule. A hydrophilic end, phosphate, and another functional group form on the cytoplasmic membrane structure's outer surface (e.g., sugar or ethanolamine) [24, 75, 98]. The phospholipid molecules' fatty acids point towards one another in the cytoplasmic membrane's inner region and procedure a hydrophobic internal area.

On the other hand, the cytoplasmic area shows on one side to the outer hydrophilic surface and on the other side to the cell wall. The cell wall serves as a solid wall to protect the cell from osmotic cell lysis [99]. Peptidoglycan is a polysaccharide layer, keeps the cell wall rigid and robust and is found in Gram-positive and Gram-negative bacteria cell wall structures [100, 101]. The peptidoglycan layer forms a hard surface around the cell with glycan tetrapeptides joined together by peptide crosslinks. A dense peptidoglycan layer formed by several peptidoglycan monolayer stacks makes up the majority of Gram-positive cell walls.

On the other hand, Gram-negative bacteria add much less of their wall structure to the peptidoglycan layer than the lipopolysaccharide outer membrane (LPS). The peptidoglycan coating of the cell wall binds to Braun lipoproteins. The LPS layer does not give any structural support to the cell, but it effectively blocks certain harmful substances, including lipophilic antibiotics. Gram-positive bacteria-inhibiting antibiotics may cause the LPS layer to appear [102] explain

ineffective against Gram-negative bacterial organisms Figure 4.

10.1 Cell membrane destruction

Since NPs bind to the bacterial cell membrane due to electrostatic forces, metabolic functioning is disrupted [103]. Damage to the cell membrane will finally cause it to rupture, allowing intracellular components such as genetic materials and minerals, as well as essential lipids and proteins, to leak out. The production of free radicals that damage the bacterial membrane is linked to AgNPs' anti-bacterial mechanism [104]. Besides, since reactive oxygen species (ROS) depolarize the bacterial membrane, it is weakened and deformed [105]. It has been found that membrane depolarization is catalyzed when iron-oxide NPs interact with bacteria. The vertices and sharp edges found on the surface of pyrrhotite nanostructures cause significant cell membrane damage. Sharp edges and vertices help in the degradation of the cell membrane system [106]. Christena et al. [107] Copper nanoparticles (Cu) NPs were discovered to inhibit the bacterial efflux pump, resulting in cell death due to cell membrane disruption. Furthermore, it is generally assumed that the positive charges provided by chitosan's primary amine groups interact readily with the negatively charged components of the exterior cell wall. This would lead to significant cell surface changes and disrupt the cells' permeability, effectively contributing to intracellular material leakage [108].

10.2 Reactive oxygen species ROS generation

ROS development usually is one of the expected outcomes in living organisms of cellular respiratory activity [109]. For instance, many vital components, proteins, lipids, and DNA are damaged when excessive ROS comes into contact with the cellular environment. [110]. Superoxide anion (O_2^-), hydroxide (OH^-) radicals, and hydrogen peroxide (H_2O_2), are mainly responsible for disrupting DNA molecules in bacterial cells and destroying essential proteins in bacterial cells concerning the anti-bacterial ROS mechanism. Many researchers consider ROS generation to be the dominant bactericidal mechanism used by numerous anti-bacterial NP agents **Figure 6**. In several studies [111, 112], photogeneration of ROS on metal NPs' surface has been recommended. Besides, ROS overgeneration is assumed to bring about a significant increase in lipid peroxidation and protein oxidation [113]. Extremely peroxidized lipids can also cause polyunsaturated lipids to degrade oxidatively. Therefore, the plasma membrane would be affected, resulting in a leakage of the membrane [114]. In terms of bacterial cell membrane ROS permeability, all Gram-negative and Gram-positive bacteria are similarly penetrable to ROS [106]; ROS's intracellular effects are the only difference. Flavin groups, superoxide, and H_2O_2 species are formed in the cytoplasm due to oxygen interaction with redox enzymes [115]. Superoxide dismutase is an enzyme that catalytically contributes to the dismutation of reactive superoxide to H_2O_2 or O_2 [106]. It is known that both superoxide and H_2O_2 species can induce an excessive deal of microbial cell damage [82]. Pal et al. noted that AgNPs released Ag ions that inhibited respiratory enzymes, causing bacterial metabolism to be disrupted and, in turn, excessive ROS production.

10.3 Photocatalytic effect

Nano-sized materials with photocatalytic properties have been shown to limit bacterial biofilm formation and microbial inhibition. The incident light can generate electron-hole pairs in these materials because incident light can break through the NP's energy bandgap barrier. In a biological context, bacterial and ROS deaths occur more frequently than the presence of free

electrons [116]. Compared to ferrous iron, hydroxyl radicals' formation is more powerfully catalyzed by ferrous sulfides [117]. Yao et al. [118] discovered exclusive consequences of photoinduced electron-hole pairs originating in the heterojunction among the lines of g-C₃N₄ and CuFe₂O₄ in another analysis on CuFe₂O₄@C₃N₄ core-shell photocatalysts. Besides, when it comes into contact with the cell membrane, the role of TiO₂ NPs in increasing lipid peroxidation is clarified by their inherent photocatalytic actions, which cause membrane breakup and inhibit cellular function respiration, and ultimately cause the death of cells [119]. When integrated into Ag-TiO₂

nanocomposites [103], the antimicrobial activity of AgNPs is increased. The photocatalytic reactivity of TiO₂-coated NiFe₂O₄ MNPs is ascribed to highly active hydroxyl radicals (-OH) [17, 24] has significantly reduced the concentration of *E. coli* bacteria in Luria-Bertani culture media. Furthermore, it shows that Fe₃O₄@TiO₂ core-shell MNPs have the probability of targeting and inhibiting numerous drug-resistant pathogenic bacteria, such as *Streptococcus pyogenes*, *Staphylococcus saprophyticus*, and *S. aureus* [120].

Table 2: Magnetic anti-bacterial NPs that are commonly used [93]

MNPs	Coated/ doped with	Size ^a , nm		Synthesis method	Target bacteria	Mechanism	Ref.
errRagX O ₂	X = Fe, Cr	AgFeO ₂ : 1.1244 AgCrO ₂ :0.1897 8	AgFeO ₂ : 48.8 (XRD), 80.4 (HRTEM) AgCrO ₂ : 77.1 (XRD), 120.9 (HRTEM)	flash auto- combustion reaction	<i>P. aeruginosa</i> <i>Neisseria</i> <i>gonorrhoeae</i> <i>E. coli</i> <i>Aureus</i> <i>Streptococcus</i> <i>faecalis</i> <i>Bacillus subtilis</i>	Formation of the free radical species from the Ag ions	[129]
CoFe ₂ O ₄	Okra (<i>Abelmoschus</i> <i>esculentus</i>) plant extract	65.31	55 (XRD) 5–50 (DLS)	green synthesis with microwave heating methods	<i>Enterobacter</i> <i>Aerogenes</i> <i>Yersinia</i> <i>enterocolitica</i> <i>S. aureus</i> <i>Micrococcus</i> <i>luteus</i>	Accumulation of NPs on the outer membranes or in the cytoplasm and production of ROS	[130]
NiO	—	not saturated	8.15 (XRD) 8–10 (HRTEM)	Green synthesis using <i>Aegle marmelos</i> extract	<i>E. coli</i> <i>S. aureus</i> <i>Streptococcus</i> <i>pneumoniae</i> <i>Escherichia</i> <i>hermannii</i>	Increased electrostatic the attraction between the Ni ions and microbial cell membrane	[131]
TbVO ₄	—	0.52	30–50 (SEM)	co- precipitation	<i>S. aureus</i> , <i>E. coli</i>	The association of NPs with bacteria's outer membrane and the halting of the respiration pathway	[132]
calcium Fe ₂ O ₄	chitosan– ampicillin	0.114	25 (XRD)	solution combustion method	<i>Staphylococcus</i> <i>epidermis</i>	With CFNP, ampicillin is released from chitosan	[133]
CuFe ₂ O ₄	Ag–tannic acid–papain	57.8/62.1	29.3/46.2 (XRD)	solvothermal	<i>S. aureus</i> , <i>E. coli</i>	Increased the permeability of the membrane and acted on the proteins	[134]
Fe ₃ O ₄	MOR and CuO	Fe ₃ O ₄ : 73.65 Fe ₃ O ₄ @MOR: 8.3 Fe ₃ O ₄ @MOR @CuO:4.2	Fe ₃ O ₄ : 16.6 mordenite (MOR): 18.43 CuO: 12	solvothermal	<i>S. aureus</i> , <i>E. coli</i>	Cu ²⁺ ions bind to the functional groups of proteins and enzymes, resulting in cell process inactivation and inhibition	[135]
Fe ₃ O ₄	Ba ₃ (PO ₄) ₂	8.7	Fe ₃ O ₄ : 100 (TEM) nanoflakes: 40 nm × 7 μm	solvothermal	<i>E. coli</i>	ROS generation damages cell integrity by modifying cell permeability and causing protein oxidation	[136]
La _{1-x} Na yMnO ₃	silica	29/34	48/47 (XRD)	sol-gel	<i>Serratia spp</i> <i>Micrococcus</i> <i>varians</i> <i>Bacillus spp</i> <i>Aspergillus spp</i>	Electrostatic attraction to the bacteria membrane's negative moieties	[137]
Ni _{1-x} Nd xO	Nd ³⁺	0.03 (for x = 0.03)	28 nm (XRD) (for x = 0.03)	co-precipitation	<i>Shigella</i> <i>dysenteriae</i> <i>S. aureus</i> <i>Klebsiella</i> <i>pneumonia</i> <i>E. coli</i> <i>Proteus Vulgaris</i>	Within the cell, Ni ²⁺ reacts with sulphhydryl groups, causing the microbe's synthetase activity to be harmed	[138]

Table 3: List of common magnetic anti-bacterial nanocomposites [93]

Nanocomposite	M_s , emu g ⁻¹	Size ^a , nm	Synthesis method	Target bacteria	Mechanism	Ref.
Co _{0.3} Zn _{0.7} Fe ₂ O ₄ /OB M/Ag	Co _{0.3} Zn _{0.7} Fe ₂ O ₄ /OB M: ~15 Co _{0.3} Zn _{0.7} Fe ₂ O ₄ /OB M/Ag: ~11	Co _{0.3} Zn _{0.7} Fe ₂ O ₄ : 65 (XRD) Ag: 10 (XRD)	sol-gel	<i>E. coli</i> <i>B. cereus</i> <i>S. aureus</i> <i>S. typhimurium</i>	Formation of free radicals by AgNPs in contaminated water	[104]
β -CoMoO ₄ /Co ₃ O ₄	12.063	β -CoMoO ₄ : 20.3 (XRD) Co ₃ O ₄ : 33.81 (XRD)	coprecipitation	<i>E. coli</i> <i>S. aureus</i> <i>P. aeruginosa</i>	ROS generation	[139]
Fe ₃ O ₄ @PTA@Ag	55.47	250 (HRSEM)	solvothermal	<i>E. coli</i> <i>S. aureus</i>	The reaction of oxygen species generated by AgNPs with the cell membrane	[140]
TiO ₂ /Fe ₃ O ₄ /chitosan/methyl pyrazolone	21	agglomerated (TEM)	solvothermal	<i>A. flavus</i> <i>E. coli</i> <i>S. aureus</i> <i>C. Albicans</i>	Inactivation of cell membrane constituents and penetration of cell membrane	[141]
Fe ₃ O ₄ @C@MgO-Cu	Fe ₃ O ₄ : 30.08 Fe ₃ O ₄ @C@MgO-Cu: 29.07	Fe ₃ O ₄ : 15 (TEM) Fe ₃ O ₄ @C@MgO-Cu: 50 (TEM)	Coprecipitation hydrothermal	<i>E. coli</i> <i>S. aureus</i>	Increased ROS, as well as a stronger physical association between the MgO-Cu NP and cell membranes, cause serious cell damage	[142]
GO@CoFe ₂ O ₄ @Ag-CFX	CoFe ₂ O ₄ : 58.022 GO@CoFe ₂ O ₄ @Ag-CFX: 37.357	CoFe ₂ O ₄ : 16 (XRD) AgNPs: 15 (XRD)	co-precipitation	<i>P. aeruginosa</i> <i>E. coli</i> <i>B. subtilis</i> <i>S. aureus</i>	Affecting the cell wall structure	[102]

^aColumn contains sizes of final coated or functionalized NPs

10.4 Cytotoxicity of anti-bacterial MNPs

Promising findings have been informed on the MNP potential safe in vivo applications and anti-bacterial effects of MNPs. Rodrigues et al. [121] provide a concise overview of iron-oxide NPs' therapeutic potential in vivo, [121] where they discuss biodistribution, drug delivery application, and toxicity of iron-oxide NPs. A recent study showed that magnetic metallopolymer-grafted NPs have a limited capacity to induce bacterial resistance and have negligible toxicity to red blood cells [13, 120]. In addition to reversible fragmentation, recyclable magnetic iron oxide NPs are bound to charge cobaltocenium-containing metallopolymer using a chain transfer polymerization process. These metallopolymer's conjugation with β -lactam antibiotics have ameliorated their viability against Gram-positive and Gram-negative bacteria. Cell viability tests such as 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) give information on cytotoxicity. Bare iron-oxide NPs have been revealed to have a biocompatible character in other studies [28, 122]. Numerous research teams have also reviewed the cytotoxicity of different coated iron-oxide NPs [17, 123-125]. Besides, the binding polymers used in anti-bacterial nanocomplexes, such as poly (4-vinyl pyridine) (PVP), can reduce the cytotoxicity of nanostructures [9, 126-128].

11 Potential way and challenges of anti-bacterial MNPs

MNPs are seen in a variety of shapes and sizes to demonstrate their potential anti-bacterial efficacy. Due to their low cost for therapeutic uses, MNPs may be converted as equivalent candidates. MNPs can be seen as tremendous resources that can practically target complex sites that other

biomedical agents cannot easily access. However, toxicity, removal, and limited existing knowledge of its metabolic outcomes are considered limitations in biomedical applications of MNPs [93].

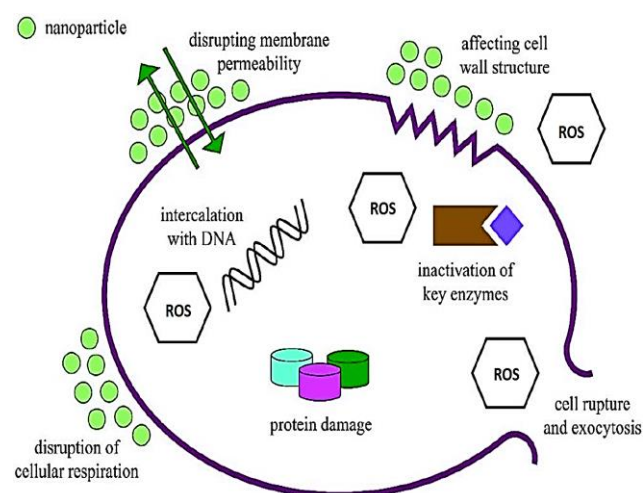


Figure 6: Anti-bacterial mechanisms of MNPs [93]

12 Conclusions and Future Perspectives

Nowadays, research has focused on identifying antimicrobial non-antibiotic agents that may attack several molecular targets by causing reactive oxygen species to disrupt microbial membranes, denaturing enzymes, altering gene

expression, and inhibiting DNA replication. EOs have fascinated considerable interest in current years for various cosmetics, medicine, and pharmaceuticals applications because of mounting evidence of their anti-bacterial, antiviral, anti-fungal, and insecticidal properties. Besides, lipids across the bacterial cell membrane due to the hydrophobic nature of EOs, and cell wall structures are subsequently broken, thereby inducing promising anti-bacterial effects; however, there has been a growing interest in nanometric systems as EO delivery carriers because environmental factors can affect the loss of bioactivity and cause EO degradation due to volatilization. As they are highly advantageous because of their primary structures, specific target tissue, non-toxicity, biodegradability, and biocompatibility, MNPs are potential candidates for developing EO-based nanosystems anti-bacterial therapies because they allow for the attachment of various therapeutics.

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Ethical issue

Authors are aware of, and comply with, best practice in publication ethics specifically with regard to authorship (avoidance of guest authorship), dual submission, manipulation of figures, competing interests and compliance with policies on research ethics. Authors adhere to publication requirements that submitted work is original and has not been published elsewhere in any language. Also, all procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All procedures performed in this studies involving animals were in accordance with the ethical standards of the institution or practice at which the studies were conducted.

Competing interests

The authors declare that there is no conflict of interest that would prejudice the impartiality of this scientific work.

Authors' contribution

All authors of this study have a complete contribution for data collection, data analyses and manuscript writing.

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