

Synthesis of Iron Oxide Nanoparticles and its Antimicrobial, Anticancer, Anti-inflammatory, Wound Healing, and Immunomodulatory Activities -A Review

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Abstract

Iron oxide nanoparticles, particularly in the form of Fe₂O₃, have gained significant attention due to their distinctive physicochemical properties and diverse biomedical applications. This review examines various synthesis methods for Fe₂O₃ nanoparticles, including co-precipitation, thermal decomposition, and green synthesis, each influencing the nanoparticles' size, morphology, and surface characteristics. Furthermore, the biological activities of Fe₂O₃ nanoparticles are discussed in detail, focusing on their antimicrobial, anticancer, anti-inflammatory, wound healing, and immunomodulatory properties. Studies show that Fe₂O₃ nanoparticles exhibit strong antimicrobial effects against a range of pathogens, including drug-resistant strains, through mechanisms such as reactive oxygen species (ROS) generation and cell membrane disruption. In cancer therapy, Fe₂O₃ nanoparticles contribute to targeted drug delivery and hyperthermia, selectively inducing apoptosis in cancer cells. Their anti-inflammatory properties aid in modulating inflammatory responses, while wound healing applications demonstrate their ability to promote cell proliferation and tissue regeneration. Additionally, the immunomodulatory effects of Fe₂O₃ nanoparticles enhance immune responses, showing potential as vaccine adjuvants and in the treatment of autoimmune conditions. This review provides a comprehensive overview of recent advancements and challenges in the application of Fe₂O₃ nanoparticles in biomedicine, suggesting future directions for optimizing their therapeutic efficacy and safety.

Keywords: Iron oxide nanoparticles, antimicrobial, anticancer, anti-inflammatory, wound healing, immunomodulation, synthesis methods, biomedical applications

1.0 INTRODUCTION

Iron oxide nanoparticles (Fe_2O_3) have gained considerable attention in recent years due to their distinctive physicochemical properties, which make them highly versatile for a wide range of biomedical applications [1]. Fe_2O_3 nanoparticles, particularly in forms such as magnetite (Fe_3O_4) and maghemite ($\gamma\text{-Fe}_2\text{O}_3$), are celebrated for their superparamagnetic properties, large surface area-to-volume ratio, tunable size and morphology, and robust biocompatibility. These characteristics enable Fe_2O_3 nanoparticles to perform effectively in environments where conventional therapeutic agents often fall short [2]. Superparamagnetism, for instance, allows these nanoparticles to respond to external magnetic fields, which is a valuable feature for drug delivery and diagnostic imaging, enabling precise control over therapeutic targeting and localization [3]. The capacity for surface functionalization further enhances their biomedical potential by allowing functional molecules, such as drugs, targeting ligands, or imaging agents, to be attached, thus creating multifunctional nanoplatforms for diagnostics and therapy[4]. Moreover, Fe_2O_3 's favorable biocompatibility and biodegradability distinguish it from other materials, supporting its use in sensitive medical applications and promoting safer interactions within biological systems [5]. The unique combination of these properties has paved the way for Fe_2O_3 nanoparticles to emerge as promising candidates in multiple areas of biomedicine[6]. They have demonstrated substantial potential in antimicrobial treatments, cancer therapeutics, anti-inflammatory applications, wound healing, and immunomodulatory strategies[7]. Each of these applications poses specific challenges within traditional treatment paradigms that Fe_2O_3 nanoparticles are well-equipped to address[8]. For instance, in antimicrobial

applications, Fe_2O_3 nanoparticles can generate reactive oxygen species (ROS) that exhibit potent bactericidal effects, a mechanism that effectively combats antibiotic-resistant strains of bacteria[9]. The emergence of antimicrobial resistance has become a significant public health concern worldwide, and Fe_2O_3 nanoparticles present a novel approach to addressing this issue by bypassing conventional resistance mechanisms [10]. In cancer therapy, Fe_2O_3 nanoparticles can be utilized as drug carriers, magnetic hyperthermia agents, and imaging contrast agents, allowing for targeted delivery, enhanced therapeutic efficacy, and minimized side effects compared to systemic therapies [11]. The magnetic properties of Fe_2O_3 enable selective targeting and retention in tumor sites, thus increasing treatment precision [12]. Fe_2O_3 nanoparticles are also gaining traction in anti-inflammatory applications due to their ability to modulate immune responses [13]. The inflammatory response is a critical component of many diseases, and uncontrolled inflammation can lead to chronic conditions and tissue damage [14]. Fe_2O_3 nanoparticles' ability to reduce inflammation through selective cell targeting or drug delivery provides a valuable tool in managing inflammatory diseases [15]. Furthermore, their application in wound healing is noteworthy, as they can promote tissue regeneration, provide antimicrobial protection, and modulate immune responses, creating an optimal environment for healing [16]. The controlled release of therapeutic agents from Fe_2O_3 nanoparticles helps to maintain effective local concentrations over extended periods, which is beneficial in chronic wound management [17]. In addition, the immunomodulatory effects of Fe_2O_3 nanoparticles offer new possibilities in regenerative medicine, where balanced immune activity is essential for successful tissue integration and repair [18].

By targeting specific immune pathways, Fe₂O₃ nanoparticles can enhance or suppress immune responses as needed, making them versatile tools for various immunological applications [19]. In light of the interdisciplinary relevance of Fe₂O₃ nanoparticles, it is essential to explore their synthesis methods, as these directly influence their physicochemical properties and, consequently, their biomedical performance [20]. This review will examine the various synthesis techniques employed to produce Fe₂O₃ nanoparticles, including chemical, physical, and green synthesis methods. Chemical synthesis methods, such as co-precipitation, sol-gel, and thermal decomposition, offer precise control over nanoparticle size, shape, and surface properties [21]. Physical methods, including mechanical milling and laser ablation, provide alternative approaches with distinct benefits in purity and yield [22]. In recent years, green synthesis methods using plant extracts, bacteria, and other biological agents have gained traction due to their eco-friendliness and reduced toxicity, making them particularly attractive for biomedical applications where biocompatibility is crucial [23]. Each synthesis technique impacts the nanoparticle properties differently, influencing their stability, biocompatibility, and functionalization capabilities, which in turn affects their efficacy in biomedical applications [24]. This review will explore and synthesize recent advancements in

understanding the mechanisms underlying Fe₂O₃ nanoparticles' antimicrobial, anticancer, anti-inflammatory, wound healing, and immunomodulatory effects. For antimicrobial activity, the generation of reactive oxygen species (ROS) and membrane disruption will be discussed as primary mechanisms. In cancer therapy, the review will delve into the use of Fe₂O₃ for drug delivery, magnetic hyperthermia, and imaging contrast. Anti-inflammatory applications will focus on how Fe₂O₃ modulates inflammatory cytokines and cellular responses. Wound healing applications will cover Fe₂O₃'s role in promoting cellular regeneration, collagen formation, and infection control, while immunomodulatory functions will explore its effects on immune cells such as macrophages and T-cells. The review aims to provide a comprehensive overview of Fe₂O₃'s biomedical applications and examine how synthesis and functionalization techniques impact their therapeutic efficacy. This extensive evaluation will highlight current trends, challenges, and future prospects, aiming to contribute to the growing understanding of Fe₂O₃ nanoparticles' potential in modern medicine.

1) Synthesis of Iron Oxide Nanoparticles

There are many methods of synthesis of iron oxide nanoparticles. Some of the main synthesis methods are as shown in **Fig. 1** below:

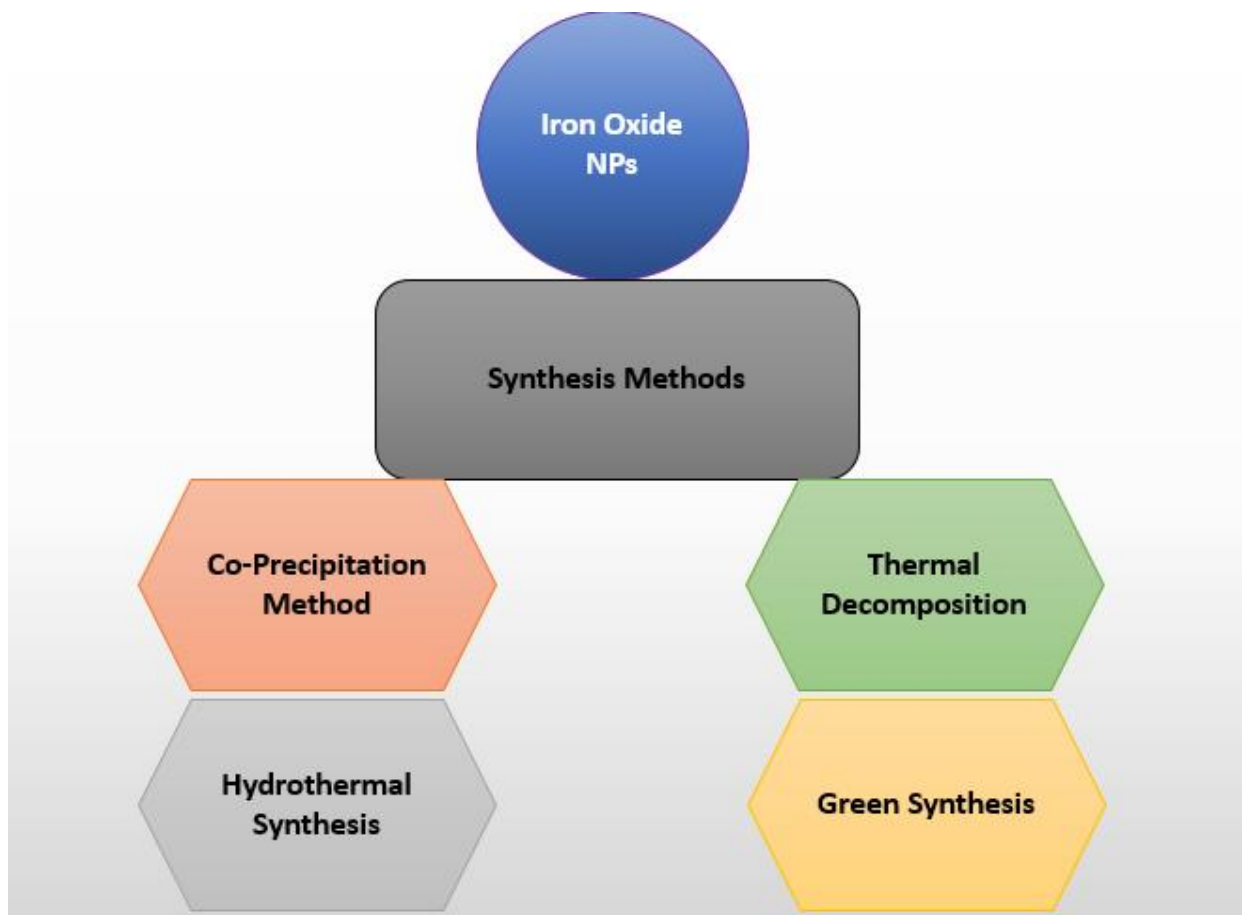


Fig. 1: Synthesis of iron oxide NPs (Source: Own)

i) Synthesis of Iron Oxide NPs via Co-Precipitation Method

The co-precipitation method is one of the most widely used techniques for synthesizing iron oxide nanoparticles due to its simplicity, cost-effectiveness, and scalability [25]. In this approach, iron salts, typically ferrous (Fe^{2+}) and ferric (Fe^{3+}) ions, are mixed in an aqueous solution under controlled pH conditions to form iron oxide precipitates [26]. The process is initiated by adding a base, such as sodium hydroxide (NaOH) or ammonium hydroxide (NH_4OH), which increases the pH and facilitates the precipitation of iron ions into nanoparticles [27]. The reaction conditions—such as the Fe^{2+} to Fe^{3+} ratio, temperature, stirring rate, and pH—play a critical role in determining the phase, morphology, and size of the resulting nanoparticles. By adjusting these parameters,

researchers can tailor the nanoparticles' properties for specific applications [28]. For example, maintaining a high pH and a nitrogen-rich atmosphere can help minimize oxidation, leading to more stable particles [29]. This method allows for the synthesis of various forms of iron oxide, such as magnetite (Fe_3O_4) and maghemite ($\gamma\text{-Fe}_2\text{O}_3$), which are popular for biomedical applications due to their magnetic properties [30]. The ease of controlling the particle size and dispersity makes co-precipitation a preferred technique in producing nanoparticles for antimicrobial, anticancer, anti-inflammatory, wound healing, and immunomodulatory applications [31]. Additionally, the nanoparticles produced by this method have high surface area and reactivity, enhancing their biological activity and efficacy in drug delivery systems, magnetic resonance imaging (MRI), and other therapeutic

interventions [32].

ii) **Synthesis of Iron Oxide NPs via thermal Decomposition**

The synthesis of iron oxide nanoparticles (NPs) via thermal decomposition is a widely used technique due to its ability to produce high-quality, uniform, and well-dispersed nanoparticles [33]. The process typically involves the breakdown of iron-containing precursors at high temperatures in the presence of surfactants and organic solvents, yielding iron oxide nanoparticles [34]. Materials and reagents used include iron precursors like iron acetylacetonate ($\text{Fe}(\text{acac})_3$), iron oleate, or iron carbonyls. These precursors are chosen for their thermal stability and ability to decompose into iron oxide at elevated temperatures [35]. Surfactants such as oleic acid, oleyl amine, or similar long-chain surfactants are added to stabilize the nanoparticles and control their size and shape. High-boiling-point organic solvents, such as benzyl ether or octadecene, provide a suitable environment for the thermal decomposition of the iron precursor at temperatures exceeding 200°C [36].

In the synthesis procedure, the iron precursor, surfactant, and solvent are mixed in a reaction vessel, often under an inert atmosphere (e.g., nitrogen or argon) to prevent unwanted oxidation. The mixture is heated gradually to dissolve the components and form a homogeneous solution. Then, the reaction mixture is heated to a high temperature (typically between 200°C and 300°C) to initiate the decomposition of the iron precursor, resulting in the formation of iron oxide nuclei [37]. The size of the nanoparticles can be controlled by adjusting factors like the reaction temperature, time, and surfactant concentration [38]. Higher temperatures and longer reaction times generally promote the growth of larger particles. After the reaction is complete, the mixture is

cooled to room temperature. The nanoparticles are then precipitated by adding a non-polar solvent (e.g., ethanol or acetone) to aggregate the particles, allowing them to be separated by centrifugation. To remove unreacted precursors, surfactants, and byproducts, the nanoparticles are typically washed several times with solvents like ethanol or hexane, which is essential for achieving pure iron oxide nanoparticles [39]. After synthesis, the nanoparticles are characterized to determine their size, morphology, crystal structure, and magnetic properties. Transmission Electron Microscopy (TEM) is used to visualize the size and shape of the nanoparticles. X-ray Diffraction (XRD) determines the crystal structure of the iron oxide phase, distinguishing between different forms (e.g., magnetite or maghemite) [40]. Dynamic Light Scattering (DLS) measures the hydrodynamic diameter of the nanoparticles in solution. Vibrating Sample Magnetometry (VSM) or Superconducting Quantum Interference Device (SQUID) assesses the magnetic properties of the nanoparticles [41]. Thermal decomposition has several advantages: it produces nanoparticles with uniform size distribution and high crystallinity, essential for applications in biomedicine, magnetic storage, and catalysis [42]. The process allows for precise control over particle size by adjusting reaction parameters and is suitable for creating both hydrophobic and hydrophilic nanoparticles, depending on the surfactants used [43]. Due to their magnetic properties and biocompatibility, iron oxide nanoparticles synthesized via thermal decomposition are commonly used in Magnetic Resonance Imaging (MRI) as contrast agents, drug delivery and targeted therapy, hyperthermia treatment for cancer, magnetic data storage, and catalysis [44]. The thermal decomposition synthesis method remains a robust technique for producing high-quality iron oxide

nanoparticles suited for advanced technological and medical applications [45].

iii) **Synthesis of Iron Oxide NPs Via Hydrothermal Synthesis**

Hydrothermal synthesis is a method used to produce iron oxide nanoparticles and various other nanomaterials. This process involves the crystallization of substances from high-temperature aqueous solutions under high pressure within a sealed reactor or autoclave [46]. Hydrothermal synthesis is especially valuable for producing nanoparticles with controlled shapes and sizes [47]. The hydrothermal synthesis process involves dissolving iron precursors (such as ferric chloride or iron nitrate) in water along with other reagents, like a pH-controlling agent (e.g., sodium hydroxide or urea), to adjust the reaction environment [48]. This solution is then placed into a high-pressure reactor and heated to temperatures between 100°C and 300°C, depending on the desired phase and particle size. Under these conditions, the precursor undergoes nucleation and growth, forming iron oxide nanoparticles. Reaction time, temperature, and precursor concentration can be controlled to influence particle size and shape [49]. Hydrothermal synthesis has several advantages. It produces high-purity and crystalline iron oxide nanoparticles due to the closed system, which minimizes contamination [50]. The high temperature and pressure promote crystallization, resulting in high-quality nanoparticles suitable for applications requiring purity and structural integrity [51]. This method also allows for precise control over particle morphology (e.g., spherical, cubic, or rod-like shapes) and size, which are important for applications in catalysis, magnetic storage, and drug delivery [52]. Adjusting factors like temperature, pH, and concentration of precursors can effectively tune the final particle characteristics. Additionally, hydrothermal

synthesis primarily uses water as the reaction medium, which is non-toxic, inexpensive, and eco-friendly [53]. Unlike methods that require organic solvents or surfactants, hydrothermal synthesis is a greener process, reducing potential environmental impact [54]. In comparison to methods like thermal decomposition, hydrothermal synthesis may require lower energy input since it operates in aqueous solutions and doesn't necessarily require high-temperature conditions [55]. This can make it more energy-efficient, particularly for producing smaller nanoparticles. The method can also accommodate the incorporation of other ions or dopants into the nanoparticles, allowing for the creation of composite materials or nanoparticles with tailored magnetic or optical properties [56]. However, there are also several limitations to hydrothermal synthesis. The need for high-pressure equipment, such as an autoclave, makes the process more complex and costly. Working with high-pressure systems also requires stringent safety measures and can make the scaling of production more challenging [57]. Although hydrothermal synthesis is effective for laboratory-scale production, scaling it up to an industrial level is challenging due to the high-pressure requirements and the need for specialized reactor. This limits its practicality for large-scale production compared to simpler synthesis methods. Hydrothermal synthesis often requires long reaction times, sometimes several hours or even days, to achieve desired particle characteristics, which can be a disadvantage for applications that demand rapid synthesis or high-throughput production [58]. While hydrothermal synthesis can operate over various temperatures, very high temperatures may cause complications in controlling particle size and shape. High temperatures can also degrade certain organic compounds if used as stabilizers

or surfactants, potentially limiting the process to certain materials [59]. Despite being energy-efficient in some cases, hydrothermal synthesis may require substantial energy for high-temperature reactions, especially for larger batches or specific nanoparticle phases that require high temperatures [60, 61]. This can increase operational costs. In summary, hydrothermal synthesis is an effective and eco-friendly method for producing high-purity iron oxide nanoparticles with controlled size and morphology. Its advantages include the production of crystalline, shape-controlled nanoparticles and environmental friendliness due to water as the solvent [62]. However, it

has limitations, including the need for high-pressure equipment, challenges in scaling, longer reaction times, and potential energy costs for high-temperature synthesis. This method is well-suited for applications where precision and purity are prioritized, such as in biomedical and research fields, though it may be less ideal for industrial-scale production due to these constraints [63]. Below is **Fig. 2** in which there is general representation of Hydrothermal Synthesis of iron oxide nanoparticles. Also there is **Table 2** of different types of iron oxide nanoparticles prepared via Hydrothermal approach.

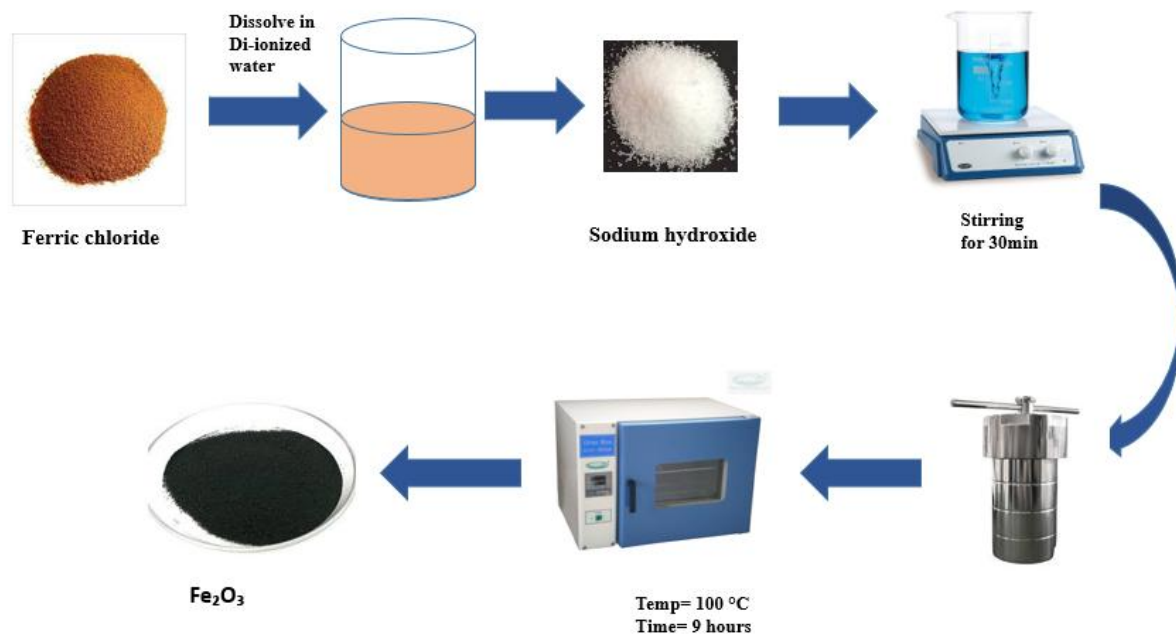


Fig. 2: Synthesis of Iron Oxide NPs via Hydrothermal method (Source: own)

Table 2: Different type of Iron Oxide NPs

Serial No	Name of the material	Morphology	Application	References
01	Iron Oxide (Fe ₃ O ₄) NPs	Sphersical/Ellipsoidal	Cancer diagnosis and treatment	[64]
02	Surface-modified iron oxide nanoparticles	Cubic (with CH ₃ (CH ₂) ₈ COOH) and Spherical (with CH ₃ (CH ₂) ₉ NH ₂)	Antimicrobial, anticancer, anti-inflammatory, wound healing, and immunomodulatory	[65]

				activities	
03	Fe ₃ O ₄ @Au composite nanoparticles (CNPs)	Integrated Fe ₃ O ₄ and Au components		Dual-mode imaging	MR/CT [66]
04	Iron oxide nanoparticles	Spherical shape with size range of 35-45 nm; maghemite phase; high levels of aggregation		Magnetic ink, storage tape and devices, medicine and medical diagnosis, MRI contrast agent, gene and drug delivery, cancer hyperthermia, wastewater treatment	[67]
05	PEI-coated iron oxide nanoparticles (Fe ₃ O ₄ -PEI NPs)	Spherical shape with size range of 11-22 nm (tunable by mass ratio)		Magnetic resonance imaging (MRI), targeted cancer imaging and therapeutics, potential for multifunctional biomedical applications (e.g., therapy, diagnostics)	[68]
06	Iron oxide (α -Fe ₂ O ₃) nanoparticles	Spherical shape; size of 21 nm		Magnetic properties, potential photocatalytic applications in effluent water treatment	[69]
07	γ -Fe ₂ O ₃ -Ag ₂ O nanocomposite	Cauliflower-like shape with size range of 44.22–73.82 nm		Antibacterial activity against Gram-positive and Gram-negative bacteria; antifungal activity against <i>Candida albicans</i>	[70]
08	Hematite (α -Fe ₂ O ₃) nanoparticles	Spherical shape; size ~8 nm		Spintronics, biomedicine (e.g., superparamagnetic applications at room temperature)	[71]
09	HA-targeted Fe ₃ O ₄ nanoparticles (Fe ₃ O ₄ NPs)	Spherical shape; size 15-16 nm		Targeted magnetic resonance (MR) imaging of tumors, CD44 receptor-specific cancer imaging,	[72]

			potential for drug delivery
10	Silver-iron oxide/reduced graphene oxide (Ag-Fe ₃ O ₄ /RGO) nanocomposite	Metal and metal oxide nanoparticles on thin 2D RGO sheets	Catalytic reduction of 4-nitrophenol, antibacterial activity (e.g., destruction of <i>Escherichia coli</i>), environmental remediation [73]
11	β-Fe ₂ O ₃ nanoparticles	Almost spherical shape; diameter ~60 ± 10 nm	Photocatalytic degradation of acridine orange (AO), electrochemical sensing of ammonia in liquid phase [74]
12	Iron oxide (Fe ₃ O ₄) nanoparticles	Narrow size distribution; monodispersed and stable	Antimicrobial and antioxidant activities; magnetic separation and repeated use in antioxidant experiments [75]
13	Iron oxide nanoparticles (Fe ₃ O ₄ , γ-Fe ₂ O ₃ , α-Fe ₂ O ₃ , etc.)	Various nano-morphologies depending on synthesis method	Catalysis, wastewater treatment, pigments, magnetic storage, medicine, water purification, biomedical applications, coatings, sensors, transparent paints, and bioseparation [76]
14	Iron-based nanocatalysts	Uniformly dispersed Fe nanoparticles (NPs) embedded in mesoporous hydrochar carbon spheres	Catalysis for biomass tar reduction, thermal decomposition of phenol, resistance to coke deposition [77]
15	FeO(OH)-PEI hybrid nanostructures	Very fine FeO (OH) nanoparticles (2–5 nm), strongly entrapped in branched PEI structure	Biomedical applications such as diagnostics, therapeutics, and theranostics; superparamagnetic behavior for targeted use [78]

16	Hematite nanoparticles	(α -Fe ₂ O ₃)	Small particle size (size decreases with temperature and natural substances)	Environmentally friendly synthesis, potential applications in catalysis, pigments, and other iron oxide applications	[79]
17	Iron nanoparticles	oxide	Dome-like structures of nanoparticles	Fabrication of flexible micro-supercapacitors, patterned growth on substrates for advanced microdevices	[80]
18	Iron nanoparticles (NPs)	oxide (Fe ₃ O ₄)	Colloidally stable; water-dispersible	Magnetic resonance (MR) imaging, photothermal therapy of cancer, dual-mode imaging, multifunctional theranostic agents for cancer diagnosis and therapy	[81]
19	Carbon-coated magneto-luminescent nanocomposites		Core@shell structure: nanosized γ -Fe ₂ O ₃ magnetic core (~9.8 nm) coated with a carbon shell	Ion detection, magnetohyperthermia, theranostics, multicolored photoluminescent applications, colloidal stability in alkaline media	[82]
20	Hematite nanoparticles	(α -Fe ₂ O ₃)	Agglomerated spherical nanoparticles; average particle size ~20 nm	Biomedical applications: drug delivery, MRI contrast agent, hyperthermia for cancer treatment	[83]

iv) Synthesis of Iron Oxide Nanoparticles via Green Synthesis

The green synthesis of iron oxide nanoparticles (IONPs) represents an eco-friendly, cost-effective, and sustainable

approach that leverages biological resources for nanoparticle production. Unlike conventional chemical and physical methods, which often involve toxic reagents and energy-intensive processes, green synthesis utilizes natural reducing agents and stabilizers derived from

plants, microorganisms, or other biological materials [84]. This method aligns with the principles of green chemistry by minimizing environmental hazards and promoting biocompatibility. Eco-friendly reducing agents such as biomolecules from plant extracts, microbial metabolites, or natural polymers serve to convert iron precursors (such as ferric chloride or ferrous sulfate) into iron oxide nanoparticles [85]. Organic compounds like proteins, polysaccharides, and phenolics from biological sources stabilize the nanoparticles, preventing aggregation and enhancing functional properties. Reactions typically occur under ambient temperatures and pressures, requiring minimal energy inputs [86]. The process involves the preparation of biological extracts from plant parts (leaves, roots, stems, or flowers) or microbial cultures to extract bioactive compounds like flavonoids, tannins, alkaloids, and terpenoids [87]. These bioactive molecules act as both reducing and capping agents, facilitating the reduction of Fe^{3+} or Fe^{2+} ions to iron oxide nanoparticles. Simultaneously, the bioactive compounds stabilize the nanoparticles by forming a surface coating, which influences particle size, shape, and functionality [88]. Various biological sources have been employed for green synthesis. Plant extracts are widely available, cost-effective, and rich in diverse bioactive compounds. Examples include leaf extracts of *Azadirachta indica* (neem) and *Ocimum sanctum* (holy basil) as well as fruit extracts from *Citrus limon* (lemon) and *Punica granatum* (pomegranate). Microorganisms such as bacteria (*Bacillus subtilis*, *Escherichia coli*), fungi (*Aspergillus niger*,

Table 3: Green synthesis of Iron oxide NPs its morphology and applications.

Fusarium oxysporum), and algae (*Chlorella vulgaris*, *Spirulina platensis*) have also been used. Other biological materials, including proteins like casein or silk fibroin and natural polysaccharides like alginate or starch, contribute to this eco-friendly synthesis approach [89]. Green synthesis offers several advantages. It eliminates the use of hazardous chemicals, enhances the biocompatibility of nanoparticles for biomedical applications, reduces the need for expensive reagents and sophisticated equipment, and is suitable for large-scale production given the abundance of natural sources. However, there are challenges such as standardizing biological sources and reaction parameters to ensure reproducibility and consistency in nanoparticle size and properties [90]. More research is needed to elucidate the exact molecular mechanisms involved in synthesis and stabilization processes and to tailor methods for specific applications such as antimicrobial, anticancer, or immunomodulatory uses. Green synthesis of iron oxide nanoparticles provides a sustainable and innovative approach for nanotechnology development, particularly in biomedical and environmental applications [91]. By relying on renewable biological resources, it addresses the limitations of conventional methods and offers opportunities for developing biocompatible and multifunctional nanoparticle formulations. **Table 3** summarizes different types of iron oxide NPs synthesized via green synthesis having different morphology and applications.

Serial No	Name of the Material	Morphology	Applications	References
01	Iron Oxide (Fe_2O_3 , γ -	Spherical	Antifungal activity against	[92]

	Fe ₂ O ₃)		Aspergillus niger and Mucorpiriformis; potential in antimicrobial nanomedicine	
02	Iron Oxide Nanoparticles (Fe ₃ O ₄ -NPs)	Cubic-shaped; size range: 30 nm - 100 nm	- Antimicrobial activity (effective against <i>Escherichia coli</i> and <i>Staphylococcus aureus</i>)	[93]
03	Iron Oxide Nanoparticles (α -Fe ₂ O ₃ , Hematite)	Crystalline, ~39 nm in size	Catalysis (degradation of Methylene Blue dye in wastewater treatment), Anticancer activity (renal tumor cell inhibition), Nanomedicine, Optoelectronics	[94]
04	Iron Oxide Nanoparticles (α -Fe ₂ O ₃ and γ -Fe ₂ O ₃)	Spherical, ~38 nm in size	Antifungal activity (effective against <i>Aspergillus niger</i> and <i>Mucor piriformis</i>), Nanomedicine, Catalysis	[95]
05	Iron Oxide Nanoparticles	Spherical, 67 nm diameter	Superparamagnetic behavior (potential in magnetic storage, MRI contrast agents), Nanomedicine, Catalysis	[96]
06	Iron Oxide Nanoparticles	Size range: 30–100 nm, varied morphology as observed through SEM and AFM	Industrial applications, Dye degradation, Environmental pollution control	[97]
07	Iron Oxide Nanoparticles (Fe ₂ O ₃ NPs)	Semi-spherical, uniformly distributed, size range: 25–55 nm	Photocatalysis (dye degradation in wastewater, reactive blue dye), Eco-benign and cost-effective synthesis	[98]
08	Iron Oxide Nanoparticles (α -Fe ₂ O ₃)	Nano-scaled, morphology confirmed through FESEM	Photocatalysis (dye degradation of remazol yellow RR), Antibacterial activity (<i>Klebsiella</i> spp., <i>E. coli</i> , <i>Pseudomonas</i> spp., <i>S. aureus</i>), Potential for tumor cell damage	[99]

				(Hela and BHK-21 cell lines)	
09	Iron Oxide NPs	-		Antibacterial activity, Anti-cancer activity, Photocatalytic activity	[100]
10	Iron Oxide Nanoparticles (FeO-NPs, including Fe ₃ O ₄ and γ -Fe ₂ O ₃ phases)	Regular structure, predominantly superparamagnetic	crystal	Environmental applications, Biocompatible for use in biological systems (low toxicity), Potential for functional nanomaterials	[101]
11	Iron Oxide Nanoparticles (Fe ₃ O ₄)	Uniform shape, size: 20–40 nm	spherical	Heavy metal removal (lead: 82%, cadmium: 77%), Environmental remediation, Adsorption of toxic metals from water	[102]
12	Iron Oxide Nanoparticles	Morphology characterized by FE-SEM and HR-TEM		Degradation of organic dyes (Methylene Blue: 82.1% in 95 min, Methyl Orange: 53.9% in 205 min), Antibacterial activity (Shigella sonnei, Staphylococcus aureus), Antifungal activity (Candida tropicalis, Candida albicans)	[103]

2) Biomedical Applications of Iron Oxide NPs

Iron oxide nanoparticles (Fe₂O₃) have significant biomedical applications due to their unique magnetic, chemical, and biocompatible properties. They are widely used in targeted drug delivery systems, enabling precise treatment with minimal side effects. In cancer therapy, Fe₂O₃ facilitates hyperthermia and acts as a contrast agent

in magnetic resonance imaging (MRI) for tumor detection. Their antimicrobial and wound-healing properties support infection control and tissue regeneration. Additionally, Fe₂O₃ shows promise in immunomodulation, enhancing immune responses in various therapeutic contexts. Some of its Applications are as in below **Fig. 3**:

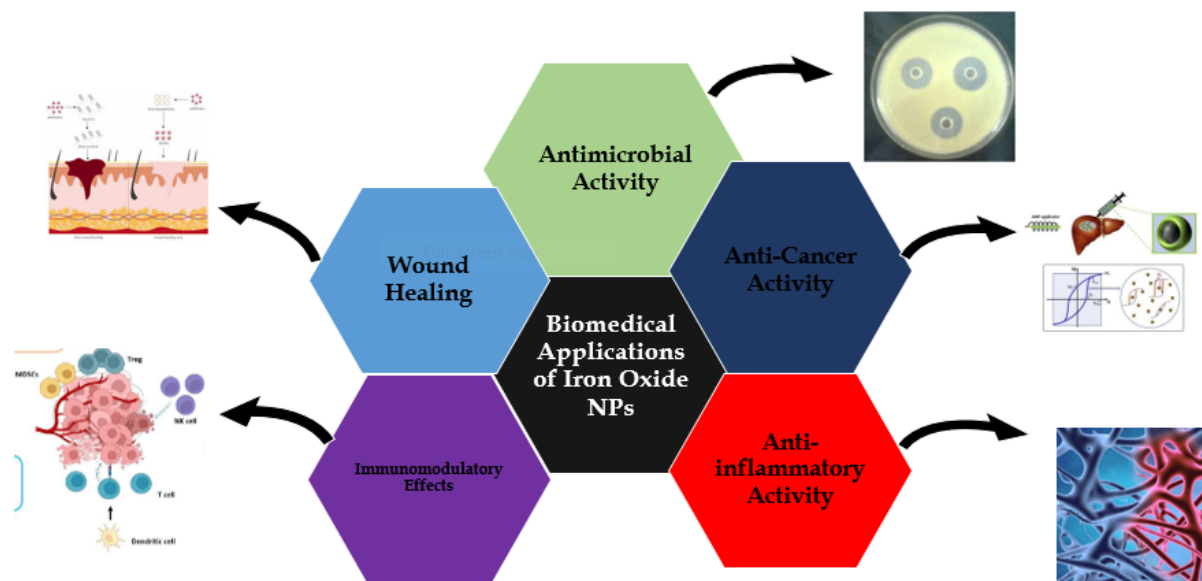


Fig. 3: Biomedical Applications of Iron Oxide NPs

i) Antimicrobial Activity

Iron oxide nanoparticles (Fe_2O_3) have demonstrated significant antimicrobial activity, making them promising agents against a variety of pathogens, including bacteria, fungi, and viruses. Their antimicrobial properties arise from their ability to generate reactive oxygen species (ROS), disrupt microbial cell membranes, and interfere with vital cellular processes [104]. The production of ROS by Fe_2O_3 nanoparticles is one of the primary mechanisms of action. These reactive species induce oxidative stress in microbial cells, leading to damage to lipids, proteins, and nucleic acids. This oxidative stress compromises the structural integrity of the microbial cell wall and membrane, ultimately causing cell lysis. The small size and high surface area of Fe_2O_3 nanoparticles enhance their interaction with microbial cells, increasing their efficacy. In addition to oxidative stress, Fe_2O_3 nanoparticles can physically disrupt microbial membranes. Their nanoscale dimensions allow them to penetrate microbial cell walls, destabilizing the lipid bilayer and impairing cellular

functions [105]. This mechanical disruption is particularly effective against drug-resistant strains, which often rely on membrane integrity for survival. Fe_2O_3 nanoparticles also exhibit the ability to bind to and disrupt enzymes or proteins essential for microbial metabolism and replication. For example, they can inhibit bacterial biofilm formation, which is a critical factor in the persistence of chronic infections. Biofilms protect bacteria from antibiotics, and the ability of Fe_2O_3 nanoparticles to prevent or disrupt biofilms enhances their utility in combating resistant infections [106]. Studies have shown the effectiveness of Fe_2O_3 nanoparticles against both Gram-positive and Gram-negative bacteria, including common pathogens such as *Escherichia coli*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. Additionally, they exhibit antifungal activity against species like *Candida albicans*, as well as antiviral potential against certain viruses [107]. The antimicrobial activity of Fe_2O_3 nanoparticles can be enhanced by functionalizing their surfaces with antimicrobial agents, such as antibiotics, peptides, or natural compounds. These

hybrid nanoparticles combine the inherent properties of Fe_2O_3 with the targeted action of the functionalizing agents, increasing their efficacy while reducing the likelihood of resistance development [108]. The broad-spectrum antimicrobial properties of Fe_2O_3 nanoparticles hold great potential in various applications, including wound dressings, coatings for medical devices, and water purification systems. Their ability to combat antibiotic-resistant pathogens makes them a valuable tool in addressing the global challenge of antimicrobial resistance [109].

ii) Anti-Cancer Activity

Iron oxide nanoparticles (Fe_2O_3) offer versatile targeting mechanisms that can be tailored for specific biomedical applications. The most prominent strategy is magnetic targeting, where an external magnetic field guides the nanoparticles to a desired site, such as a tumor or infection. This approach leverages the superparamagnetic properties of Fe_2O_3 , enabling precise localization and retention at the target site while minimizing systemic distribution. Another common targeting mechanism involves surface functionalization of Fe_2O_3 nanoparticles with ligands, antibodies, or peptides that bind selectively to receptors overexpressed on target cells, such as cancer cells or pathogenic microbes [1]. For instance, folic acid, aptamers, or monoclonal antibodies can be attached to the nanoparticle surface to enhance receptor-mediated endocytosis, ensuring targeted cellular uptake. Dual targeting strategies, combining magnetic guidance with receptor-specific binding, further improve specificity and efficacy. Cytotoxicity is a critical consideration for the biomedical application of Fe_2O_3 nanoparticles [110]. Numerous *in vitro* and *in vivo* studies have evaluated their biocompatibility, focusing on parameters such as cell viability, oxidative stress, and immune response. Fe_2O_3

nanoparticles are generally considered biocompatible at low concentrations, but their toxicity is influenced by size, shape, surface charge, and functionalization [111]. At the cellular level, excessive production of reactive oxygen species (ROS) by Fe_2O_3 nanoparticles can induce oxidative stress, leading to mitochondrial dysfunction, DNA damage, and apoptosis. Surface modifications with biocompatible coatings, such as polyethylene glycol (PEG), dextran, or chitosan, have been shown to reduce cytotoxicity by minimizing ROS generation and nonspecific protein adsorption. *In vivo* studies have reported minimal adverse effects when Fe_2O_3 nanoparticles are administered at therapeutic doses [112]. However, long-term accumulation in organs such as the liver, spleen, and lungs can pose toxicity risks. To address this, biodegradable coatings and size optimization are being explored to ensure efficient clearance from the body. Fe_2O_3 nanoparticles have significant potential as drug delivery vehicles due to their magnetic properties, biocompatibility, and ease of functionalization. They can serve as carriers for hydrophobic and hydrophilic drugs, enabling sustained and controlled release at the target site [113]. The high surface area of Fe_2O_3 nanoparticles allows for the loading of therapeutic agents, including small molecules, peptides, and nucleic acids. Magnetic targeting enhances the accumulation of drug-loaded nanoparticles at specific sites, improving therapeutic efficacy while reducing off-target effects. Moreover, Fe_2O_3 nanoparticles can be engineered to release drugs in response to environmental stimuli, such as pH, temperature, or enzyme activity. This feature is particularly beneficial for applications like cancer therapy, where acidic tumor microenvironments or elevated temperatures from hyperthermia can trigger drug release [114]. Fe_2O_3 nanoparticles are also being explored for combination

therapies, where they deliver drugs alongside other treatments, such as hyperthermia or photothermal therapy. Their ability to act as contrast agents for magnetic resonance imaging (MRI) further enables real-time tracking of drug delivery, offering theranostic capabilities [115]. In conclusion, the targeting mechanisms, cytotoxicity studies, and drug delivery potential of Fe₂O₃ nanoparticles position them as a versatile platform for advanced biomedical applications. Continued research into surface functionalization, biocompatibility optimization, and therapeutic payload integration will further enhance their clinical utility [116].

iii) Anti-inflammatory Activity

Iron oxide nanoparticles (Fe₂O₃) have demonstrated promising anti-inflammatory activity, making them a potential therapeutic tool for managing inflammatory conditions. Studies highlight their ability to modulate immune responses and reduce inflammation through various biological pathways. Fe₂O₃ nanoparticles can suppress inflammation by regulating the release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF- α), interleukin-6 (IL-6), and interleukin-1 β (IL-1 β). By inhibiting the overactivation of macrophages, which are key players in the inflammatory response, Fe₂O₃ helps prevent excessive immune reactions [117]. For instance, surface-modified Fe₂O₃ nanoparticles with biocompatible coatings like dextran or polyethylene glycol (PEG) have shown enhanced immunomodulatory effects, reducing the release of these cytokines in inflammatory environments. Pathway studies suggest that Fe₂O₃ influences nuclear factor-kappa B (NF- κ B) signaling, a critical pathway in inflammation. NF- κ B activation leads to the transcription of genes responsible for the production of inflammatory mediators [118]. Fe₂O₃ nanoparticles have been observed to inhibit the activation

of this pathway, thereby reducing inflammation at the molecular level. Additionally, they can modulate oxidative stress by scavenging reactive oxygen species (ROS), which play a key role in triggering and sustaining inflammatory processes [119]. Another mechanism involves the polarization of macrophages. Fe₂O₃ nanoparticles can shift macrophages from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype, promoting tissue repair and resolution of inflammation. This polarization has been observed in *in vitro* and *in vivo* studies, particularly in models of inflammatory diseases such as arthritis and colitis [120].

Studies in animal models have further supported the anti-inflammatory potential of Fe₂O₃ nanoparticles. For example, in mouse models of acute inflammation, Fe₂O₃ nanoparticles reduced edema and neutrophil infiltration in inflamed tissues. In a study on rheumatoid arthritis, Fe₂O₃ decreased synovial inflammation and joint destruction by attenuating the production of inflammatory mediators and oxidative stress markers. The anti-inflammatory effects of Fe₂O₃ nanoparticles, combined with their biocompatibility and functionalization potential, suggest a broad range of applications [121]. They could be used in drug delivery systems to deliver anti-inflammatory agents directly to inflamed tissues, or as stand-alone therapies in conditions like autoimmune diseases, wound healing, and chronic inflammatory disorders. Continued research into their mechanisms of action and long-term safety will be crucial for translating these findings into clinical applications [122].

iv) Wound Healing

Iron oxide nanoparticles (Fe₂O₃) play a significant role in promoting wound healing by enhancing key biological processes such as cell proliferation, collagen deposition, and other mechanisms critical to tissue repair and

regeneration. Fe₂O₃ nanoparticles stimulate cell proliferation, particularly in fibroblasts and keratinocytes, which are essential for wound closure. Fibroblasts play a pivotal role in forming the extracellular matrix (ECM) and providing structural support for tissue regeneration, while keratinocytes facilitate re-epithelialization by migrating across the wound bed to restore the epidermis [123]. Fe₂O₃ nanoparticles interact with these cells to enhance their proliferation and migration, potentially by activating signaling pathways like the PI3K/Akt and MAPK pathways, which are associated with cell survival and growth. Collagen deposition is another critical aspect of wound healing influenced by Fe₂O₃ nanoparticles. Collagen, a major structural protein in the ECM, provides strength and integrity to the regenerating tissue. Fe₂O₃ nanoparticles have been shown to upregulate the expression of genes involved in collagen synthesis, such as collagen type I and III. By promoting fibroblast activity and ECM remodeling, Fe₂O₃ nanoparticles contribute to the structural reorganization and mechanical resilience of the healed tissue. In addition to stimulating cell proliferation and collagen synthesis, Fe₂O₃ nanoparticles support other wound healing mechanisms [124]. They enhance angiogenesis, the process of new blood vessel formation, by stimulating endothelial cell proliferation and migration. Angiogenesis ensures an adequate supply of oxygen and nutrients to the wound site, facilitating faster and more effective tissue repair. Fe₂O₃ nanoparticles may also release iron ions in a controlled manner, which are known to be critical for enzymatic activities involved in tissue remodeling. Fe₂O₃ nanoparticles help regulate the inflammatory phase of wound healing, preventing excessive inflammation that can impede repair [125]. By modulating macrophage polarization, they promote a transition from the pro-

inflammatory M1 phenotype to the anti-inflammatory M2 phenotype, which is associated with tissue repair and regeneration. This immunomodulatory effect accelerates the resolution of inflammation and creates an environment conducive to healing. Their antimicrobial properties further aid in wound healing by reducing the risk of infection, which can delay the repair process [126]. Fe₂O₃ nanoparticles generate reactive oxygen species (ROS) that target microbial cells without harming host tissues, providing a dual benefit of infection control and promoting a sterile healing environment [127]. In experimental models, Fe₂O₃ nanoparticles have been incorporated into hydrogels, scaffolds, or dressings to demonstrate their efficacy in enhancing wound healing [128]. These formulations have been shown to reduce healing time, improve tissue quality, and support the formation of new, functional skin [129]. Overall, Fe₂O₃ nanoparticles offer a multifaceted approach to wound healing by combining cell proliferation, collagen deposition, angiogenesis, immunomodulation, and infection control. Future research should explore their integration into advanced therapeutic platforms and validate their performance in clinical settings.

v) Immunomodulatory Effects

Iron oxide nanoparticles (Fe₂O₃) have demonstrated significant effects on immune cells, highlighting their potential in immunotherapy applications. These nanoparticles interact with various components of the immune system, modulating immune responses in ways that can be harnessed for therapeutic purposes in cancer, autoimmune diseases, and infectious diseases [130]. Fe₂O₃ nanoparticles influence macrophage behavior, a critical aspect of their immunomodulatory effects. They can promote the polarization of macrophages from the pro-inflammatory M1 phenotype to the anti-inflammatory

M2 phenotype. This shift is beneficial in reducing chronic inflammation and promoting tissue repair in inflammatory diseases. Conversely, in cancer immunotherapy, Fe₂O₃ nanoparticles can be designed to enhance M1 polarization, boosting the immune system's ability to attack tumors [131]. Dendritic cells (DCs), which play a pivotal role in antigen presentation and initiating adaptive immune responses, are also affected by Fe₂O₃ nanoparticles. Studies have shown that Fe₂O₃ can enhance the maturation and antigen-presenting capabilities of DCs, making them more effective in stimulating T-cell responses [132]. This property is particularly valuable in cancer immunotherapy, where robust activation of cytotoxic T-cells is necessary to eliminate tumor cells. Fe₂O₃ nanoparticles also impact T-cells directly. By functionalizing their surface with specific antigens or immunostimulatory molecules, Fe₂O₃ nanoparticles can be used to deliver targeted stimuli to T-cells, enhancing their proliferation and activation [133, 134]. This approach has potential applications in adoptive T-cell therapies, where nanoparticle-based stimulation could improve the efficacy of therapeutic T-cells. Another important effect of Fe₂O₃ nanoparticles is their ability to modulate the production of cytokines. Depending on their surface chemistry and functionalization, they can either promote or suppress the release of pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF- α), and interleukin-1 β (IL-1 β). This tunable cytokine regulation makes Fe₂O₃ nanoparticles a versatile tool in managing immune responses for conditions ranging from hyperinflammatory states to immunosuppression. In cancer immunotherapy, Fe₂O₃ nanoparticles have been explored as carriers for immune checkpoint inhibitors, vaccines, or other immunostimulatory agents [135]. Their

superparamagnetic properties allow for precise delivery to the tumor microenvironment using magnetic guidance, enhancing the concentration of therapeutic agents at the target site while minimizing systemic side effects [136]. Additionally, their intrinsic properties can stimulate tumor-associated macrophages (TAMs) to adopt an M1 phenotype, reducing tumor immunosuppression and enhancing anti-tumor immunity. In autoimmune diseases, Fe₂O₃ nanoparticles have shown promise in dampening hyperactive immune responses. By modulating macrophages and T-cell activity, these nanoparticles help to restore immune homeostasis, potentially reducing tissue damage caused by excessive inflammation. The ability of Fe₂O₃ nanoparticles to interact with immune cells, regulate cytokine production, and serve as delivery vehicles for immunotherapeutic agents highlights their potential in advancing immunotherapy [137]. Ongoing research is focused on optimizing their size, surface chemistry, and functionalization to maximize their therapeutic efficacy and ensure biocompatibility, paving the way for their integration into clinical immunotherapy strategies.

3) Challenges and Limitations

Despite their promising applications, Fe₂O₃ nanoparticles face several challenges and limitations. One major concern is their potential toxicity, particularly at higher doses or with prolonged exposure, which can lead to oxidative stress, inflammation, or organ accumulation. Ensuring consistent size, shape, and surface functionalization is another challenge, as these factors significantly impact their biological interactions and efficacy. Additionally, the long-term biodegradability and clearance of Fe₂O₃ nanoparticles need further investigation to minimize risks of accumulation. Regulatory hurdles and scalability of production also pose

barriers to clinical translation. Addressing these issues through advanced engineering and rigorous safety assessments is crucial for their broader adoption.

i) Toxicity Concerns

The potential toxicity of Fe₂O₃ nanoparticles (IONPs) is a critical consideration in their biomedical applications. These nanoparticles, while highly versatile, can induce adverse effects that need to be thoroughly understood and mitigated for safe and effective use. Their toxicity is influenced by several factors, including size, shape, surface charge, dose, and duration of exposure, as well as the presence or absence of surface functionalization. A significant concern is the generation of reactive oxygen species (ROS) by Fe₂O₃ nanoparticles. ROS are highly reactive molecules that can cause oxidative stress, leading to damage of cellular components such as lipids, proteins, and DNA. This oxidative damage can trigger inflammatory responses, mitochondrial dysfunction, and even cell death, particularly in sensitive cell types. While controlled ROS production can be beneficial for antimicrobial or anticancer applications, excessive levels pose risks to healthy tissues. Uncoated or poorly functionalized Fe₂O₃ nanoparticles tend to aggregate, leading to enhanced toxicity due to nonspecific interactions with cells and tissues. The surface charge of nanoparticles also plays a role, as highly charged nanoparticles can disrupt cell membranes or interact with proteins, altering their structure and function. For example, positively charged nanoparticles may exhibit higher cytotoxicity due to stronger interactions with negatively charged cell membranes. Long-term accumulation of Fe₂O₃ nanoparticles in vital organs such as the liver, spleen, lungs, and kidneys raise concerns about chronic toxicity. Animal studies have shown that nanoparticles administered at high doses or over extended

periods can remain in the body, potentially causing persistent inflammation, fibrosis, or organ dysfunction. The lack of efficient clearance pathways, particularly for larger or aggregated nanoparticles, exacerbates these risks. Surface functionalization is a critical strategy to mitigate toxicity. Coating Fe₂O₃ nanoparticles with biocompatible materials like polyethylene glycol (PEG), dextran, chitosan, or proteins can improve stability, reduce aggregation, and minimize nonspecific interactions with cells. Functionalization can also decrease ROS generation, thus lowering oxidative stress. Additionally, targeting moieties such as ligands or antibodies can be added to ensure selective interaction with diseased tissues, sparing healthy cells. Another consideration is the impact of Fe₂O₃ nanoparticles on immune responses. While they can modulate inflammation beneficially in some contexts, inappropriate immune activation may lead to hypersensitivity or autoimmune reactions. Investigations into dose-dependent effects are crucial to determine safe therapeutic windows and avoid unintended immune stimulation. Comprehensive *in vitro* and *in vivo* studies are necessary to evaluate the biocompatibility and toxicity of Fe₂O₃ nanoparticles across different biological systems. These studies should assess acute and chronic effects, biodistribution, clearance mechanisms, and potential for long-term accumulation. Advanced imaging and analytical techniques are being employed to track the fate of nanoparticles in the body, providing insights into their safety profiles. To address these toxicity concerns, regulatory frameworks require rigorous preclinical testing before Fe₂O₃ nanoparticles can be approved for clinical applications. Balancing their therapeutic benefits with potential risks is essential, and ongoing research aims to optimize their design to maximize efficacy while

minimizing toxicity. Through tailored engineering, improved functionalization, and detailed safety evaluations, the challenges associated with Fe₂O₃ nanoparticles can be effectively managed, paving the way for their safe integration into biomedical applications.

ii) Pharmacokinetics and Biodistribution

Iron oxide nanoparticles (Fe₂O₃) exhibit unique pharmacokinetic and biodistribution profiles that are influenced by their size, shape, surface charge, and functionalization. Understanding how the body absorbs, distributes, metabolizes, and excretes Fe₂O₃ nanoparticles is critical for optimizing their efficacy and safety in biomedical applications. When administered intravenously, Fe₂O₃ nanoparticles bypass the gastrointestinal tract and enter systemic circulation directly. Their surface properties and functionalization significantly impact their absorption by tissues. Nanoparticles designed for passive targeting may rely on the enhanced permeability and retention (EPR) effect, which allows them to accumulate in areas with leaky vasculature, such as tumors or inflamed tissues. Functionalization with specific ligands or antibodies enables active targeting, facilitating receptor-mediated uptake by cells. Once in circulation, Fe₂O₃ nanoparticles interact with plasma proteins, forming a "protein corona" that influences their distribution and cellular uptake. The nanoparticles are typically distributed to highly perfused organs such as the liver, spleen, lungs, and kidneys, due to the filtration and clearance mechanisms of the mononuclear phagocyte system (MPS). The liver and spleen, as key components of the MPS, are particularly involved in nanoparticle sequestration and metabolism, which can limit their availability for targeted delivery. Fe₂O₃ nanoparticles are metabolized in the liver by macrophages, where they are broken down into their

constituent iron ions. These ions are incorporated into the body's natural iron metabolic pathways, such as hemoglobin synthesis or storage in ferritin. The biocompatibility of Fe₂O₃ nanoparticles is largely attributed to this ability to integrate with physiological iron processing. However, excessive doses or prolonged exposure can overwhelm these pathways, leading to iron overload and potential toxicity. The size and surface properties of Fe₂O₃ nanoparticles determine their clearance pathways. Smaller nanoparticles (<10 nm) may be cleared via renal excretion, while larger nanoparticles are primarily cleared through the hepatic pathway and excreted in bile. Inefficient clearance can result in long-term accumulation in organs, raising concerns about chronic toxicity and necessitating the development of biodegradable coatings to enhance clearance rates. Despite advancements in surface engineering, achieving precise targeted delivery of Fe₂O₃ nanoparticles remains challenging. The protein corona can alter the nanoparticles' targeting capabilities by masking functionalized ligands, reducing their ability to bind to specific receptors on target cells. Additionally, rapid clearance by the MPS can limit the circulation time of Fe₂O₃ nanoparticles, reducing their efficacy for systemic therapies. Non-specific uptake by non-target tissues, especially the liver and spleen, further reduces the availability of Fe₂O₃ nanoparticles at the intended site of action. Overcoming these issues requires careful optimization of nanoparticle size, surface charge, and functionalization. Strategies such as stealth coatings (e.g., polyethylene glycol) can reduce immune recognition and prolong circulation time. Dual-targeting approaches, combining passive targeting via the EPR effect with active targeting through ligands, are being explored to enhance precision. In conclusion, the pharmacokinetics and

biodistribution of Fe₂O₃ nanoparticles are governed by complex interactions with biological systems. Addressing challenges in absorption, distribution, metabolism, and excretion, as well as issues with targeted delivery, is essential for maximizing their therapeutic potential while minimizing off-target effects and toxicity.

iii) Regulatory and Clinical Barriers

Iron oxide nanoparticles (Fe₂O₃) face several regulatory and clinical barriers that complicate their approval for medical use. The unique properties of nanoparticles, such as their small size, high reactivity, and ability to interact with biological systems in complex ways, present challenges in ensuring safety, efficacy, and quality control. One major barrier is the lack of standardized protocols for assessing the safety and efficacy of Fe₂O₃ nanoparticles. Current regulatory frameworks are primarily designed for traditional pharmaceuticals and medical devices, which may not adequately address the unique behaviors of nanoparticles. Comprehensive preclinical evaluations, including toxicity studies, biodistribution analysis, and long-term safety assessments, are essential but often time-consuming and costly. Another challenge is the variability in the synthesis and functionalization of Fe₂O₃ nanoparticles. Small changes in their size, surface charge, or coating materials can significantly alter their biological interactions and therapeutic outcomes. Ensuring consistency in nanoparticle production at a large scale is critical, and regulatory agencies require robust quality control measures to address potential batch-to-batch variations. The potential for unforeseen long-term effects, such as accumulation in organs or chronic inflammation, also raises concerns. Regulatory agencies demand extensive in vivo studies to evaluate these risks, which can delay the approval process. Additionally, the lack of long-term

clinical data on nanoparticle-based therapies limits the confidence of regulators in approving new applications. Another hurdle is the classification of Fe₂O₃ nanoparticles under existing regulatory frameworks. They may fall under multiple categories, such as drugs, medical devices, or combination products, depending on their intended use. This ambiguity can result in overlapping regulatory requirements, increasing the complexity and cost of the approval process. Furthermore, public perception and skepticism about nanotechnology-based products can influence regulatory decisions. Agencies often adopt a conservative approach, requiring exhaustive evidence of safety and efficacy to address potential societal concerns. To overcome these barriers, collaborative efforts between researchers, manufacturers, and regulatory bodies are necessary to establish standardized guidelines for nanoparticle evaluation. Innovative testing models, such as organ-on-a-chip systems or advanced computational simulations, can accelerate safety assessments. Clearer definitions and classification criteria for nanoparticle-based products will also streamline the approval process. Addressing these challenges is essential for realizing the full potential of Fe₂O₃ nanoparticles in medical applications.

4) Conclusion and Future Perspectives

Iron oxide nanoparticles (Fe₂O₃) have demonstrated immense potential across diverse biomedical applications due to their unique physical, chemical, and biological properties. As highlighted in this review, Fe₂O₃ nanoparticles have shown promising results in antimicrobial, anticancer, anti-inflammatory, wound healing, and immunomodulatory activities. These multifunctional nanoparticles have opened new avenues for developing advanced therapeutic and diagnostic tools that address critical healthcare challenges, such as

antimicrobial resistance, targeted cancer therapies, and regenerative medicine. The synthesis of Fe_2O_3 nanoparticles has seen substantial advancements, particularly in the use of green synthesis methods. These environmentally friendly approaches leverage plant extracts, microorganisms, and other biological materials to produce nanoparticles with enhanced biocompatibility and reduced toxicity. Such techniques align with the principles of green chemistry and offer scalable, cost-effective alternatives to conventional methods. However, despite these advances, challenges remain in ensuring consistent size, morphology, and functionalization of the nanoparticles, which are crucial for their reproducibility and efficacy in biomedical applications. The antimicrobial activity of Fe_2O_3 nanoparticles has shown their ability to combat multidrug-resistant pathogens, disrupt biofilms, and act as effective agents for infection control. Their anticancer properties, including targeted drug delivery, hyperthermia induction, and ROS-mediated cytotoxicity, demonstrate significant potential in overcoming limitations of traditional cancer therapies. Furthermore, their role in anti-inflammatory and immunomodulatory activities highlights their ability to fine-tune immune responses, making them valuable for autoimmune diseases and chronic inflammatory conditions. In wound healing, Fe_2O_3 nanoparticles promote cell proliferation, collagen deposition, and angiogenesis, enhancing tissue regeneration and recovery. These applications underscore the versatility and adaptability of Fe_2O_3 nanoparticles in addressing complex medical needs. Despite their wide-ranging applications, there are several challenges associated with the clinical translation of Fe_2O_3 nanoparticles. One of the most critical concerns is their potential toxicity, which arises from the generation of reactive oxygen species (ROS), long-term organ

accumulation, and dose-dependent effects. Surface functionalization with biocompatible coatings such as polyethylene glycol (PEG) or dextran has shown promise in mitigating these risks by improving stability, reducing nonspecific interactions, and enhancing clearance from the body. Rigorous preclinical and clinical evaluations are necessary to better understand their biodistribution, metabolism, and clearance mechanisms to ensure long-term safety. Regulatory and clinical barriers also pose significant hurdles to the adoption of Fe_2O_3 nanoparticles in medicine. Current regulatory frameworks, primarily designed for conventional drugs and devices, struggle to address the complexities of nanoparticle-based therapies. Developing standardized protocols for assessing their safety, efficacy, and quality is imperative. Additionally, the scalability of nanoparticle synthesis, particularly through green methods, needs further optimization to ensure cost-effective and reproducible production suitable for clinical use. Looking ahead, the future of Fe_2O_3 nanoparticles lies in their integration into multifunctional platforms. Theranostics, which combine therapeutic and diagnostic functionalities into a single nanoparticle system, represent a particularly exciting frontier. For example, Fe_2O_3 nanoparticles could be used to deliver drugs, monitor treatment responses through magnetic resonance imaging (MRI), and simultaneously provide hyperthermic cancer therapy. Advances in surface engineering, such as the incorporation of targeting ligands, antibodies, or peptides, will further enhance the specificity and efficacy of Fe_2O_3 nanoparticles, minimizing off-target effects and maximizing therapeutic outcomes.

Research into biodegradable coatings and hybrid materials combining Fe_2O_3 with other nanoparticles or polymers could address concerns related to long-term

toxicity and enhance their biocompatibility. Moreover, exploring innovative stimuli-responsive systems, where nanoparticles release drugs or exhibit therapeutic effects in response to pH, temperature, or enzymatic activity, will expand their applicability in personalized medicine. Interdisciplinary collaboration between material scientists, biologists, clinicians, and regulatory authorities is essential to overcome the current limitations of Fe₂O₃ nanoparticles. Establishing clear guidelines for their clinical use, improving production techniques, and conducting large-scale clinical trials will be crucial steps in translating laboratory research into practical healthcare solutions. In conclusion, Fe₂O₃ nanoparticles represent a transformative tool in modern medicine, offering innovative solutions to pressing biomedical challenges. While significant progress has been made in understanding their synthesis, mechanisms, and applications, addressing their limitations will unlock their full potential. With continued research and development, Fe₂O₃ nanoparticles have the potential to revolutionize

fields such as infectious disease control, cancer treatment, tissue regeneration, and immunotherapy, making them an integral part of the future of healthcare.

4.0 CONCLUSION

The findings of this study substantiate the traditional medicinal use of *Melia azedarach* extract for its anti-diabetic and anti-inflammatory properties. The extract exhibited significant glucose uptake activity, supporting its potential as an anti-diabetic agent, and demonstrated promising anti-inflammatory effects through membrane stabilization. These results highlight *Melia azedarach* as a natural source with potential therapeutic benefits against diabetes mellitus and inflammation. However, further *vivo* research is warranted to confirm these effects and explore their full therapeutic potential.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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