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Review Article

Exploring Iron Oxide Nanoparticles Innovations and Applications in Cancer Therapy

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ABSTRACT

Iron Oxide Nanoparticles (IONPs) are exciting technology in cancer therapy that represents agents with a unique combination of super paramagnetism, biocompatibility and the capability for surface functionalization toward targeted applications. The following review describes the current innovations and various applications of IONPs against cancer, dealing with their roles in targeted drug delivery, hyperthermia and imaging. IONPs can be synthesized by various chemical and physical methods, for instance, co-precipitation or thermal decomposition. Characterization techniques for their structural and magnetic properties include transmission electron microscopy and vibrating sample magnetometry. IONPs allow for targeted drug delivery by the release of therapeutic agents at a specific location, reducing systemic toxicity. In magnetic hyperthermia applications, they exploit the ability to produce heat during the alternating magnetic field exposure and induce apoptosis in tumor cells. Moreover, IONPs serve as magnetic resonance contrast imaging agents, enhancing tumors' imaging. Even with the great promise of IONPs, concerns about toxicity and biocompatibility and scalable production methods have yet to be realized. Combination therapies interlacing IONPs with other therapeutic modalities, as well as further research into their elicited immunomodulatory effects, are some of the future perspectives that have been outlined. Taken together, advancements in IONP technology herald a new frontier in cancer therapy, offering innovative strategies to improve treatment efficacy and the lives of patients.

Keywords: Cancer Therapy, Hyperthermia Treatment, Iron Oxide Nanoparticles, Photodynamic Therapy, Photothermal Therapy, Superparamagnetic Iron Oxide Nanoparticles, Targeted Drug Delivery.

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INTRODUCTION

Cancer has a strong influence on the health of the world's population and is responsible for leading the statistics of death acquired from non-communicable diseases. According to the WHO, almost 10 million cancer-related deaths occurred in 2020, thereby attaching a critical impact on public health (Cancer, 2024). The genetic disease is mainly a result of an accumulation of genetic mutations that leads to the formation of cells having an unstable genome and an increased proliferation rate, hence leading to the formation of a tumor growing in an invasive manner into the tissues of the host (Hanahan and Weinberg, 2011). Established cancer treatment modalities include surgical, chemotherapeutic and radiotherapeutic procedures. However, a patient's individual needs may not accord with such treatment approaches because these are organ-based subtypes of cancer cells that can display different characteristics. This creates diagnosis and treatment strategies that are complex (Wild, 2012). Some conventional therapies may inadvertently select more resistant cancer cell subtypes. As such, treatment resistance and recurrence in some cases cause worse patient outcomes (Cree and Charlton, 2017). Nanotechnology, in this respect, becomes the potential platform for cancer treatment. Some unique physical and chemical properties that can be manipulated at the nanoscale level of 1 to 100 nm could be exploited to provide better therapeutic efficiency with reduced side effects. The nanomaterials can be made multifunctional to permit targeted delivery of drugs and enable improved diagnosis (Boverhof *et al.*, 2015). Nanotechnology does offer a lot of opportunities in biomedicine because it implies very tough requirements regarding purity, biocompatibility and stability. Functionalization will endow nanomaterials with the capacity for therapeutic agents, targeting molecules and diagnostic markers-in other words, sophisticated Nano biomaterials that can respond intelligently to the intricacies of diseases such as cancer. This new way might reshuffle the cards in cancer diagnosis and treatment, leading to possibly more powerful and less harmful therapeutic options in the near future (Jang *et al.*, 2016).

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Iron Oxide Nanoparticles (IONPs) have been developed as a potential platform for the treatment of cancer and have some advantages compared to traditional modalities of therapy (Alphandér, 2020). With the superparamagnetic property and capability of versatile surface functionalization, it opened new avenues in targeted drug delivery, hyperthermia treatment and imaging against malignancies. In this respect, the introduction of IONPs into the field of cancer therapy opened new avenues for treating this devastating disease and gave rise to new hopes for more effective and personalized treatment strategies (Xu *et al.*, 2021).

Introduction to Iron Oxide Nanoparticles

Iron Oxide Nanoparticles (IONPs) have generated significant interest in recent years, since they exhibit unique physicochemical properties, as well as promising applications in various fields (Baabu *et al.*, 2023). IONPs are defined as sub-nanosized particles composed of iron oxide materials and possess superior properties that make them ideal candidates for applications in biomedicine (e.g., MRI contrast agents, drug delivery vehicles), the environment (e.g., wastewater treatment) and industry. The size- and shape-dependent physical and chemical properties of IONPs primarily stem from their nanoscale dimensions, which provide a high surface area to volume ratio. In addition, other attributes are derived from their controlled morphologies (e.g., spherical or non-spherical shapes-cubic, spindle-shaped spheres that can also be prepared by fine-tuning synthetic approaches such as co-precipitation reaction conditions), resulting in tunable magnetic characteristics and stabilities (Ali *et al.*, 2016).

This property makes them highly useful for applications such as magnetic resonance imaging and hyperthermia treatments in cancer therapy, besides targeted drug delivery. Functionalization on their surface can modulate this magnetic property to a very fine degree. In addition to making the magnetic nanoparticles more stable and biocompatible, such surface modification can provide the requisite cellular/biomolecular targets due to selective interactions. By modifying the surface chemistry, dispersibility of IONPs in biological environments can be increased and their toxicity reduced; therefore, the applicability of IONPs in medical and environmental areas will be expanded (Dadfar *et al.*, 2019).

Surface functionalization of iron oxide nanoparticles is the process where different chemical groups or biomolecules attach to their surface, dramatically affecting their behavior in terms of interaction with biological systems. This technique opens the way for nanoparticle versatility that can be further conjugated with a therapeutic agent, imaging agent, or targeting ligand. The frequently used ways of functionalization involve polymers, silica coatings and biological molecules such as antibodies or peptides (Martinez-Boubeta *et al.*, 2013). The enable them to avoid nonspecific interactions and therefore be more effective in therapeutic applications (Montiel *et al.*, 2022). With a special combination of size, shape, magnetic properties and surface functionalization, iron oxide nanoparticles become an extremely flexible tool for nanotechnology development in many fields. The damaging effect on cells is usually explained by the production of reactive oxygen species. Under acidic conditions, formation of such radicals can occur if H_2O_2 is present and magnetite particles supply Fe^{2+} ions as Fenton catalysts. Figure 1 shows Overview of the various applications, structural changes and surface interactions of iron oxide nanoparticles at the nanoscale.

For biological applications, MNPs must be designed to be both chemically and mechanically inert to achieve high separation capabilities with the appropriate affinities towards biomolecules involved in procedures like protein purification, cell sorting, algae harvesting and virus removal (Marín *et al.*, 2016). Interestingly, MNPs have been approved by FDA for several biomedical applications, among which are the following: hyperthermia treatment, targeted drug delivery and contrast agents for magnetic resonance imaging (Roth *et al.*, 2016). On the other hand, in catalytic applications like Fenton chemistry, a high reactivity of MNPs is required. While huge research has been done on the modification and functionalization of MNPs, their formation process, phase transitions and nature at the surface are still not fully understood (Thanh, 2012). In this study, a few synthesis pathways have been evaluated for the synthesis of iron oxide nanoparticles, namely, polyol, hydrothermal (Daou *et al.*, 2006), electrochemical (Ramimoghadam *et al.*, 2014), pyrolytic (Kluge *et al.*, 2015), and co-precipitative methods (Ahn *et al.*, 2012). Different synthesis parameters, like temperature, pH and concentration of iron ions, have been changed to determine their effects on the size, morphology and composition of iron oxide nanoparticles (Bateer *et al.*, 2013; Lim *et al.*, 2016; Forge *et al.*, 2008), The control of surface reactivity is very critical, which can be altered by different ions, biomolecules, or polymers and impact particles' performance. In the case of magnetite, for example, ferrous ions have been linked to cytotoxicity and catalytic activity. Several studies have shown the inhibition of cell growth in various microorganisms by magnetite nanoparticles, whereas maghemite nanoparticles exhibited lower toxicity (Aruoja *et al.*, 2015), This cell-damaging activity was frequently ascribed to the generation of reactive oxygen species, especially under acidic conditions, in which magnetite may act as a Fenton catalyst. The iron ions can crystallize into more than 20 different forms of Oxides and (Oxy) hydroxides. Besides, the crystal structure, particle size and magnetization of iron oxides can be tuned by a range of reaction conditions (Book Reviews, 1997), However, in nanoparticles, compared to bulk materials, the transformation between the iron oxide forms happens so fast, increasing the need for better understanding of transition states at the nanoparticle level. Moreover, the oxidation of magnetite nanoparticles, especially under ambient conditions, could alter their composition and properties, in some way limiting their applications. Mild oxidation might bring some benefits in terms of particle stability and the creation of new structure-property relationships. In this paper, we report an investigation on the oxidation process of magnetite nanoparticles under mild and harsh conditions by tracking the changes of their magnetic properties, size and zeta potential. Mossbauer and Raman spectroscopy techniques will be complemented by X-ray diffraction to distinguish magnetite from maghemite and further outline the implications of these transformations regarding catalytic and cytotoxic behavior (Grosvenor *et al.*, 2004). The interaction among synthesis conditions, environmental factors and surface modifications implies the need for continuous research in the field of magnetic nanoparticles to enable their full potential for application.

Importance and Advantages of Iron Oxide Nanoparticles in Cancer Therapy

Magnetic iron oxide nanoparticles can be synthesized by several methods, including physical, chemical and microbial techniques. The choice of the preparation method has significantly influenced the physical and chemical properties of these nanoparticles. Out of these, the chemical methods are the most prevalent due to the reasons of low cost and high yield. Commonly used chemical methods for synthesizing Fe_3O_4 NPs include thermal decomposition, hydrothermal, co-precipitation and microemulsion methods. Obviously, the most applied one is the co-precipitation method, whereby relatively easy and viable routes to the synthesis of magnetic nanoparticles with desired properties are found. Detailed knowledge of all methods will, in any case, be helpful in improving the synthesis for magnetic nanoparticles for many applications. Table 1 summarizes various methods for synthesizing nanoparticles, highlighting their principles, advantages, disadvantages, impact factors and references for further reading.

Although the process of preparing Fe_3O_4 NPs has reached its maturity, it is still challenged by various problems, some of which pertain to the production and others to the application. Aggregate formation is the major issue associated with Fe_3O_4 NPs; this basically results from the fact that these nanoparticles are less stable. This could reduce the efficiency of Fe_3O_4 NPs for different applications, mostly biomedical applications. According to Mohammadi *et al.*, (2013), instability should be overcome (Mohammadi *et al.*, 2013).

This, therefore, means there is a need to further modify the surface of Fe_3O_4 NPs to enhance their performance. Appropriate surface modifications will significantly increase the stability, targeting ability and biocompatibility of such nanoparticles for proper application in drug delivery and imaging (Arias *et al.*, 2018). During modification of iron oxide nanoparticles, several materials can be utilized, each with their advantages and probably applications. For instance, various surfactants or stabilizers can be added to obtain homogeneous distribution of size and avoid aggregation; for these particles, this represents one of the most important factors in activity related to therapeutic and diagnostic applications (Arias *et al.*, 2018).

The choice of surface modification material does not only affect the physical nature of the nanoparticles but also interaction with biological systems. Optimizing these modifications for enhancing the overall efficacy of Fe_3O_4 NPs in targeted applications is one of

Table 1: Characteristics of Different Synthesis Methods of IONPs.

Method Name	Principle	Advantages	Disadvantages	Impact Factors	References
Microwave	It involves microwave radiation rapid heating of the precursors.	Short reaction time, higher yields, excellent reproducibility.	It is expensive and not suitable for scaling up and monitoring reactions.	Reaction time, precursor concentration.	(Saleem *et al.*, 2021)
Spray Pyrolysis	It involves aerosol formation followed by thermal decomposition.	Consistent size and shape, with small particle size.	Aggregation of particles, high cost.	Temperature, precursor type.	(Workie *et al.*, 2023)
Laser Pyrolysis	Laser-induced vaporization of precursors.	Small particle size, narrow size distribution.	Complicated, very expensive.	Laser intensity, precursor properties.	(D'Amato *et al.*, 2013)
Thermal Decomposition	Decomposition of metal-organic precursors at high temperature.	Produces highly monodispersed particles.	High cost, long synthesis time, high temperature.	Heating rate, precursor type.	(Fereshteh *et al.*, 2017)
Microemulsion	Formation of nanoparticles in a microemulsion system.	Monodispersed nanoparticles with various morphologies.	Low efficiency, difficult to scale up.	Surfactant type, phase ratio.	(Malik *et al.*, 2012)

Table 2: Properties of different modifying materials for IONPs.

Classification	Representative	Advantage	Application	References
Inorganic Coatings	Silica	Enhances stability, reduces cytotoxicity.	Biomedical applications, drug delivery.	(Soenen *et al.*, 2015)
Biopolymer Coatings	Chitosan	Improves biocompatibility and dispersion.	Tissue engineering, drug delivery.	(Desai *et al.*, 2023)
Polymer Coatings	Polyethylene Glycol (PEG)	Improves biocompatibility and dispersion.	Targeted drug delivery, imaging	(Shi *et al.*, 2021)
Metal Coatings	Gold	Enhances magnetic properties and stability.	Biosensing, imaging.	(Dheyab *et al.*, 2020)
Cross-linked Polymers	Poly (maleic anhydride-alt-1-octadecene)-PEG	Increases stability and reduces leaching	Biomedical applications, drug delivery	(Karakoti *et al.*, 2015)
Polymeric Matrixes	Polylactic Acid (PLA)	Biocompatible, reduces toxicity.	Drug delivery, tissue engineering.	(Sharma *et al.*, 2021)
Surfactants	Cetyltrimethylammonium Bromide (CTAB)	Improves dispersion and stability.	Drug delivery, imaging.	(Liu *et al.*, 2020)

the aspects ongoing research projects is geared towards. The high count of materials at one's disposal in modifying, as reported in Table 2, underlines the versatility and potential of Fe_3O_4 NPs within several scientific and medical fields.

Synthesis and Characterization Techniques of Iron Oxide Nanoparticles

Iron oxide nanoparticles synthesis methods

In general, there are 2 broad categories for the synthesis of nanoparticles: top-down and bottom-up approaches. Top-down techniques mostly involve breaking down bulk material into smaller particles using mechanical energy by crushing, milling, or grinding. Another technique in this category includes laser ablation, sputtering, etching and electron beam deposition. While these are basically environment-friendly methods, they tend to be time-consuming and energy-intensive (Soenen *et al.*, 2015). The bottom-up approach relies on the chemical interactions between certain atoms, ions, or molecules to generate nanoparticles (Desai *et al.*, 2023; Shi *et al.*, 2021). All these methods of synthesis can be generalized by being divided into three groups according to the nature of the processes: the physical ones, which are somehow close to the top-down ones; the chemical methods, among which one can mention co-precipitation, sol-gel, thermal decomposition, emulsion and microemulsion, hydrothermal, microwave-assisted techniques; and the biological methods, which rely on plants or microorganisms to produce the nanoparticles. The latter two categories relate to bottom-up strategies (Shi *et al.*, 2021).

Iron Oxide Nanoparticles

IONPs have gained considerable attention due to their unique properties and applications across different disciplines like biomedicine, environmental remediation and uses in electronics. Their nanoparticle synthesis can be carried out using different methodologies, with each having its various pros and cons. Typically employed techniques are co-precipitation, sol-gel synthesis, microemulsion, thermal decomposition, hydrothermal synthesis and green synthesis (Shi *et al.*, 2021; Dheyab *et al.*, 2020; Karakoti *et al.*, 2015; Sharma *et al.*, 2021) (Figure 2). Comparison of the most used methods for the synthesis of Iron Oxide Nanoparticles.

Co-Precipitation Techniques in Nanomaterial Synthesis

Co-precipitation is the most popular method for synthesizing IONPs because of the simplicity and low cost involved. Iron salts are mixed in an aqueous solution and a precipitating agent is added to provoke the formation of nanoparticles. Figure 3 illustrates the major types of methods for synthesizing iron oxide nanoparticles, with a particular emphasis on co-precipitation techniques in nanomaterial synthesis.

The size and morphology of the formed nanoparticles are controlled by tuning some reaction parameters like pH, temperature and reactants' concentration. However, it is difficult to obtain a uniform particle size and prevent agglomeration. Mascolo *et al.*, 2013 reviewed the synthesis of magnetite nanoparticles by co-precipitation at room temperature within a wide pH range with the use of different bases; therefore, it confirmed that such techniques were quite easy for the control of particle features. Their findings further highlight the impact of pH on nanoparticle morphology and size in catalysis and biomedical applications (Liu *et al.*, 2020). Sharma *et al.*, 2016 went further to contribute to the co-precipitation discourse by focusing on synthesizing Fe_3O_4-supported Nano catalysts. They were able to synthesize and characterize such catalysts and apply them in various coupling reactions. Their work has been able to highlight the efficacy of iron oxide nanoparticles in catalysis and hence may probably open their utilization toward green chemical applications (Niculescu *et al.*, 2022). Deregibus *et al.*, 2016 contributed to this through a charge-based precipitation strategy for the isolation of extracellular vesicles that gives example of the amenability of co-precipitation methods beyond the traditional synthesis of nanoparticles, generalizing their applications in biological systems (Aryal *et al.*, 2019).

Theiss *et al.*, 2016 reviewed the synthesis of layered double hydroxides by co-precipitation methods. It is shown that metal cations exert a serious influence on the choice of conditions for the structural and physicochemical properties of the resulting LDHs. With such controllable properties through co-precipitation, these materials could be applicable for such areas as catalysis, drug delivery, or waste remediation (Singh *et al.*, 2020). Dippong *et al.*, (2021) reported on the recent progress in MFe_2O_4 synthesis and applications with M=Co, Cu, Mn, Ni, Zn nanoparticles through co-precipitation. Their review focuses on methods and consequent features of such nanoparticles relevant for their application in magnetic separation, drug delivery and as MRI contrast agents (Niculescu *et al.*, 2022).

Although co-precipitation techniques have developed tremendously, there are many knowledge gaps that need to be bridged. First, the effects of different environmental conditions like temperature, ionic strength and the presence of surfactants on the co-precipitation process and the resultant nanoparticle properties. Although co-precipitation has shown great promise as a method for synthesizing a wide range of nanoparticles, the scalability of such processes for industrial applications has remained underexplored. Future studies must therefore be focused on the optimization methods in co-precipitation for large-scale production, where uniformity and reproducibility in nanoparticle characteristics are guaranteed. Their integration with co-precipitation techniques could, however, give rise to new synthesis methodologies, such as sol-gel or hydrothermal processes for the development of nanomaterials with enhanced functionalities. Such hybrid approaches could lead to new routes for the tailoring of materials with specific applications in catalysis, biomedicine and environmental remediation.

Sol-Gel Synthesis of Nanoparticles

Sol-gel systems undergo a transition of a liquid solution-to-solid gel phase, making it possible to control the size and morphology of the nanoparticles. It also offers the ability to yield homogeneous nanoparticles with high purity, but the process generally takes longer time, and the environment must be controlled quite well.

The sol-gel route for the synthesis of iron oxide nanoparticles is a quite reliable way to synthesize them with controlled characteristics. According to Bokov *et al.*, 2021, this process is much simpler and allows one to obtain homogeneous materials with predetermined properties. This will allow for control of pH, temperature, precursor concentration, etc.-parameters that tend to have a direct effect on the characteristics of synthesized nanoparticles (Mihai *et al.*, 2020).

According to Cui *et al.*, the low-temperature sol-gel synthesis of iron oxide was reported to have a phase transition between α-Fe_2O_3, γ-Fe_2O_3 and Fe_3O_4. The results underline how control over the conditions of synthesis is necessary to get the required phase purity and homogeneity. Normally, it forms a good example of how, by tuning sol-gel parameters, phase transitions can be controlled (Rashid *et al.*, 2020). Parashar *et al.*, 2020 commented in their paper on a review about the synthesis, characterization and applications of the metal oxide nanoparticles technique using the sol-gel method, which is versatile and efficient (Mascolo *et al.*, 2013).

Wu *et al.*, 2015 further discussed the surface functionalization strategies of magnetic iron oxide nanoparticles, which are very important in improving their biocompatibility and stability in biomedical applications. The possibility of functionalizing IONPs during the sol-gel process opens new opportunities for them in targeted drug delivery and magnetic resonance imaging (Sharma *et al.*, 2016).

Although the sol-gel synthesis of iron oxide nanoparticles has advanced tremendously over recent years, many gaps remain in knowledge. More specifically, concerning long-term stability and toxicity in green-synthesized nanoparticles within biological systems, as highlighted by (Arias *et al.*, 2018), this needs deeper work. Safe knowledge on the biodistribution and degradation pathways of such nanoparticles is required for the use in biomedicine.

Although the sol-gel technique allows the synthesis of nanoparticles with specific properties, the scalability of such processes for commercial applications remains an open challenge. Future investigations should be oriented toward the optimization of sol-gel synthesis parameters for large-scale production without losses at the level of quality and homogeneity of the nanoparticles (Deregibus *et al.*, 2016).

Microemulsion techniques for the synthesis of iron oxide nanoparticles

The microemulsion technique uses surfactants to stabilize the formation of nanoparticles in the microemulsion system, leading to highly homogeneous and well-dispersed IONPs. In this process, very good control over particle size and shape can be achieved, but surfactants are used, which complicates further purification processes.

One of the phenomenal advantages of this micro-emulsion technique is the exceptional control required over the size and shape of the particles used. By proper adjustments in concentration in surfactants, oil, water and reaction conditions, the method can be well-controlled for synthesizing IONP of desired properties. For instance, the size of the nanoparticles may be changed through variations in the surfactant-to-oil ratio, while their morphology might be adjusted through the choice of surfactant. This kind of control becomes quite important when dealing with applications where the magnetic behavior, surface reactivity, or biocompatibility of the nanoparticles depend crucially on their size and shape. Equally important is that uniformity is obtained through microemulsion technique. Surfactants create a confined space for the nanoparticles to be formed, with reduced chances of aggregation and assurance of well-dispersed particles in solutions. This kind of homogeneity becomes an important criterion for many bio applications, where the batch-to-batch consistency of properties in a material becomes an important aspect, for example, in drug delivery, imaging and catalysis. For the field of biomedical applications, where targeting and controlled release must take place at precise points, the efficacy of IONPs can be further enhanced due to the well-defined size distribution of the particles.

The microemulsion methods are outstanding, particularly owing to their capability of developing nanoparticles that are uniform in size and shape. It involves the formation of a thermodynamically stable isotropic liquid mixture comprising water, oil and surfactant, acting as nanoreactors for the synthesis of nanoparticles. This controlled environment allows modifying the particle properties very precisely, hence being one of the most preferred options for the synthesis of IONPs in various applications by Wu *et al*., 2015 (Sharma *et al*., 2016).

Overall, a combination of state-of-the-art characterization tools is needed to understand generally the structure-property relationships of iron oxide nanoparticles. It can be very helpful in understanding how different synthesis conditions affect the functional properties of IONPs to design tailored nanoparticles for appropriate use.

Thermal Decomposition for the Synthesis of Iron Nanoparticles

Another effective technique is that of thermal decomposition, where iron precursors are decomposed at very high temperatures to obtain nanoparticles.

It has been shown that surfactants such as oleic acid, when applied in the process of thermal decomposition, make it possible to produce monodisperse superparamagnetic Fe_3O_4 nanoparticles. Not only is magnetic performance improved, but size variability is significantly reduced-a factor that is very critical where the absolute value of magnetism is required for an application (Theiss *et al*., 2016). The development of this synthesis technique has placed the method at the forefront of technology in the production of monodisperse, spherical iron oxide nanoparticles with size and morphology that could be modified at will (Dippong *et al*., 2021).

Although the synthesis of iron nanoparticles through thermal decomposition has seen many developments, it is still not devoid of knowledge gaps. The energy intensity involved in the process of thermal decomposition is a major limitation to its large-scale applications. Future studies should therefore aim at optimizing the thermal decomposition process so that it reduces energy consumption without compromising the quality of synthesized nanoparticles. Also, fully unequivocal advantages in improving the properties of iron nanoparticles by surfactants have been evident; however, more studies are required to be conducted on the long-term stability and biocompatibility of these surfactant-coated nanoparticles. Interactions of surfactants with the biological system need to be understood for translation of results from the laboratory to clinics. Complications brought about by mixed iron oxide phases and crystal defects in the absence of oxygen underline the requirement for much more in-depth studies on the effects of synthesis conditions on nanoparticle properties. The exploitation of alternative syntheses or changes in the synthesis procedure will help avoid these problems and improve the magnetic properties of the nanoparticles.

Advanced iron oxide nanoparticles characterization techniques

Iron oxide nanoparticles have been receiving escalated interest since their inception because of some outstanding properties such as superparamagnetic, high surface area and biocompatibility feats that make these feasible for almost every application, be it in the biomedical or environmental fields (Bokov *et al*., 2021). Such characterizations of nanoparticles are indispensable for the understanding of their structure, magnetic and chemical properties, which have a direct relevance to their functionality in applications related to drug delivery, magnetic resonance imaging and environmental remediation. Size, morphology, crystallinity and surface characteristics of IONPs are attainable from advanced characterization techniques such as transmission electron microscopy, scanning electron microscopy, X-ray diffraction and dynamic light scattering (Cui *et al*., 2013). In this regard, TEM is necessary to visualize the size and shape of particles at the nanoscale, while XRD is used to determine crystalline phases and purities in the synthesis of nanoparticles. Other surface characterization techniques that focus on the surface chemistry of the nanoparticles are Fourier-Transform Infrared Spectroscopy (FTIR) and Thermogravimetric Analysis (TGA), which is aimed at illustrating its thermal stability. Thus, such techniques have advanced the potential to develop specific properties of IONPs into broad application utilities across the scientific and industrial worlds. Therefore, clearly, these characterization techniques have provided the underpinning that paves the way to the meaningful applications of these special nanoparticles (Parashar *et al.*, 2020).

The shape of iron oxide nanoparticles conditions their behavior and induces potential cell toxicity. Thus, at the stage of their synthesis, there is an important control of the shape of the nanoparticles to avoid harmful impacts. Electron microscopy methods are normally applied to control morphology and shape of such nanoparticles. Besides shape, crystal structure and chemical composition remain the other two characterization parameters in the development of IONPs. Among all the prevailing techniques, X-ray diffraction is used for assessing crystal structure and phases (Wu *et al.*, 2015). However, it has been reported that in the case of nanoparticles smaller than 5 nm, the XRD patterns can be influenced profoundly, thus requiring other alternatives to perform the analysis. One such promising alternative to X-ray analyses is selected-area electron diffraction, which can provide a more realistic and accurate representation of the nanoparticle crystal structures. Lastly, the chemical and elemental compositional tests must be determined for the nanoparticle to estimate purity and impact upon electrochemical activity. Electron energy loss spectroscopy techniques can differentiate between Iron (II) and Iron (III), which will be helpful in differentiating the phases of iron oxides present in the nanoparticles (Ciriminna *et al.*, 2013).

While high surface areas of IONPs might tend to cause agglomeration, they are of immense importance in applications requiring high surface areas for maximizing pollutant sorption and maximum efficiency with respect to pollutants. Various gas sorption-based methods, particularly BET analysis, are commonly used for measuring surface area (Hufschmid *et al.*, 2015).

The surface charge on IONPs is directly linked to their colloidal stability and interactions *in vivo* environments, which regulate the formation of a protein corona on their surface and determine cellular uptake. Surface charge is characterized by the zeta potential, measured by a zeta potentiometer, in millivolts. Usually, a zeta potential above+15 mV or below-15 mV is found to be sufficient to give rise to electrostatic repulsion for the prevention of aggregation in colloidally stable suspensions. The zeta potential can be dramatically affected by factors such as pH, ionic strength and the presence of both charged and uncharged molecules (Cui *et al.*, 2013; He *et al.*, 2013).

Photothermal Therapy (PTT)

Photothermal Therapy (PTT) procedure is a novel and innovative treatment method that operates by introducing heat into the intended tissue like tumors using electromagnetic radiation, especially near-infrared light. Thermal ablation is where heat localizes the area of damage and destroys cancer cells by raising their temperature to thermal levels. The advantage of PTT is its non-invasive nature, targeting specificity and minimal invasion to normal tissues. Researchers are particularly interested in this technique, especially in cancer treatment, because it could very precisely destroy only tumors without affecting normal cells (Roca *et al.*, 2019).

By virtue of their unique properties, Photothermal Therapy (PTT) Employing Iron Oxide Nanoparticles (IONPs) has emerged as a promising strategy in cancer treatment, leveraging light irradiation to enhance therapeutic capabilities (Anu *et al.*, 2017). IONPs exhibit high Photothermal Conversion Efficiency (PCE) Under Near-Infrared (NIR) laser irradiation due to improved tissue penetration with minimal non-specific scattering and absorption. This allows targeted heating of tumor cells while avoiding damage to healthy tissue, reducing side effects compared to traditional methods (Mourdikoudis *et al.*, 2018). Advances in IONP synthesis and functionalization have led to biocompatible nanoparticles with improved photothermal efficiency, making them suitable for clinical use. For instance, conjugating gold coatings on IONPs has significantly improved their PTT properties, effectively destroying cancer cells like MCF-7 breast cancer cells under NIR irradiation. Functionalizing IONPs with tumor-targeting ligands enhances their accumulation in cancer tissues, minimizing systemic exposure. Researchers are also exploring the synergistic effects of combining PTT with

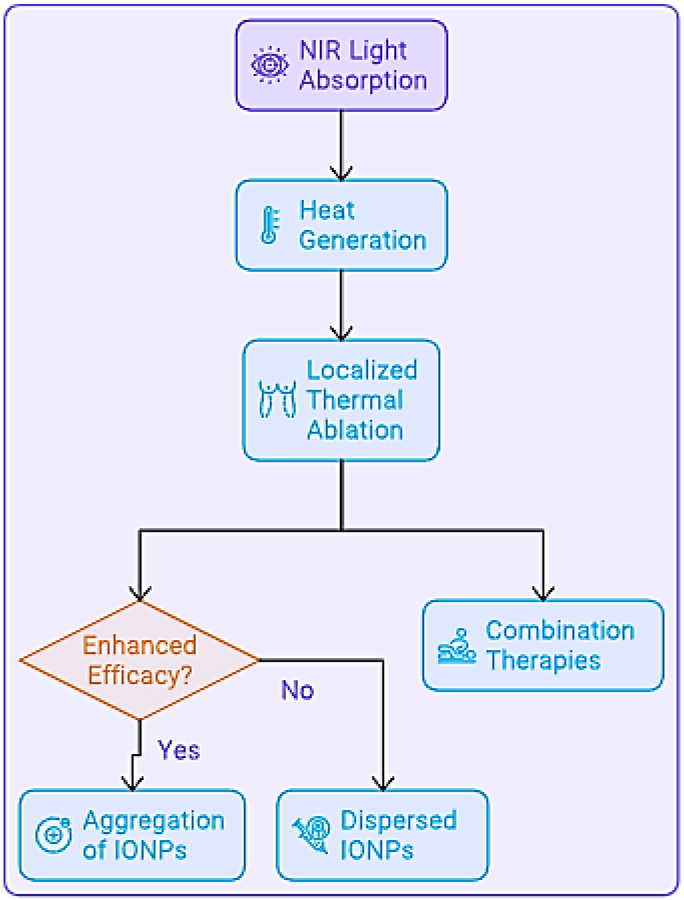

Figure 4: Mechanism of Action Schematic of Iron Oxide NPs for PTT.

chemotherapy or immunotherapy to achieve superior therapeutic efficacy. As research progresses, IONPs are expanding the potential for innovative cancer treatment strategies that harness nanotechnology (Koopmans *et al.*, 2020).

Iron Oxide NPs for PTT

IONPs show a high potential to be used as agents. Besides, they can also act as photothermal agents. Espinosa *et al.*, pointed out that IONPs have a twofold ability in cancer treatment; therefore, a combination of MHT with PTT would enhance the outcome significantly because heating efficiency will be multiplied. It is through this bimodal therapy treatment that the tumor gets thermally ablated while the healthy tissue around it remains safe (Anu *et al.*, 2017). It has been established through research that incorporating iron oxide nanoparticles with other nanoparticles like gold can yield some results. In one of the studies conducted on 2017 by Yang *et al.*, loading iron oxide and gold nanoparticles into phosphorus sheets proved capable of slowing tumor growth. To attain this, the study had applied PTT coupled with photodynamic therapy. The result shows the potential of application applicability for IONPs under different treatment strategies (Ismail *et al.*, 2019).

IONPs are known to be very good photothermal agents, with a light absorption ability in the near-infrared 700-1100 nm range, a factor that allows them to penetrate tissues while minimizing damage to the surrounding healthy cells. IONPs, upon NIR light illumination, convert the absorbed light energy into heat (Modena *et al.*, 2019). Their efficiency in the process is mainly governed by factors such as concentration, power density and duration of exposure. This heat produced has the result of increasing the temperature of the tumor environment and often exceeds 42°C (Zhao *et al.*, 2021). This leads to the destruction of the structure and the cells by apoptosis. More interestingly, the efficacy of IONPs in photothermal therapy can be enhanced when they aggregate together (Estelrich *et al.*, 2018). This could result in more efficient production of heat since the more aggregated

Table 3: Case Studies and Clinical Experience.

Case Study	Nanoparticle Innovation	Cancer Type	Key Findings	References
Magnetic fluid hyperthermia.	Iron oxide nanoparticles for magnetic hyperthermia.	Various	Successful demonstration to enhance overall survival in clinical trials, but struggles to establish a wider clinical presence.	(Chung *et al.*, 2021; Mulens-Arias *et al.*, 2021)
Immune-modulating potential of iron oxide nanoparticles.	Harnessing immune-nanoparticle interactions to induce anti-tumor immune responses.	Various	Recent data demonstrates interactions between immune cells and iron oxide nanoparticles can induce anti-tumor immune responses.	(Khatua *et al.*, 2024; ; Cheng *et al.*, 2021; Etemadi *et al.*, 2020)
Targeted delivery of paclitaxel to breast cancer cells.	Anti-HER2/neu peptide-conjugated iron oxide nanoparticles.	Breast cancer.	Nanoparticles successfully delivered paclitaxel to breast cancer cells overexpressing HER2/neu.	(Vassallo *et al.*, 2023)
Improving antitumor potential and reducing resistance in HER2-positive breast cancer.	Multivalent exposure of trastuzumab on iron oxide nanoparticles.	Breast cancer.	Multivalent trastuzumab on iron oxide nanoparticles improved antitumor potential and reduced resistance in HER2-positive breast cancer cells.	(Obaidat *et al.*, 2019; Blanco-Andujar *et al.*, 2016; Khorana *et al.*, 2016)
Targeted delivery of doxorubicin to breast cancer cells.	Mucin-1 aptamer-armed superparamagnetic iron oxide nanoparticles.	Ovarian cancer.	Mucin-1 aptamer-armed iron oxide nanoparticles successfully delivered doxorubicin to breast cancer cells overexpressing Mucin-1.	(Vilgelm *et al.*, 2019)
Sensitization of cisplatin-resistant ovarian cancer cells.	Magnetite iron oxide nanoparticles.	Breast cancer.	Iron oxide nanoparticles sensitized cisplatin-resistant ovarian cancer cells to cisplatin treatment *in vitro.*	(Yang *et al.*, 2018)
Inducing oxidative stress and cell cycle arrest in breast cancer cells.	Doxorubicin-loaded iron oxide nanoparticles.	Breast cancer.	Doxorubicin-loaded iron oxide nanoparticles induced oxidative stress and cell cycle arrest in breast cancer cells.	(Ru *et al.*, 2019)

the nanoparticles, the more absorption of NIR light. Moreover, IONPs can be combined with therapeutic approaches targeting or drug delivery systems to enhance the effectiveness of tumor ablation. Mechanism of Action Schematic of Iron Oxide NPs for PTT shown in Figure 4.

IONPs are one of the most promising nanoparticles to transform cancer treatment into innovative ways in PTT. Their characteristics, including strong light absorption, efficient conversion and generation of heat when exposed to a laser, make them extremely effective as agents (Yu *et al.*, 2024). Compared to traditional methods of treating cancer, the main advantages of PTT using IONPs are specificity, minimal invasiveness and precise control over time and space. IONPs could target and kill cancer cells of tumors or locally spread metastases. A crucial role of IONPs in cancer treatment can also be in conjunction with conventional techniques against metastatic sites. Different results have shown the efficacy of IONPs-mediated PTT in studies on models with metastases in the lungs, bones, or lymph nodes. Research is underway to produce biocompatible IONPs and therapeutically efficient nanostructures that would further their use in a medical setting (Giménez *et al.*, 2022). Methods using nanocubes or magnetic nanoclusters have been shown to generate heat and improve tumor destruction following NIR laser light exposure. Researchers are working on multifunctional IONPs that integrate PTT with targeting, MRI and drug delivery for full cancer treatment (Espinosa *et al.*, 2018). IONPs will play a major role in cancer detection and treatment methods that are developing as fast as technology does. These nanoparticles, due to their unique properties and versatility, are sure to make a revolution in cancer therapy by opening new ways of PTT and other applications in cancer therapy. Therefore, future studies in this field hold immense promise for helping enhance outcomes for patients and advancing in the fight against cancer (Anu *et al.*, 2017).

Photodynamic Therapy (PDT)

Overview of Photodynamic Therapy (PDT)

PDT induces the destruction of tumors through three major mechanisms, as indicated in Figure 5. Nanoparticles in Photodynamic therapy, also known as IONPs, open up a whole new frontier of treatment options against cancer, simply by altering the properties of these particles to achieve successful treatment results (Yang *et al.*, 2017). PDT uses photosensitizers that involve the generation of ROS, which upon illumination by light at a specific wavelength result in cell death. Inclusion of IONP into PDT presents several advantages on solubility, targeted delivery and tissue penetration, all of which increase the maximum effect of the treatments. The study illustrated that

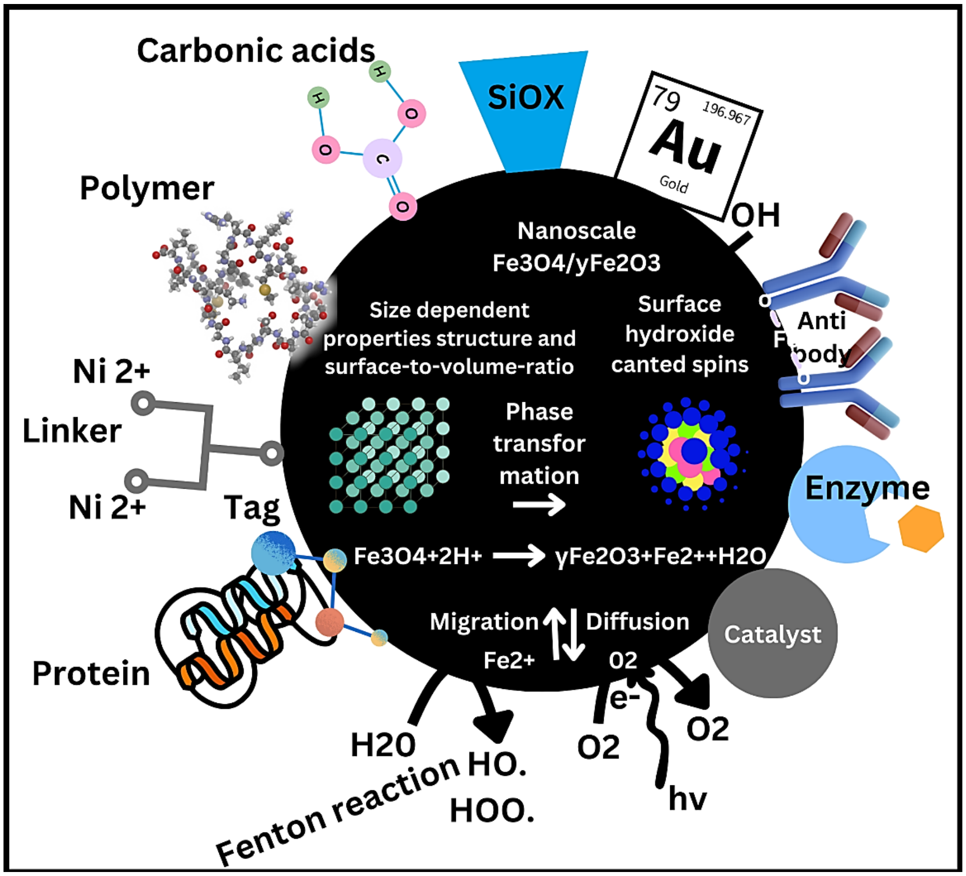

Figure 1: Overview of the various applications, structural changes and surface interactions of iron oxide nanoparticles at the nanoscale.

nanoparticles, IONPs, when combined with photosensitizers like porphyrins, are highly capable of handling cancer. (Yang *et al.*, 2017) For example, tetra-sulfonatophenyl porphyrin modified γ-Fe_2O_3 nanoparticles had some success in targeting human melanoma cells upon light exposure. This suggests that these nanoparticle complexes are capable of effectively generating ROS to inhibit the growth of tumor cells. The potential of IONPs to load and deliver therapeutic levels of photosensitizers into the regions of tumors strengthens their use in PDT, especially for hydrophobic photosensitizers that normally have poor solubility properties.

IONPs have been shown to increase the production of $^1O_2$, a key ROS utilized in PDT therapy to elicit cell death in cancer. The work by Ling *et al.*, presents one such pH responsive approach whereby IONPs enable a Fenton-like reaction only in the reductive, acidic tumor environment. This reaction increases the yield of $^1O_2$, permitting targeted toxicity toward cancer cells while minimizing harm to surrounding healthy tissue (Amatya *et al.*, 2021). About the attachment of Linoleic Acid Hydroperoxide (LAHP) to IONPs, Dulińska-Litewka *et al.*, demonstrated an increase in oxygen generation. This increase is useful for photodynamic therapy since it enhances the effectiveness of $^1O_2$ production in a variety of environments. The release of Iron (II) ions from the IONPs participates in the activation of this system, which places much emphasis on pH in the treatment outcome. This mechanism does not allow better selectivity of treatment. It is also indicative of the potential role of IONPs in developing advanced targeted cancer therapy based on the properties of the tumor microenvironment (Guo *et al.*, 2022).

PDT is a treatment using a substance that would be more concentrated in rapidly dividing cells, those undergoing cancerous changes. One exposes this substance to light; it changes to produce ROS-singlet oxygen and free radicals (Vallabani *et al.*, 2018).

Another critical aspect of PDT is the proper selection of light wavelengths for activation. This wavelength should have satisfactory tissue penetration such that it gets the photosensitizer activated throughout the tumor. The normal wavelengths used for PDT are in the range of 600 to 850 nanometers because they have maximum tissue penetration. This range has less absorption by hemoglobin and water, hence can reach the deep tissues before it losses it is intensity (Vallabani *et al.*, 2018). What sets PDT apart is its capability to precisely focus on the tumor site using light while minimizing damage to surrounding healthy tissues by activating the photosensitizer solely in that area. The use of iron oxide nanoparticles in photodynamic therapy marks progress in cancer treatment approaches. These nanoparticles can produce oxygen in conditions and their compatibility along with their versatile properties make them a potential platform for developing treatment methods. To ensure effective use in cancer care it's crucial to fill the knowledge gaps and focus on research areas (Rethi *et al.*, 2023).

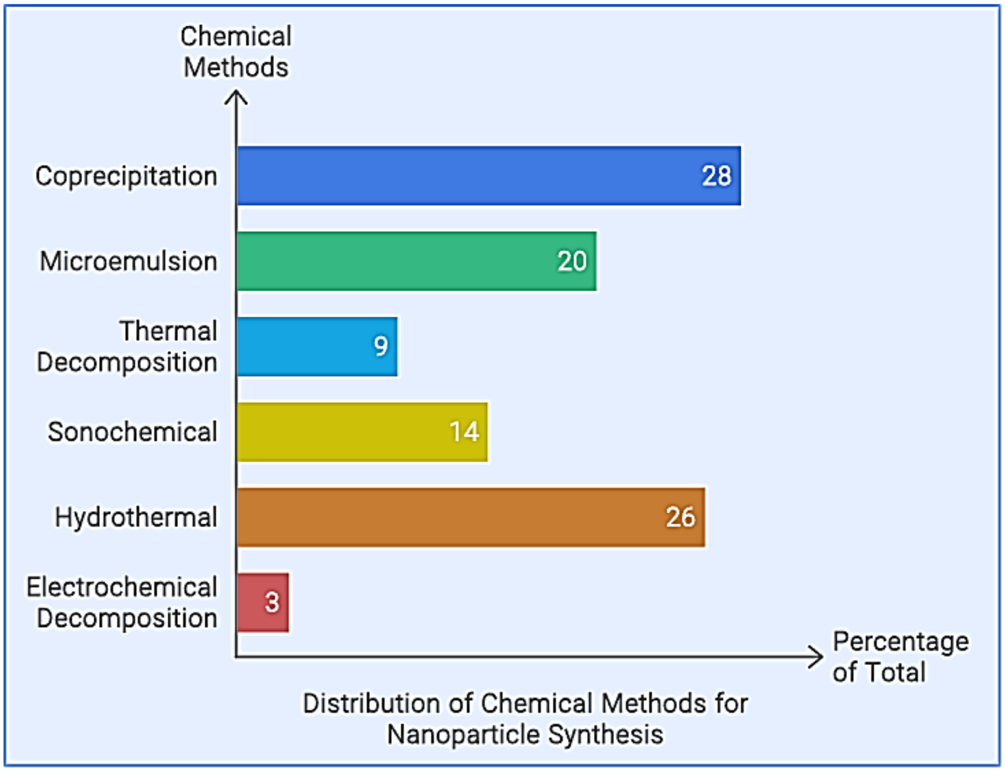

Figure 2: This is a graphical representation of the prevalence of the most common methods for nanoparticle synthesis.

Iron and Composites for Imaging Guided PDT

Imaging guided PDT has remained in the forefront with iron and composite materials. This new modality of treatment deploys a combination of light-activated PS and ROS generation for the selective destruction of tumors. Iron-based compounds, particularly IONPs, revolutionized the PDT strategy by offering enhanced imaging capabilities and treatment effectiveness. Such properties allow IONPs to act as contrast agents in MRI during PDT procedures, permitting the real-time visualization of locations of tumors.

The wide potential of IONPs in research ranges from imaging and drug delivery to their application as therapeutic agents. Among them, a very important one is the self-assembly of IONPs with MoS_2 nanosheets, shown by Liu *et al.*, for the generation of MoS_2 IO nanocomposites (Grancharova *et al.*, 2024). PEG in this composite enhances its stability and permits the use of cancer treatment enabled by multimodal imaging guidance. These self-assembling systems offer a flexible approach to incorporating imaging and therapeutic capabilities in one system.

While Ling *et al.*, reported the development of tumor pH-sensitive magnetic Nano grenades using pH responsive ligands. It is not only that the said Nano grenades aid in imaging, as they also enhance the localized therapeutic effect of photodynamic therapy because of the selective release of agents in the acidic tumor microenvironment. This strategy went on to underline responsiveness in achieving better treatment outcomes (Amatya *et al.*, 2021).

Despite all the progress in the use of iron and its composites for imaging-guided photodynamic therapy, knowledge gaps remain. Most of the research works are focused on the development and characterization of these materials; only a few studies provide emphasis on long-term compatibility and effects on the body. Future studies should focus on the deep evaluation for the toxicity test of nanoparticles to ensure their safety for clinical

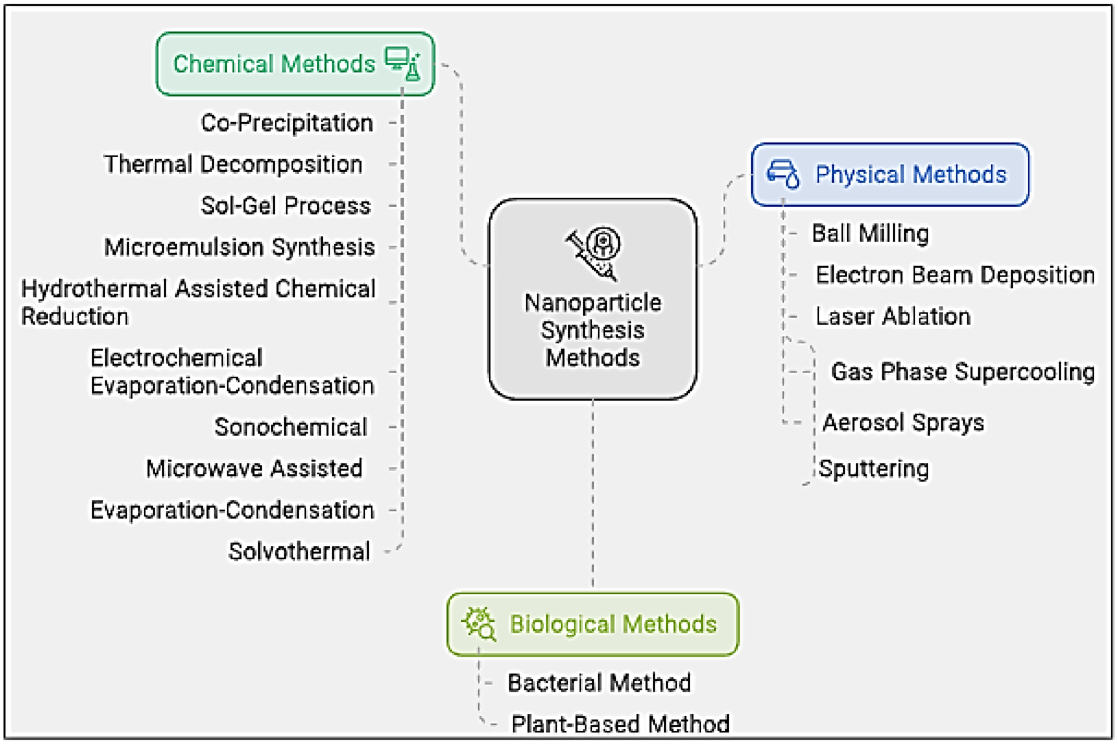

Figure 3: The major types of methods for the synthesis of Iron Oxide Nanoparticles are.

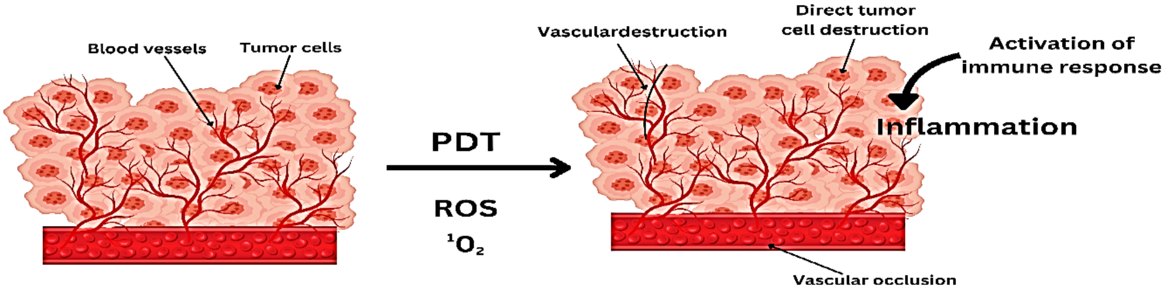

Figure 5: PDT mechanisms for tumor destruction (Meng *et al.*, 2024).

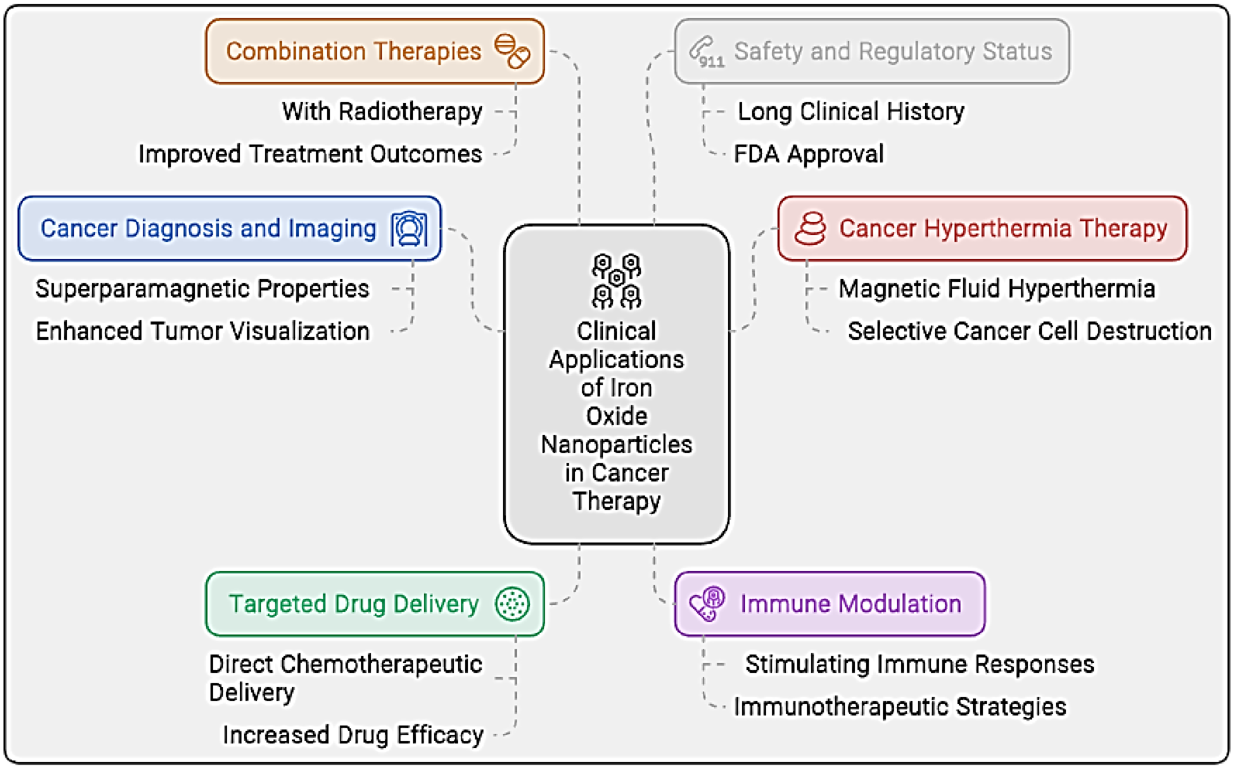

Figure 6: Clinical Applications of Iron Oxide Nanoparticles in Cancer Therapy.

use. Secondly, the interaction of PDT agents with the tumor microenvironment is still not very clear and needs to be well explored. Investigations on the influence of factors like acidity, hypoxia and other environmental conditions on the effectiveness of iron-based composites could culminate in treatment protocols. Finally, there is an emerging need to study the potential of personalized medicine approaches in imaging-guided PDT. Tailoring treatment plans based on the characteristics of the tumors and individual responses may enhance outcomes and minimize side effects.

Clinical Applications and Case Studies

Clinical Applications of Iron Oxide Nanoparticles in Cancer Therapy

The application of iron oxide nanoparticles is one of the most important tools of cancer therapy that exhibits its characteristic features both in diagnostic and therapeutic purposes. Below Figure 6 shows an overview of their clinical applications, particularly in cancer treatment.

Cancer Diagnosis and Imaging

IONPs have become an exciting tool in the diagnosis and imaging of cancer, particularly because of their unique features and functionalization capabilities. Among the major advantages of IONPs is the potential to be functionalized using targeting ligands, such as antibodies or peptides that enhance the specificity of the latter to the chosen cancer cells. This significantly increases the sensitivity of magnetic resonance imaging and allows molecular imaging needed for many cancers, including those in the breast, liver and brain (Dolmans *et al.*, 2003). These dual functions increase treatment efficacy while reducing side effects. Superparamagnetic properties of IONPs contribute to improved MRI contrast, thereby allowing better differentiation of tumors, especially small ones. Finally, magnetic IONPs used for the isolation and enrichment of rare tumor cells from blood samples provide a good avenue in the setting of early cancer detection and on-carrying monitoring. These applications, therefore, are going to underscore the potential that IONPs are to have in advancing cancer diagnostic and treatment strategies (Ling *et al.*, 2014). Very recent research has pointed out the multifunctionality of IONPs, which can be fabricated to generate particles that play dual functions in diagnostic imaging and therapeutic delivery. For instance, Cheng *et al.*, have commented that functionalized IONPs would not only be internalized for magnetic resonance imaging but also for PAT, therefore providing a multimodal platform for imaging that can improve the detection and characterization of tumors. Hence, this potential dual capability may be the indication that IONPs can do much in the simplification of cancer diagnosis by providing integrated imaging information in one platform (Dulińska-Litewka *et al.*, 2019).

Immune modulation therapy

Iron oxide nanoparticles represent one such tool under development to modulate the immune system against cancer. Recent studies reveal a new role for IONPs in interacting with different immune cells and eliciting anti-tumor immune responses, capable of enhancing cancer immunotherapies (Correia *et al*., 2021). This capability to modulate the immune system opens new avenues for combinatorial applications of IONPs with immunotherapy strategies and potentially offers improvements in the effectiveness of cancer treatments. One of the key mechanisms underlying IONP-mediated immunomodulation is related to their ability to reprogram tumor-associated macrophages. IONPs were shown to polarize TAMs into a pro-inflammatory M1 phenotype through the overexpression of genes related to this subtype, including IL-12 and TNF-α. This type of reprogramming is very important for the induction of antitumor immune responses because M1 macrophages are able to trap, phagocytose and kill tumor cells (Allison *et al*., 2013).

The pro-inflammatory properties of IONPs, including skewing macrophages and Dendritic Cells (DCs) toward a pro-inflammatory phenotype, have been harnessed with cancer vaccines (Agostinis *et al*., 2011). The IONPs were used to carry antigens and to boost the internalization, processing and presentation of antigens to the T cell within a microenvironment of inflammation (Allison *et al*., 2013). Preclinical applicability is proved for these vaccines, as IONP-based vaccines could delay tumor progress and lower metastasis in animal models. IONPs have also shown potential in the modulation of different aspects of the tumor microenvironment toward creating a more conducive environment for anti-sufficient immunity, such as hypoxic and immunosuppressive factors. For example, IONPs can deliver drugs, antigens and adjuvants to the tumor site, overcoming obstacles like the extracellular matrix while avoiding their possible degradation and clearance. In this way, a targeted delivery approach allows for a greater effective concentration of such immunomodulatory agents at the desired site for potentially higher therapeutic efficacy (Liu *et al*., 2015).

Hyperthermia Therapy

Another major clinical application of iron oxide nanoparticle is magnetic fluid hyperthermia, in which an alternating magnetic field is applied, directly heating the tumor tissues. Adopting this new approach enhances the sensitivity of tumor cells to conventional cancer therapies like chemotherapy and radiation, increasing their effectiveness (Cortajarena *et al*., 2014). Clinical trials have shown that MFH can improve the survival rate in patients with various cancers; therefore, it can become a very useful treatment. Magnetic hyperthermia is currently the only thermal nanomedicine approved by FDA; thus, it has high clinical value despite issues of acceptance and translating it in everyday clinical use. The technique is based on the injection of superparamagnetic iron-oxide nanoparticles into the tumor itself or nearby; these nanoparticles will, in turn, be exposed to an alternating magnetic field (Farinha *et al*., 2021). The nanoparticles will then heat up due to magnetic hysteresis and relaxation processes in response, leading to increases in the local temperature to levels that could attain therapeutic temperatures of about 42-45°C (Allison *et al*., 2013). Such temperatures can initiate the process of apoptosis, or programmed cell death, in tumor cells while sparing surrounding healthy tissue. However, limitations such as the low potency of the IONP fluid to dissipate enough heat, nanoparticles' insufficient concentration at the site of the tumor and inhomogeneous distribution of these fluids within the tumor may greatly impede treatment effectiveness (Cheng *et al*., 2011). Table 3 shows Case Studies and Clinical Experience.

CONCLUSION

It is expected that the development of iron oxide nanoparticles in cancer therapy will represent a new frontier in the search for active and targeted treatment modalities. This review has underlined IONP multifunctional roles: their unique properties of superparamagnetic, biocompatibility and surface functionalization enhance their application in targeted drug delivery, hyperthermia and imaging. As discussed, IONPs can bring about a dramatic change in the therapeutic outcome of such treatments, making them localized to reduce systemic toxicity. They are known to induce apoptosis in tumoral cells after controlling heating in magnetic hyperthermia and improve tumor visualization for diagnosis and better planning of treatment when used as magnetic resonance imaging contrast agents. While synthesis and characterization of IONPs have significantly evolved over the past years, many challenges remain to be overcome, mainly concerning biocompatibility and scaling-up production methods. Further studies on the subject will need to focus on solving such issues. More specifically, this may be through combination therapy developing IONPs with other treatment modalities and further studies into their immunomodulatory effects. The present inventions of iron oxide nanoparticles show new hope in the therapy of cancer, providing both personalized and more effective treatment strategies. Further research is required in this area to completely explore the potential of IONPs so that better outcomes can be ensured for patients and the quality of life can be enhanced.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

IONPs: Iron Oxide Nanoparticles; **MRI:** Magnetic Resonance Imaging; **FDA:** Food and Drug Administration; **WHO:** World Health Organization; **MNPs:** Magnetic Nanoparticles; **Fe_3O_4 NPs:** Iron (II, III) Oxide Nanoparticles (commonly known as magnetite nanoparticles); **PEG:** Polyethylene Glycol; **PTT:** Photothermal Therapy; **PDT:** Photodynamic Therapy; **TAMs:** Tumor-Associated Macrophages; **DCs:** Dendritic cells.

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