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Nanotechnology and Applications of Magnetic Nanoparticles, A Review

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Abstract

Magnetic nanoparticles (MNPs) are of great interest due to their intriguing properties and their vast applicability, notably in biomedicine. Their synthesis, functionalization, and utilization are addressed herein under review with specific focus being put on drug delivery using iron oxide nanoparticles (IONPs), magnetic resonance imaging (MRI), hyperthermia, and bio-sensing. A systematic literature review approach was used, comparing studies from 2010 to 2023 to include both established knowledge and new trends. Different synthesis routes, such as co-precipitation, sol-gel synthesis, and thermal decomposition, and surface functionalization strategies are presented to increase stability and biocompatibility. Although they hold great promise, toxicity, regulatory, and scalability issues limit clinical translation. Overcoming these shortcomings using cutting-edge biocompatible coatings, enhanced large-scale production methods, and regulated standardization of legislative mechanisms will be essential for the long-term commercialization of MNPs. This review offers a glimpse into current advancements and forthcoming future directions in research needed to realize the complete potential of MNPs in biomedical and industrial applications.

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Introduction

Nanotechnology may be described as the investigation, use, manufacture, and manipulation of forms in a quite tiny size range. It is a multidisciplinary science that encompasses biology, chemistry, physics, engineering, and a multitude of other fields (Govindankutty, 2015). It is the processing of individual atoms, molecules, or compounds on the nanoscale finishing with devices or applications possessing unique properties in size range (1-100 nm) (Alsaffar, 2014). Nanometer is described by taking the size of the Earth and comparing it with the size of a marble (Abiodun Solanke *et al*., 2014). It results in a new material that functions much differently (Alsaffar, 2014) and possesses physical, chemical, and biological characteristics (Zohaib *et al*., 2015) that differ from larger materials. These characteristics are beneficial for many different uses (Nikalje, 2015). It has two principal methods: (1) bottom-up, and (2) top-down (Garimella and Eltorai, 2017). In the bottom-up, individual atoms and molecules are transferred into nanostructures for further applications. While in top-down approaches size reduction of large structures is involved (Alsaffar, 2014; Nikalje, 2015; Badry and Mattar, 2017).

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1. History of Nanotechnology

The initial peak in this field was by Richard Feynman who delivered a lecture in 1959 in which he discussed the potential and effectiveness of nanotechnology. The word "Nanotechnology" was first coined in 1974 by Taniguchi 15 years after (Zohaib *et al*., 2015; Abiodun *et al*., 2014; Garimella and Eltorai, 2017). The golden age of nanotechnology started with Kroto, Smalley, and Curl discovering fullerenes in the 1980s. Nanotechnology went further when carbon nanotubes were created by Iijima. The 21st century has boosted curiosity in the newly developing branch of nanotechnology (Hulla and Hayes, 2015).

2. Applications of Nanotechnology

Nanotechnology has extensive industrial and clinical usage such as medicine. It is possible to utilize it in drug delivery, tissue engineering, and diagnostics. While in chemistry and environment, catalysis and filtration can be employed. In the field of energy, it has the capability of reducing the usage of energy as well as optimizing the efficiency in producing energy (Abiodun *et al*., 2014 , Hulla and Hayes, 2015).

3. Methodology: Systematic Literature Review

This review adopts a systematic approach to finding and studying relevant studies on magnetic nanoparticles (MNPs) for biomedical uses. The process involves the following steps:

3.1. Inclusion and Exclusion Criteria

Selection criteria: The research was selected based on relevance with the synthesis, functionalization, applications, and challenges of MNPs in biomedical applications, i.e., drug delivery, hyperthermia, MRI, and bio-sensing. Peer-reviewed journals from 2010 to 2023 were taken into consideration, thus encompassing foundational and recent work. Only English articles were considered. Exclusion criteria: Not considered were studies on biomedical applications of MNPs that were unrelated, those that predated 2010, and non-peer-reviewed journal articles. Also not included were those that examined only other nanoparticles or purely non-medical applications.

3.2. Search Strategy

A systematic review of the literature was conducted in the following databases: PubMed, Scopus, and Google Scholar. The search keywords were:

- "Magnetic nanoparticles" OR "iron oxide nanoparticles"
- "Biomedical applications" OR "drug delivery" OR "MRI" OR "hyperthermia"
- "Functionalization" OR "surface modification"
- "Toxicity" OR "biocompatibility" OR "regulatory challenges"

For the purpose of capturing recent developments, a secondary search for publications from 2020 to 2023 was conducted, for new trends and developments in nanoparticle functionalization and clinical applications.

3.3. Data Synthesis and Extraction

After the relevant studies were researched, the following information was synthesized:

- **Study purpose**
- **Method** (synthesis, functionalization, or application)
- **Main findings** (efficacy, limitations, or challenges)
- **Pertinence to biomedical applications** (drug delivery, imaging, etc.)

Narrative synthesis was used to determine common themes, main challenges, and literature gaps.

4. Summary of Key Studies

Major studies reviewed are listed in Table 1, their fields of focus, methodology, and key findings.

Table 1: Summary of Key Studies Reviewed

Study	Year	Objective	Methodology	Key Findings
Demirera, B, and Kizilel	2015	Synthesis and preparation of biocompatible MNPs	Co-precipitation, dextran coating	Improved biocompatibility in vivo
Mohammed et al.	2017	MNPs for drug delivery	Targeted drug release using functionalized MNPs	Good, Decent drug targeting efficiency; moderate toxicity
Yao et al.	2020	Analysis of MNPs toxicity	In vitro cell culture, various coatings	Silica-coated MNPs exhibited lower cytotoxicity
Marekova et al.	2020	SPIONs in glioblastoma treatment	Clinical trials	Raised ethical issues and highlighted unknown long-term outcomes
Kus-liśkiewicz, Fickers, & Ben Tahar	2021	Biocompatibility and cytotoxicity of gold nanoparticles	Review of methodologies and regulations	Emphasized regulatory challenges and methods to assess nanoparticle safety
At et al.	2022	Scalability of MNP production	Large-scale synthesis via thermal decomposition	Scalability issues in maintaining particle uniformity
Butler et al.	2023	Review of antimicrobial Nano coatings in medicine	Literature review	Highlighted mechanisms of action, biocompatibility, and safety concerns
Mohammad et al.	2023	Influence of surface coating on ZnO nanoparticles	In vitro studies	Controlled toxicity observed with surface modifications
Rahman	2023	MRI and iron-oxide nanoparticles in personalized medicine	Case studies and reviews	Identified regulatory hurdles and the potential for customized applications

4.1. Magnetic Nanoparticles

Magnetic nanoparticles (MNPs) exhibit certain optical, magnetic, and electrical activity characteristics. Magnetic nanoparticles (MNPs) have been applied in various uses in recent years based on ease of separation and other improved characteristics. MNPs can be synthesized with Cobalt, Nickel, or Iron Oxide (Nguyen *et al.*, 2015). Iron oxides are preferred since they are (1) stable, (2) biocompatible, (3) nontoxic, and (4) possess high relaxation values (Demirera and Kizilel, 2015) while Cobalt is not favorable as a result of its toxicity (Ramimoghadam *et al.*, 2014).

Sixteen phases of iron oxides have been identified to date. These include magnetite, hematite, Maghemite, hydroxides such as Iron (III) hydroxide or Bernalite, oxy-hydroxides Goethite, Lepidocrocite, and others. Maghemite (γ-Fe_2O_3), Magnetite (Fe_3O_4), and Hematite (α-Fe_2O_3) are the most common (Hasany *et al.*, 2013). Distinctive properties of these compounds are (1) trivalent state, (2) distinct colors, and (3) low solubility (Ramimoghadam *et al.*, 2014; Shariful *et al.*, 2012, Mohapatra and Anand, 2011). Table 2 below represents several types of iron oxides with a brief description.

Table 2: several types of iron oxides with a brief description

Type	Description	Ref
Iron ferrite or magnetite (Fe_3O_4)	Ferromagnetic is the most common type of iron oxide. It is black in color, crystal structure type is octahedral with a surface area of 4-100 m2g, and it is a catalyst.	(Greta *et al.*, 2016)
Hematite (α Fe_2O_3)	With hexagonal crystal structure a = 5.034 À, c=13.752 À lattice parameter, in their system two Fe are coordinated to each O via a covalent bond, with surface area 10-90 m^2g^{-1}, commonly used for magnetic data storage.	(Ramimoghadam *et al.*, 2014; Zhiyao *et al.*, 2018)
Goethite **(**α-FeO (OH))	Having an orthogonal crystal structure with a= 9.95 À b=3.01 À c= 4.62 À and with surface area 8-200 m^2g^{-1}, usually used in MRI.	(Ramimoghadam *et al.*, 2014)
Ferrihydrite	It does not have any fixed chemical formula. It has one chemical formula Fe5 $(O_4H_3)_3$, surface area 100-700 m^2g^{-1}, which is usually applied in lubrication.	(Marc *et al.*, 2010; Jens *et al*., 2013)
Iron (II) oxide, wüstite (FeO)	Stable at high temperature and low pressure, an uncommon type of iron oxide.	(Hoang *et al.*, 2010; Mohammed *et al.*, 2011)
Beta phase, (β-Fe_2O_3)	One of the cubic face-centered crystal structure iron oxy-hydroxides changes to the alpha phase at temperatures greater than 500 °C.	(Ramimoghadam *et al.*, 2014**;** Mohammed *et al.*l, 2011)
Gamma phase, maghemite (γ-Fe_2O_3)	With orthorhombic crystal structure, normally used in pigment.	(Ehsan *et al.*i, 2015; Gnanaprakash *et al.*, 2010)

4.2. Fabrication of Iron Oxide MNPs

Magnetic nanoparticles can be fabricated by three methods (i) Chemical (bottom-up) synthesis methods including (1) flow injection method, (2) polyol, (3) sol-gel reaction, (4) aerosol/vapor method, (5) Thermal decomposition, (6) co-precipitation, and many others (Ramimoghadam, Bagheri and Hamid, 2014) (Kammari, Das and Das, 2017, E. Tombacz , R. Turcu, V. Socoliuc, 2015, Acharya, Mitra and Cholkar, 2017), (ii) Physical (top-down) methods that entail: (1) reduction of the size of large particles to the nanometer scale and dispersion in an aqueous solution through the use of the classical colloidal routes and (b) gas-phase deposition, and (c) electron beam lithography (Sun *et al*.., 2014, Seyed *et al*, 2019) or (iii) Microbial processes where (MNPs) are synthesized in a bio-mineralization process (Leena *et al*, 2017). This section will briefly outline some of these fabrication routes.

4.2.1. Sol-gel method

Sol-gel processing involves the formation of an oxide network through the poly-condensation reaction of a precursor molecule in a liquid. The reactions include hydroxylation and condensation of the precursor in solution to yield a 3D iron oxide network called a wet gel (Ramimoghadam, Bagheri and Hamid, 2014)(Sophie Laurent et al., 2010). There are various parameters through which the structure and properties of the gel can be modified, and these include (1) temperature, (2) solvent nature, (3) pH, (4) concentration and nature of the precursor salt used, and (5) agitation (Sophie *et al.*, 2010).

It can be considered the most suitable process for iron oxide nanoparticle synthesis since it is blessed with several advantages including (1) regulation of the particle size, (2) monodispersing, (3) high regulation of the homogeneity and microstructure of the reaction products, (5) capability of synthesizing pure amorphous phases (Hasany,and Abdurahman, 2013; Sophie *et al*, 2010).

4.2.2. Polyol method

The polyol process is an easy chemical route for the synthesis of well-defined shapes and controlled size MNPs (Laurent *et al*., 2010). The other benefit of this method is that the solvent employed as polyol (i.e., polyethylene glycol) possesses quite remarkable properties, including (1) comparatively high boiling points, (2) compatibility with organic substances, and also (3) high dielectric constant. In this method, a suspension of a precursor compound and polyol liquid is prepared, stirred, and heated until reaching its boiling point (Indira and Lakshmi, 2010; Sophie *et al.,* 2010).

This is quicker and has several advantages compared to traditional aqueous methods. They are (1) pre-synthesized MNPs are easily coated by a hydrophilic polyol ligand (Sophie and Bridot, 2010), i.e., no need for additional coating step, (2) Secondly high temperature reaction results in magnetization of the larger particles, and (3) finally ability to produce iron oxide Nano-particles of novel morphologies like hollow Nano-spheres, dense Nano-spheres and flower-like Nano-spheres (Cheng and Gu, 2011).

4.2.3. Flow injection method

The method is used to synthesize MNPs with small and equal particle size. The shape of the particles can also be altered. Flow injection synthesis uses a continuous or discrete reagent mixture within the capillary reactor, and the flow should be continuous (Ramimoghadam *et al.*, 2014). The method contains high homogeneity of mixing, high reproducibility, and positive external control of the process (Sophie et al., 2010).

4.2.4. Aerosol-vapor method

One of the methods is similar to spray pyrolysis or spray drying used in high-product yield processes. In this, the iron oxide solution is coated over the reactor and then sprayed with an organic solvent. The aerosol solute is condensed whereas the organic solvent is evaporated. The particle size of the resulting particles will be based on the initial droplet size used in the process (Ramimoghadam *et al.*, 2014; Hasany *et al.*, 2013; Indira and Lakshmi, 2010).

4.2.5. Co-precipitation method

Over the last decades, the most appropriate way of accessing MNPs was the Co-precipitation method because of its simplicity and high production rate (Demirera and Kizilel, 2015; Susana *et al.*, 2015). The process is a simple chemical reaction of ferric and ferrous ions in the molar ratio (1:2) respectively, in highly alkaline solution at room temperature or high temperature, to achieve a good yield of magnetite, pH of solution should be kept between 9 and 14 (Demirera and Kizilel, 2015; Ramimoghadam *et al.*, 2014; Carvalho *et al.*, 2013). The chemical reaction involved may be formulated as given in the following equation:

$$Fe^{+2}\,(aq) + 2Fe^{+3}\,(aq) + 8OH^{-}\,(aq) \longrightarrow Fe_3O_4\,(s) + 4H_2O\,(l) \quad \text{--------- Eq. (1)}$$

The mechanism of the Co-precipitation process involves two major steps: the first involves short initial nucleation in which reactant concentrations reach critical supersaturation. The second mechanism of growth occurs step by step through diffusion of the solutes onto the crystal surface for its growth gradually.

It is important to point out that Fe_3O_4 MNPs are intrinsically unstable under ambient conditions, with a high tendency to become oxidized, forming Fe_2O_3, or to dissolve under acidic conditions (Shen *et al.*, 2011). Therefore, the synthesis of ferric MNPs must be carried out in an anaerobic environment (Demirera and Kizilel, 2015). But its sole limitation is that size and size distribution can be controlled very minimally (Hans-Christian *et al.*, 2015). Size and shape of resultant MNPs have also been found to be controlled by modifying reaction conditions like (1) temperature, (2) pH, (3) ionic strength, (4) stoichiometry, and (5) nature of reacted salts (Dimitri *et al.*, 2015; Sun *et al.*, 2014).

4.2.6. Thermal decomposition

Thermal decomposition may be considered an efficient pathway for the synthesis of high-quality monodispersed MNPs. Thermal decomposition of organometallic precursors in a solvent organic system with the aid of a surfactant is the method. The most commonly employed surfactants are oleylamine, oleic acid, hexadecylamine, fatty acids, and steric acid (Demirera and Kizilel, 2015). The size and morphology of MNPs developed can be tailored by varying the conditions of synthesis involving (1) concentration of reactants, (2) solvent characteristics, (3) reaction temperature, (4) precursor nature, and (5) synthesis duration. The drawback of this method of synthesis is that it creates hydrophobic MNPs that dissolve in nonpolar solvents alone (Demirera and Kizilel, 2015).

4.2.7. Sonolysis

Magnetic nanoparticles (MNPs) of iron oxide may also be synthesized by the sonolysis decomposition of an organometallic precursor. It is a method where polymers, organic capping agents, or structural hosts are used to control nanoparticle growth. The general process of iron oxide synthesis using the sonolysis technique is shown in (Figure 1) below (Hasany *et al.*, 2013).

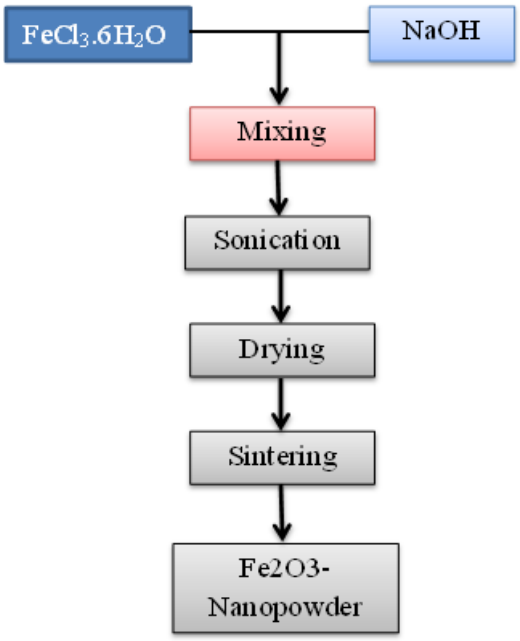

Fig. 1. Overall procedures of iron oxide synthesis by Sonolysis process

5. Coating of Iron Oxide MNPs

Coating Materials: Nanoparticles are generally coated with organic or inorganic materials to ensure stability, avoid aggregation, and ensure bioavailability. Coating materials such as dextran, silica, chitosan, and gold have been commonly used to protect the surface, decrease toxicity, and allow functionalization in applications concerning targeted drug delivery, among others. This chapter consolidates key information on such materials to avoid redundancy and improve readability.

5.1. Coating Materials Overview

Coating is really important regarding the stability, storage, and functional use of IONPs. Both polymeric and non-polymeric coating materials' properties, advantages, and limitations have been highlighted here in this section.(Demirera and Kizilel, 2015).

5.2. Polymeric Coating Materials

5.2.1 Dextran

Among clinically approved polymers, dextran is widely employed to prevent nanoparticle aggregation. Dextran can be utilized in MRI-related and drug delivery-targeting applications due to its biocompatibility. However, dextran is non-biodegradable inside the human

body and weak bonding with the IONP surface may further limit its applications. Generally, dextran-coated IONPs are prepared through the co-precipitation method, in which dextran is mixed with iron salts and precipitated with ammonia. (Demirera and Kizilel, 2015).

5.2.2 Chitosan

Biodegradable and biocompatible chitosan possesses an antimicrobial effect. It decomposes into nontoxic amino sugars that enable the usage of this material for both drug delivery and tissue engineering applications. Coated IONPs by chitosan exhibit superparamagnetic nature. Usually, these chitosan coatings were prepared via a co-precipitation technique. Its advantage includes limitations concerning the limited solubility of chitosan (Demirera and Kizilel, 2015).

5.3. Coating with Non-Polymeric Materials

5.3.1 Silica

Silica is one of the most important inorganic coating materials for IONPs because of its possible prevention of aggregation, enhancement of chemical stability, and biocompatibility. The hydrophilic structure can be easily bound with biological ligand; thus, it can be useful in biosensing and drug delivery. However, the main challenge still exists to achieve appropriate thickness in the silica shell since the uniform coating may induce inhomogeneous heating during hyperthermia (Demirera and Kizilel, 2015).

5.3.2 Gold

The gold coating prevents oxidation of the iron oxide core and provides very high colloidal stability. Excellent biocompatibility, together with optical properties and functionalization capability, makes gold a very promising choice for IONPs surface modification. Gold-coated IONPs are stable at neutral and acidic pH values and find applications in imaging and drug delivery (Table 3). However, the high cost of gold remains a limitation.(Demirera and Kizilel, 2015).

Table 3: Comparison of MNP Coating Materials

Coating Material	Properties	Applications	Advantages	Limitations
Dextran	Biocompatible, prevents aggregation	MRI, drug delivery	Low toxicity, high stability	Weak bonding with MNP surface
Chitosan	Biodegradable, antimicrobial	Drug delivery, tissue engineering	High biocompatibility, non-toxic degradation	Limited solubility
Silica	Hydrophilic, functionalizable	Bio-sensing, drug delivery	High chemical stability, bio-functionalization	Uneven shell thickness
Gold	Stable, biocompatible	Drug delivery, imaging	Protects from oxidation, excellent biocompatibility	High cost

6. Applications

6.1. Industrial applications

Iron oxide magnetic nanoparticles are utilized in several applications due to their enhanced properties. Among these are (1) data storage and magnetic recording material, (2) catalysis, (3) magnetic ferrofluids, (4) magnetic inks (Shariful Islam et al., 2012), (5) magneto-

optical devices, (6) gas sensors, (7) wastewater purification (Ramimoghadam *et al.*, 2014), (8) coloring and coating material (Mohapatra and Anand, 2011; Ehsan et al., 2015), (9) giant magnetoresistance (GMR) sensors (Bashar and Ihab, 2013) and others.

6.2. Biomedical applications

Biomedical applications of magnetic nanoparticles are either in vitro (within the body) or in vivo (outside the body). In vitro application is predominant in (1) diagnostic sorting (2) magneto-relaxometry, and picking. Whereas, in vivo application is further categorized into (1) diagnostic usage (magnetic resonance imaging MRI) and (2) therapy usage (Akbarzadeh *et al.*, 2012; Mohapatra and Anand, 2011, Krishnendu *et al.*, 2014). Magnetic Nanoparticles have great potential for many biomedical applications because they have a large surface area (Wei *et al.*, 2015) that controls the magnetic characteristics and causes (1) superparamagnetic behavior and (2) quantum tunneling of magnetization (Kayal and Ramanujan, 2010).

Potential of biomedical application of iron oxide magnetic nanoparticles results from manipulation by an external gradient magnetic field of iron oxide phases (Pedro Tartaj et al., 2011). One of the primary concerns for biomedical applications is (1) biocompatibility and (2) iron oxide nanoparticle (IONP) toxicity. They are primarily controlled by the magnetically responsive component composition, and the final composite particle size, including the core and the coating (shell). For effective application in biomedicine, iron oxide composite nanoparticles should possess high magnetization so that their motion would be externally controlled within the body through an external magnetic field. This can accomplish precise targeting and immobilization at diseased tissues (Wei *et al.*, 2015).

6.2.1 In vivo applications

IONPs have a number of in vivo uses, which can be categorized into three general groups: (1) magnetic resonance imaging (MRI) with the assistance of magnetic contrast agents, (2) drug delivery with the assistance of magnetic vectors guided to a target site using a magnetic field gradient and, (3) hyperthermia where the magnetic particles get heated when a high-frequency magnetic field is utilized (Wei *et al.*, 2015). Size and surface properties are two of major significance in IONPs' in vivo applications (Wei et al., 2015). In-vivo bio-distribution is greatly influenced by the size of the IONPs. IONPs sized 10-40 nm are capable of penetrating through capillary walls and are commonly phagocytosed by macrophages that travel to the lymph nodes and bone marrow. Hence, IONPs of such sizes are important for long-term circulation in blood (Akbarzadeh *et al.*, 2012)

6.2.1.1 Therapeutic applications

Hyperthermia by magnetic nanoparticles produces heat due to various forms of energy losses (Šafařík, and Šafaříková, 2011). The magnetization direction between antiparallel and parallel directions of iron oxide is randomly switched, making it possible to transfer magnetic energy as heat to the particles. This property can be utilized to increase the temperature of cancerous tissues, more than that of normal tissues, between 42°C and 46°C. Controlled heat induces hyperthermia, a treatment process that selectively destroys pathological cells without causing much harm to the surrounding normal tissue (Vinardell and Mitjans, 2015, Bucak, and Sezer, 2012, Wei *et al.*, 2015). One of the primary approaches proposed to be utilized in effective cancer treatment is the warming of cancer cells to treat hyperthermia through cell irradiation proven by using magnetic nanoparticles (Akbarzadeh *et al.*, 2012). Hyperthermia itself is less harmful by reducing damage to normal tissues (Vinardell and Mitjans, 2015), unlike chemotherapy and radiotherapy (Šafařík and Šafaříková, 2011). There are certain difficulties associated while keeping the usual tissues cold and warming the tumor section to a temperature high enough. For most conditions, local hyperthermia is used with novel techniques in cancer treatment. Radio-frequency waves, microwaves, and ultrasounds are techniques designed for the therapy of cancers by localized heating (Wei *et al.* 2015).

When the magnetic field is eliminated, IONP magnetization disappears. This is a highly important fact because magnetization and nanoparticle aggregation are induced, known as a phenomenon which is highly dangerous to the patient after the treatment, but during the treatment, it is tolerable, especially large aggregates that may block the clearance of nanoparticles and create health risks. In in vivo hyperthermia treatment, to prevent the formation of ferromagnetic nanoparticles, iron oxide nanoparticle size needs to be strictly less than 30–40 nm. The size threshold will assure their best magnetic characteristic to render them most useful for biomedical applications with fewer risks of aggregation and unwanted magnetic interaction. In applications of magnetic hyperthermia, a larger particle size may result in larger values for saturation magnetization and superior performance but only if the particle is below the previously mentioned

critical size when magnetic nanoparticles are ferromagnetic, an undesirable magnetic characteristic for biomedical applications that can lead to particle agglomeration (Vinardell and Mitjans, 2015).

6.2.1.2 Drug delivery

Drug targeting is a complex drug delivery technology that utilizes the magnetic nature of specific nanoparticles. Due to its high surface-to-volume ratio, drug molecules can be encapsulated and stored within these nanoparticles efficiently. Furthermore, with their own characteristic magnetic properties, they can be made vulnerable to an externally introduced magnetic force. With controlled magnetic guidance hence utilized, the magnetic nanoparticles may be guided efficiently to the target site, enhancing the drug delivery efficiency and target specificity. The in vivo clustering of Magnetic nanoparticles may be avoided with regard to the iron oxide particles do not exhibit any magnetization after the external magnetic field has been removed. This advantage has made iron oxide nanoparticles an option for in vivo usage (Leena Mohammed *et al.*, 2017). Over the past few years, there has been increased potential for drug targeting using iron oxide magnetic nanoparticles. The externally applied magnetic field has a crucial role to play in steering the deposition of the magnetic nanoparticles to the point of interest. With precise field direction, careful localization is maintained and efficacy of drug delivery as well as of therapy is maximized. MNPs are deposited at the local site and the drug is released and turns locally (magnetic drug targeting). In this technique, the magnetic field gradient guides the drug-delivering nanoparticles to the target location for precise drug delivery. As a result, the therapeutic dose is delivered efficiently and minimizes systemic exposure, therefore decreasing potential side effects (Morteza *et al*., 2011) with increased localized drug levels (Nabil and Zunino, 2016). Sustained release is obtained by high local drug concentrations in a target site (Šafařík, and Šafaříková, 2011; Pedro Tartaj *et al.*, 2011). To functionalize these particles even further, various bioactive molecules are conjugated. Surfaces are functionalized with organic polymers and inorganic metals or oxides, making them biocompatible and suitable (Akbarzadeh *et al.*, 2012).

Once the MNPs are internalized within the cells, the coating will inevitably break down and leave the exposed bare particles in jeopardy of interacting with other cellular elements and organelles thereby, possibly affecting the general safety of the cells. Stiff coatings are likely to delay this failure (Morteza *et al.*, 2011). Several parameters are considered in the magnetic drug delivery systems like (1) particle size and magnetic nature, (2) capacity of drug loading, and (3) availability of target tissue (Agnieszka *et al.*, 2012).

Drugs can be bound onto magnetic nanoparticles via covalent binding, electrostatic attraction, adsorption, or encapsulation process. Targeted drug delivery by magnetic targeted drug delivery systems (MTDDS) is possible through passive or active mechanisms depending on the surface chemistry and size of the nanoparticles. Passive targeting is a consequence of the EPR effect in cancer tissues, where leaky vasculature allows nanoparticles to be retained at the tumor site without the need for specific targeting ligands. While, active strategy depends on the targeting of nanoparticles to the site by attraction produced by recognition ligands attached to MNP's surface and by control over an external magnetic field (Agnieszka *et al., 2012).*

Drug targeting method includes:

1- Drug immobilization in the Nanoparticles.

2- The drug/carrier component injection into the subject.

3- Steering of the component and focusing the same at aimed sites by extraneous magnetic fields. The medication is released when the component gets focused at the target in vivo from the magnetic carrier (Coated magnetic particles) (Kayal and Ramanujan, 2010). Cancer cells facilitate an increased drug uptake at target sites (Joan and Elvira, 2015)

6.2.1.3 Diagnostic applications

Magnetic resonance imaging (MRI):

Applications of magnetic nanoparticles include their use as contrast agents in magnetic resonance imaging (MRI). Contrast agents are magnetic nanoparticles of different sizes, including ultra-small particles measuring 10-40 nm in diameter, small particles of a diameter of 60-150 nm, and big particles (oral) particles of a diameter measuring 300 nm-3.5 mm (Šafařík, and Šafaříková, 2011). Magneto-

pharmaceuticals represent a new group of drugs that can be applied to enhance the MRI method of clinical case diagnosis. These drugs are produced mostly for the sake of enhancing the diagnostic imaging property along with the simultaneous treatment of the patients. Magneto-pharmaceuticals target a definite organ function or blood flow and even enhance the contrast between disease and normal tissues in order to enable identification and assessment of the sites of diseases. This twofold method integrates therapeutic function with increased diagnostic potential, maximizing the precision and efficacy of clinical imaging and therapy planning (Akbarzadeh *et al.*, 2012).

6.2.2 In vitro applications

6.2.2.1 Bio-separation

Magnetic separation has attracted substantial interest in biomedical studies of late because of its distinguishing features of low toxicity, high surface/volume ratios, and biocompatibility (Bashar and Ihab, 2013). The rapidly growing field of biotechnology has an inherent need for easy, rapid, and high-capacity methods of biomolecule extraction from suspended solutions. Isolation and purification of such biomolecules like DNAs, proteins, antigens antibodies, and nucleic acids highly purified forms is a quite challenging process (Fatima and Kim, 2017). Magnetic nanoparticles employed for functional purposes can be chosen to bind targets and isolated without any difficulty from the solution by applying magnetism. Magnetic separation technology is composed of two main parts: 1) magnetic nanoparticles and 2) the external magnetic field (Banert and Peuker, 2007).

Bio-separation uses are emerging as one of the most promising uses of MNPs. And turned out to be beneficial in nearly every division of biosciences. Magnetic bio-separation follows a very simple principle as compared to other conventional techniques Figure 2 below is a schematic representation of magnetic nanoparticle bio-separation comprising the following steps; (1) MNP synthesis, (2) MNP modification, (3) Adsorption (4) Separation (5) washing (6) Elution and (7) Recycling (Fatima and Kim, 2017).

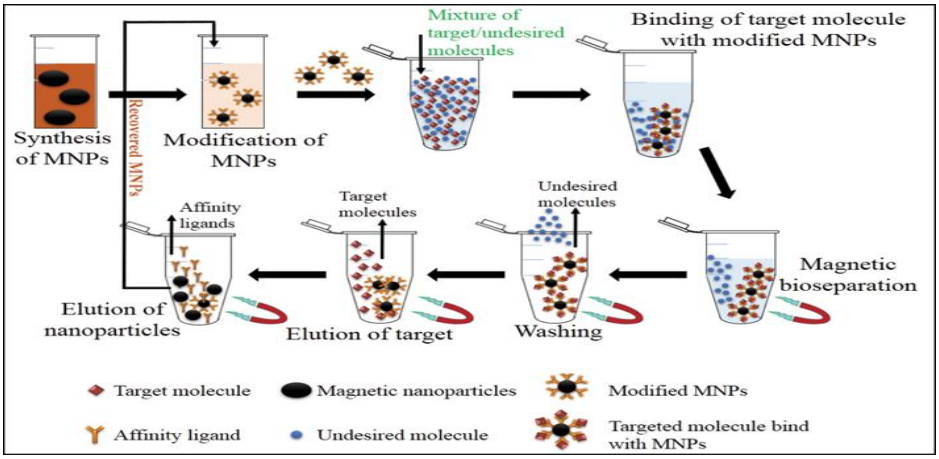

Fig. 2: Schematic illustration of magnetic nanoparticle bio-separation

Magnetic nanoparticles and micro-particles are very important for various technology, medicine, and bio-separation applications. Here, we briefly mention bio-separation applications.

Viral RNA extraction

Albertoni et al. (2011) studied the use of MNP technology for viral RNA extraction from serum in blood bank screening. They found that the manual magnetic NPs-based extraction combined with reverse transcriptase-polymerase chain reaction (RT-PCR) detection can be routinely used for screening blood donations for hepatitis C virus (HCV) and human immunodeficiency virus (HIV) to further enhance the safety of blood products.

Isolating DNA from cells

Chi-Hsien Liu and coworkers (2010) studied the use of MNPs for DNA isolation from cells (Figure 3). They found that magnetic nanoparticles can effectively adsorb plasmid DNA.

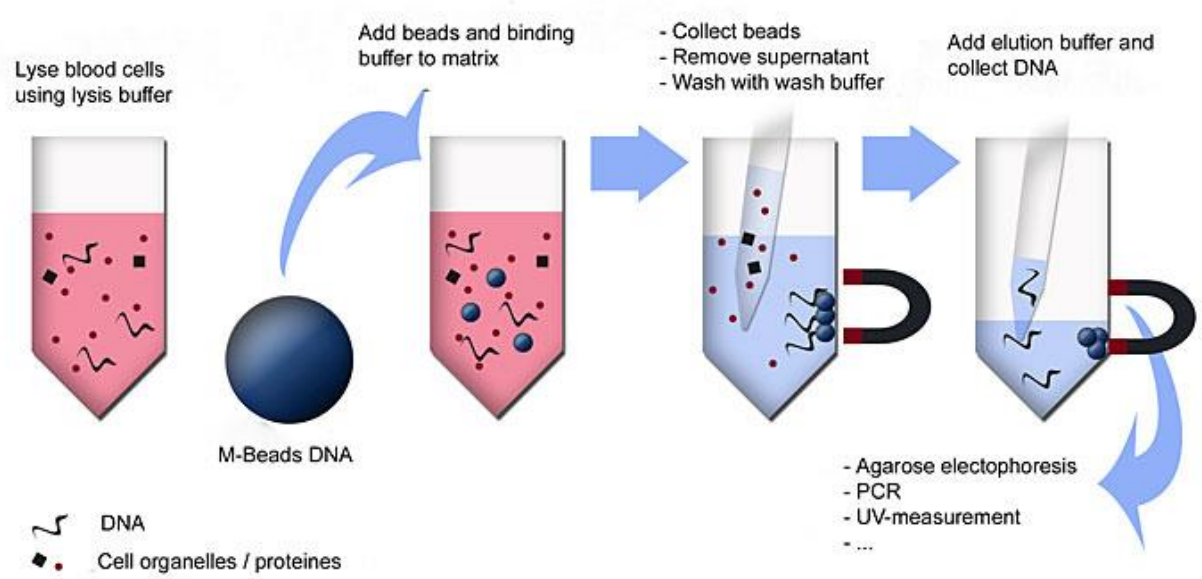

Fig. 3: A schematic representation of DNA extraction from blood using MNPs (Chi -Hsien Liu and Hsien, 2010)

Protein separation

The selective isolation of target molecules from complex mixtures by magnetic nanoparticles (MNPs) has made these nanoparticles effective adsorbents for protein separation from various media or as support carriers for enzyme immobilization. Mostly, cheap and handy proteins such as bovine serum albumin (BSA), yeast alcohol dehydrogenase (YADH), lysozyme (LYZ), and human serum albumin (HAS) are used to investigate and find out conditions of adsorption, as well as to estimate immobilized enzymes' maximum capacities and activities. The feature enhances their potential towards diverse applications in the biotechnology and biomedicine fields (Hickstein, 2009). Figure 4 below presents a diagrammatic outline of a protein purification protocol from cell lysate using MNPs.

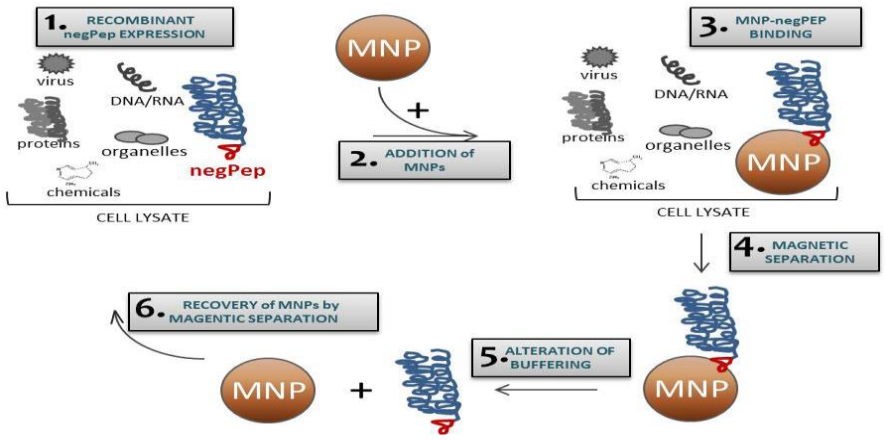

Fig. 4: Schematic diagram of a protein purification process from cell lysate using magnetic NPs (Hickstein, 2009).

E-coli detection in water

Golberg et al. (2014) carried out a study on the identification of live E. coli in contaminated water using MNPs coated with the targeted antibodies effectively to trap the E.coli from the contaminated water (Figure 5) (AlexAlexander *et al.*, 2014)

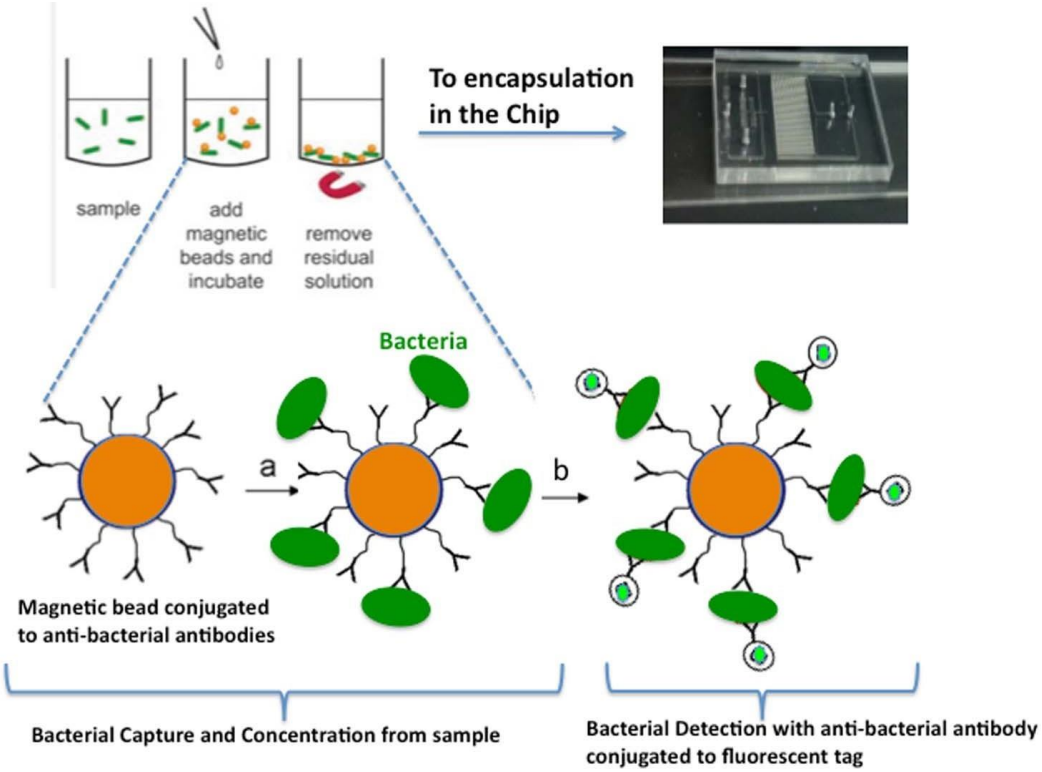

Fig. 5: Uptake of E. coli by MNPs from concentrated water samples (AlexAlexander Golberg et al, 2014).

7. Challenges and Restrictions of MNPs in Biomedical Applications

7.1. Toxicity of MNPs

Even though magnetic nanoparticles (MNPs) or, in a more precise term, iron oxide nanoparticles (IONPs) have been highly promising in a variety of biomedical applications such as magnetic resonance imaging (MRI), drug delivery, and hyperthermia therapy, their toxicity remains an issue of much concern. The primary toxic effects are based on the nanoparticle size, charge, and type of coating utilized (James et al., 2023; Faruq et al., 2023).

- In vivo toxicity: Studies have proven that nanoparticles less than 10 nm are more toxic due to the fact that they can penetrate deeper into cells and tissue, where they can induce oxidative stress or inflammation. Iron oxide nanoparticles are commonly biocompatible, yet their surface coating used for stabilization (e.g., dextran, chitosan, silica) can degrade or metabolize, wherein there exists the possibility of releasing bare particles to the biological environment and creating toxicity.
- Environmental impact: Environmental nanoparticle contamination, particularly of water sources, is of concern to the long-term ecological effects. Some research claims that nanoparticle toxicity is dangerous to aquatic organisms due to being tiny and extremely reactive.

In response to such poisonous effects, researchers are considering novel coatings, surface modifications, and biodegradable substances that decrease unwanted biological interactions (Kus-liśkiewicz *et al*., 2021). Despite MNPs having been applied to numerous purposes, facts up to this moment concerning their toxicity are minimal, and a number of studies have presented questionable findings on the

same.(Vanessa *et al.*, 2016; Colognato *et al.*, 2012; Kunzmann, *et al.* 2011). In view of the future and potential biomedical applications of iron oxide MNPs that involve direct organ and tissue contact to elicit their effect, the majority of the studies accounted for that their potential toxicity is pertinent particularly (Vanessa *et al.*, 2016). The nature of the coating material used to functionalize the MNP into the intended application contributes heavily to the MNPs' toxicity profile (Yan *et al*., 2013; Agemy *et al.*, 2011; Jenkins *et al.* 2011). For example, no harmful effects on cells were demonstrated in (1) polyethyleneimine (PEI) coated Iron Oxide MNPs treated primary rat cerebellar cortex astrocytes (Cuyper, 2010; Yiu *et al*., 2012), (2) murine bone marrow cells exposed to uncoated or citrate-corrected Iron Oxide MNPs (Sae-Yeol et al., 2015), (3) in human T lymphocytes treated with polyacrylic acid (PAA) coated or bare Iron Oxide MNPs (Chung-Yi *et al*., 2011; Paolo *et al*., 2012).

In short, Iron Oxide MNPs seem to be nontoxic initially for biomedical applications (Mohanan, 2016; Susana *et al.*, 2015; Xinfeng *et al.*, 2019) since their cytotoxicity (wherever present) will be very small and confined and can be accounted for based on their parameters like size and surface coatings (Carla *et al.*, 2016; Ying and Hwang, 2010; Christopher *et al.*, 2012; Qiyi Feng *et al.* , 2018; Aitziber *et al.*, 2014).

7.2. Regulatory Issues

The clearance mechanism of nanoparticles in biomedical applications is another main challenge. Because nanoparticles lie at the nexus of biology, chemistry, and engineering, it makes the regulatory framework both complex and in a state of constant flux.

- **Lack of standardized guidelines:** The governing authorities such as the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) have yet to formulate inclusive, standardized guidelines regarding the clinical use of MNPs. Although certain nanoparticles, for example, some MRI contrast agents have been approved, new nanomaterials' approval remains questionable, especially for therapy and drug delivery systems. For example, iron oxide nanoparticles have already been used in certain FDA-approved MRI contrast agents, and therefore there is an evident regulatory pathway for such use. Yet, regarding MNPs for drug delivery or combined therapeutic applications, such as magnetic hyperthermia against cancer, a complete lack of clarity on standards has delayed approvals and discouraged investment in clinical trials (Rahman, 2023).
- **Case Study:** The approval of Ferumoxytol, an iron-based nanoparticle used for the treatment of anemia, is illustrative of these challenges. Although approved for restricted use due to safety concerns like severe allergic reactions, the case of Ferumoxytol underlines the challenge in the balance between therapeutic benefit and strict safety requirements (Kowalczyk *et al.*, 2011).
- **Safety and efficacy testing:** One of the greatest challenges is the prolonged safety and efficacy testing before clinical approval. The regulatory authorities demand strict toxicity tests, biocompatibility testing, and long-term studies to determine whether magnetic nanoparticles (MNPs) are safe for application in human health. This can be costly and time-consuming, particularly for freshly developed nanoparticle formulations. For example, the case of nanoparticles based on dendrimers for drug delivery is a good example. Even though the nanoparticles can lend themselves to lessened toxicity and better drug targeting, the apprehension that they might cross the blood-brain barrier and be accumulated in non-target tissues elongates their preclinical and clinical evaluation (Abedi-Gaballu *et al*., 2016).
- **Case Study:** One of the earliest nanotechnology-based drugs, PEGylated liposomal doxorubicin (Doxil), was required to provide extensive proof for reduced cardiotoxicity in comparison to free doxorubicin. Ultimately approved, but at a pace substantially slower than typical for small-molecule drugs (Yao *et al.*, 2020).
- **Ethical considerations:** Often, for novel experimental therapies including cancer treatment and targeted drug delivery, ethical considerations of MNPs must often go through processes of careful review against potential risks such as long-term accumulation, unexpected immune response, and off-target effects weighted against the presumed benefits (Yao *et al.*, 2020; Dahua *et al*., 2023).
- **Example:** "Ethical issues involve the application of MNPs in pediatric oncology. Due to the developing systems in children, they are more susceptible to the unknown side effects." Most ethical debate revolves around the issue of adopting innovative treatments over established protocols (Shicheng *et al*., 2021).
- **Case Study:** Superparamagnetic Iron Oxide Nanoparticles (SPIONs) used in clinical trials for glioblastoma treatment faced lots of ethical issues, due to the invasive nature of the procedures like intracranial injection involved and also because the long-term outcomes are not known (Marekova *et al*., 2020).

7.3. Scalability and Commercialization

Large-scale production of MNPs is extremely difficult, particularly in an economical, uniform, and reproducible manner. While MNPs are readily synthesized on a small scale, their large-scale production for industrial or commercial use is more problematic due to the following factors:

- Uniformity of particle size: Uniform particle shape and size for large batches are critical for the reliable performance of MNPs in medical applications. Size modifications may affect drug-delivery properties, bio-distribution, or magnetism of nanoparticles and thus cause reduced efficacy or enhanced toxicity. Techniques like thermal decomposition, co-precipitation, and microfluidic synthesis have been developed to gain better control over particle homogeneity in bulk synthesis.
- Surface functionalization: Maintenance of the MNPs' surface continuously functionalized is also important for their application in targeted drug delivery or imaging. Scaling up the modification or coating of nanoparticles and maintaining them stable and bioactive remains a genuine challenge. The reproducibility of dextran, silica, or gold coatings, for instance, must be regulated strictly to maintain the desired biocompatibility and magnetic properties.
- Cost and resource-intensive processes: Scaleable synthesis pathways such as sonolysis or thermal decomposition are costly as they need high-priced equipment and chemicals to provide magnetic nanoparticles (MNPs) on the industrial scale. Furthermore, environmental parameters (e.g., inert environment to suppress oxidation) also cause problems in scaling up. It is also hard to upscale microbial or biological processes of synthesis due to extended process time and poor yields.

7.4. Future Directions

To overcome such challenges, more research needs to be done to establish scalable and inexpensive ways of producing MNPs. Advances in Nano-manufacturing, as well as stricter regulatory regimes, will be central to taking MNPs from the laboratory to the clinic and the marketplace. Furthermore, continued advances in biocompatible coatings and biodegradable materials will reduce issues of toxicity and enhance the safety profile of MNPs for broader biomedical applications.

Conclusions

Among MNPs, IONPs have emerged as highly promising for different biomedical applications involving drug delivery, imaging, hyperthermia, and bio-sensing. The current review summarized recent research on the topic, emphasizing progress and discussing challenges preventing the clinical translation of MNPs.Toxicity and biocompatibility are key issues that require less toxic coatings and further research into long-term health and environmental consequences. Besides these, regulatory barriers pose problems, meaning there is a need to standardize guidelines and collaborate between researchers and regulatory agencies for safe and effective applications. Scalability remains an obstacle, while most of the current synthesis techniques have failed to produce uniform particles commercially. Investigation into scalable production techniques is critical to reduce the costs and extend the clinical usage of this class of materials. In conclusion, the barriers regarding toxicity, regulations, and scalability are very important and have to be resolved to allow MNPs to fully express their role in biomedical technology development.

References

Abedi-Gaballu F, Dehghan G, Ghaffari M, Yekta R, Abbaspour-Ravasjani S, Baradaran B, Dolatabadi JEN, H.M. ''PAMAM dendrimers as efficient drug and gene delivery nanosystems for cancer therapy'', *Physiology & behavior* , 176(1), 139–148, (2016)

Abiodun Solanke, I., Ajayi, D. and Arigbede, A. ''Nanotechnology and its application in dentistry'', *Annals of Medical and Health Sciences Research*, 4(9), 171–177, (2014).

Acharya, G., Mitra, A.K. and Cholkar, K., "*Nanosystems for Diagnostic Imaging, Biodetectors, and Biosensors"*, *Emerging Nanotechnologies for Diagnostics, Drug Delivery and Medical Devices*, 217–248, (2017).

Agemy, D. Friedmann-Morvinski, V.R. Kotamraju, L. Roth, K.N. Sugahara, O.M. Girard, R.F. Mattrey, I.M. Verma, E.R. ''Targeted nanoparticleenhanced proapoptotic peptide as potential therapy for glioblastoma'', *Proc.Natl. Acad. Sci. U. S. A. 108, 17450–17455*, (2011).

Agnieszka Z. Wilczewska, Katarzyna Niemirowicz, Karolina H. Markiewicz, H.C. ''Nanoparticles as drug delivery systems systematic review'', Pharmacol Rep., 1020–1037, (2012).

Aitziber L. Cortajarena, Daniel Ortega, Sandra M. Ocampo, Gonzalez-García, Alberto Pierre Couleaud, Rodolfo Miranda, C.B.-I. and and Angel Ayuso-Sacidox, ''Engineering Iron Oxide Nanoparticles for Clinical Settings'', *Nanobiomedicine* , 1–21, (2014).

Akbarzadeh, A., Samiei, M. and Davaran, S. ''Magnetic nanoparticles: preparation, physical properties, and applications in biomedicine'', *Artificial Cells, Nanomedicine and Biotechnology* 46(7), 1314–1330, (2012).

AlexAlexander Golberg, Gregory Linshiz, Ilia Kravets, Nina Stawski, Nathan J Hillson, Martin L Yarmush, Robert S Marks, Tania Konryander Golberg, Gregory Linshiz, Ilia Kravets, Nina Stawski, Nathan J Hillson, Martin L Yarmush, Robert S Marks, T.K. ''Cloud-Enabled Microscopy and Droplet Microfluidic Platform for Specific Detection of Escherichia coli in Water'', *PLoS ONE*, 9(1), 1–9, (2014).

Alsaffar, K.A. ''Review of The Use of Nanotechnology in Construction Sector'', *Al-Qadisiya Journal For Engineering Sciences*, 7(1), 68-80, (2014).

Badry, A. El and Mattar, M.A.''Nanotechnology in Neurosurgical Practice'', *EC NEUROLOGY*, 4(5), 149–171, (2017).

Banert, T. and Peuker, U.A.''Synthesis of magnetic beads for bio-separation using the solution method'', *Chemical Engineering Communications*, 194(6), 707–719, (2007).

Bashar Issa, Ihab M. Obaidat, B.A.A. and Y.H. ''Magnetic nanoparticles: Surface effects and properties related to biomedicine applications'', *International Journal of Molecular Sciences*, 14(11), 21266–21305, (2013).

Bucak, S., Yavuztürk, B. and Sezer, A.D. ''Magnetic Nanoparticles: Synthesis, Surface Modifications and Application in Drug Delivery'', *School of Enviromental Sciences*, (2012).

Carla Costa, Fátima Brandão, Maria João Bessa, Solange Costa, Vanessa Valdiglesias, Gözde Kiliç, Natalia Fernández-Bertólez, Pedro Quaresma, Eulália Pereira, Eduardo Pásaro, B.L. and J.P.T. ''In vitro cytotoxicity of superparamagnetic iron oxide nanoparticles on neuronal and glial cells. Evaluation of nanoparticle interference with viability tests'', *Journal of Applied Toxicology*, 36(3), 361–372, (2016).

Carvalho, F. Henriques, L.P. Ferreira, M. Godinho, M.M.C. ''Iron oxide nanoparticles: The Influence of synthesis method and size on composition and magnetic properties'', *Journal of Solid State Chemistry*, 201, 144–152, (2013).

Cheng, C., Xu, F. and Gu, H. ''Facile synthesis and morphology evolution of magnetic iron oxide nanoparticles in different polyol processes'', *New Journal of Chemistry*, 35(5), 1072–1079, (2011).

Chi -Hsien Liu and Hsien, Y.F.''Functionalization and characterization of magnetic nanoparticles for bioseparation''*Materials Science, Biology, Chemistry, Medicine*, (2010).

Christopher J. Rivet, Yuan Yuan, Diana-Andra Borca-Tasciuc, and R.J.G. ''Altering iron oxide nanoparticle surface properties induce cortical neuron cytotoxicity'', *Chemical Research in Toxicology*, 25(1), 153–161, (2012).

Chung-Yi Yang, Jong-Kai Hsiao, Ming-Fong Tai, Shin-Tai Chen, Hui-Ying Cheng, Jaw-Lin Wang, H.-M.L. ''Direct labeling of hMSC with SPIO: The long-term influence on toxicity, chondrogenic differentiation capacity, and intracellular distribution'', *Molecular Imaging and Biology*, 13(3), 443–451, (2011).

Colognato, M.V.D.Z. Park, P. Wick, W.H. De Jong, "Interactions with the human body" *Adverse Effects of Engineered Nanomaterials—Exposure, Toxicology, and Impact on Human Health, 3–24*, (2012).

Cuyper, S.J.S.M. De ''Assessing iron oxide nanoparticle toxicity in vitro: Current status and future prospects'', *Nanomedicine*, 5(8), 1261–1275, (2010).

Dahua Fan, Yongkai Cao, Meiqun Cao, Yajun Wang, Y.C.& T.G. ''Nanomedicine in cancer therapy'', *Signal Transduction and Targeted Therapy*, 8(1),1–34, (2023).

Demirera, G.S., B, A.C.O. and Kizilel, S. ''Synthesis and Design of Biologically Inspired Biocompatible Iron Oxide Nanoparticles for Biomedical Applications'', *Journal of Materials Chemistry B*, 3(40), 7831–7849, (2015).

Dimitri Stanicki, Luce Vander Elst, Robert N Muller, and S.L.''Synthesis and processing of magnetic nanoparticles'', *Current Opinion in Chemical Engineering*, 8 (4), 7–14, (2015).

Ehsan Parsianpour, Mohammad Gholami, Nima Shahbazi, F.S. ''Influence of thermal annealing on the structural and optical properties of maghemite (γ-Fe) nanoparticle thin films'', *Surface and Interface Analysis*, 47(5), 612–617, (2015).

Faruq Mohammad, Ibrahim Birma Bwatanglang, Hamad A. Al-Lohedan, Jilani Purusottapatnam Shaik, H.H.A.-T. and A.A.S.''Influence of Surface Coating towards the Controlled Toxicity of ZnO Nanoparticles In Vitro'', *Coatings*, 13(1), 172–191 (2023).

Fatima, H. and Kim, K.S. ''Magnetic nanoparticles for bioseparation'', *Korean Journal of Chemical Engineering*, 34(3), 589–599, (2017).

Garimella, R. and Eltorai, A.E.M. ''Nanotechnology in orthopedics'', *Journal of Orthopaedics*, 14(1), 30–33, (2017).

Gnanaprakash, S. Ayyappan, T. Jayakumar, J. Philip, B.R. ''Magnetic nanoparticles with enhanced γ-Fe2O3 to α-Fe2O3 phase transition temperature'', *Nanotechnology*, 17(23), 5851–5857, (2010).

Govindankutty, D. ''Applications of nanotechnology in orthodontics and its future implications : A review'', *International Journal of Applied Dental Sciences* , 1(18), 166–171, (2015).

Greta Jarockyte, Egle Daugelaite, Marius Stasys, Urte Statkute, Vilius Poderys, Ting-Chen Tseng, Shan-Hui Hsu, Vitalijus Karabanovas, and R.R.''Accumulation and toxicity of superparamagnetic iron oxide nanoparticles in cells and experimental animals'', *International Journal of Molecular Sciences*, 17(8), 1193–1206, (2016).

Guilherme Ambrozio Albertoni, Carine Prisco Barreto, Patricia Regina Barboza Araujo, Sheila Siqueira Andrade, Fabrício Oliveira Carvalho, Manoel João Batista, Castello Girão Nestor Schor, J.A. ''Magnetic bead technology for viral RNA extraction from serum in blood bank screening'', *Brazilian Journal of Infectious Diseases*, 15(6), 547–552, (2011).

Hans-Christian Roth, Sebastian P. Schwaminger, Michael Schindler, Friedrich E. Wagner, S.B. ''Influencing factors in the CO-precipitation process of

superparamagnetic iron oxide nano particles: A model based study'', *Journal of Magnetism and Magnetic Materials*, 377, 81–89, (2015).

Hasany, I. Ahmed, Rajan J, A.R. ''Systematic Review of the Preparation Techniques of Iron Oxide Magnetic Nanoparticles'', *Nanoscience and Nanotechnology*, 2(6), 148–158, (2013).

Hasany, N.H. Abdurahman, A.R.S. and R.J. ''Magnetic Iron Oxide Nanoparticles: Chemical Synthesis and Applications Review'', *Current Nanoscience* , 9(5), 561–575, (2013).

Hickstein, B. ''Magnetic beads for bioseparation processes - Synthesis and application properties'', PhD thesis, TU Clausthal-Zellerfeld., (2009).

Hoang Tri Hai, Hai Tao Yang, Hiroaki Kura, Daiji Hasegawa, Yasunobu Ogata, Migaku Takahashi, T.O. ''Size control and characterization of wustite (core)/spinel (shell) nanocubes obtained by decomposition of iron oleate complex'', *Journal of Colloid and Interface Science*, 346(1), 37–42, (2010).

Hulla, J.E., Sahu, S.C. and Hayes, A.W. ''Nanotechnology: History and future'', *Human and Experimental Toxicology*, 34(12), 1318–1321, (2015).

Indira, T.K. and Lakshmi, P.K. ''Magnetic Nanoparticles : A Review'', *international journal of pharmaceutical sciences and nanotecnology*, 91(7), 868–870, (2010).

James Butler, Richard D. Handy, Mathew Upton, A.B. ''Review of Antimicrobial Nanocoatings in Medicine and Dentistry: Mechanisms of Action, Biocompatibility Performance, Safety, and Benefits Compared to Antibiotics'', *ACS Nano*, 17(8), 7064–7092, (2023).

Jenkins, D.L. Halaney, K.V. Sokolov, L.L. Ma, H.J. Shipley, S. Mahajan, C.L.Louden, R. Asmis, T.E. Milner, K.P. Johnston, M.D.F.''Excretion andtoxicity of gold-iron nanoparticles',', *Nanomedicine*, 356–365, (2011).

Jens Baumgartne, Archan Dey, Paul H H Bomans, Cécile Le Coadou, Peter Fratzl, Nico A J M Sommerdijk, D.F. ''Nucleation and growth of magnetite from solution'', *Nature Materials*, 12(4), 310–314, (2013).

Joan Estelrich, Elvira Escribano, J.Q. and M.A.B. ''Iron oxide nanoparticles for magnetically-guided and magnetically-responsive drug delivery'', *International Journal of Molecular Sciences*, 16(4), 8070–8101, (2015).

Kammari, R., Das, N.G. and Das, S.K. Nanoparticulate Systems for Therapeutic and Diagnostic Applications, *Emerging Nanotechnologies for Diagnostics, Drug Delivery and Medical Devices*, 105–144, (2017).

Kayal, S. and Ramanujan, R. V. ''Doxorubicin loaded PVA coated iron oxide nanoparticles for targeted drug delivery'', *Materials Science and Engineering C* , 30(3), 484–490, (2010).

Kowalczyk, M., Banach, M. and Rysz, J. ''Ferumoxytol: A new era of iron deficiency anemia treatment for patients with chronic kidney disease'', *Journal of Nephrology*, 24(6), 717–722, (2011).

Krishnendu Chatterjee, Sreerupa Sarkar, K. Jagajjanani Rao, S.''Core/shell nanoparticles in biomedical applications'', *Advances in Colloid and Interface Science*, 209(1), 8–39, (2014).

Kunzmann, B. Andersson, C. Vogt, N. Feliu, F. Ye, S. Gabrielsson, M.S.Toprak, T. Buerki-Thurnherr, S. Laurent, M. Vahter, H. Krug, M. Muhammed, A. Scheynius, B.F. ''Efficient internalization of silica-coated iron oxidenanoparticles of different sizes by primary human macrophages anddendritic cells'', *Toxicol. Appl. Pharmacol. 253*, 81–93, (2011).

Kus-liśkiewicz, M., Fickers, P. and Ben Tahar, I. ''Biocompatibility and cytotoxicity of gold nanoparticles: Recent advances in methodologies and regulations'', *International Journal of Molecular Sciences*, 22(20), 10952–973 (2021).

Leena Mohammed, Hassan G. Gomaa, Doaa Ragab, J.Z.''Magnetic nanoparticles for environmental and biomedical applications: A review'', *Particuology* , 1–14, (2017).

Marekova D., Turnovcova K., Sursal T.H., Gandhi C.D., J.P. ''Potential for treatment of glioblastoma: New aspects of superparamagnetic iron oxide nanoparticles'', *Anticancer Research*, 40(11), 5989–5994, (2020).

Marc Michela, Vidal Barrón, José Torrent, María P. Morales, Carlos J. Serna, Jean-François Boily, Qingsong Liu , Andrea Ambrosini, A. Cristina Cismasu, and G.E.B.J.''Ordered ferrimagnetic form of ferrihydrite reveals links among structure, composition, and magnetism'', *Proceedings of the National Academy of Sciences*, 107(7), 2787–2792, (2010).

Mohammed M. Rahman, Sher Bahadar Khan, Aslam Jamal, M.F. and A.M.A. ''Iron Oxide Nanoparticles'', *Nanomaterials* ,(2011).

Mohapatra, M. and Anand, S. ''Synthesis and applications of nano-structured iron oxides/hydroxides – a review'', *International Journal of Engineering, Science and Technology*, 2(8), 127–146, (2011).

Morteza Mahmoudi, Shilpa Sant, Ben Wang, Sophie Laurent, T. Sen ''Superparamagnetic iron oxide nanoparticles (SPIONs): Development, surface modification and applications in chemotherapy'', *Advanced Drug Delivery Reviews*, 63(1–2), 24–46, (2011).

Nabil, M. and Zunino, P. ''A computational study of cancer hyperthermia based on vascular magnetic nanoconstructs'', *Royal Society Open Science*, 3(9), : 160287–160302, (2016).

Nguyen Viet Long, Yong Yang, Toshiharu Teranishi, Cao Minh Thi, Yanqin Cao, and M.N. ''Biomedical Applications of Advanced Multifunctional Magnetic Nanoparticles'', *Journal of Nanoscience and Nanotechnology*, 15(12), 10091–10107, (2015).

Nikalje, A.P. ''Nanotechnology and its Applications in Medicine'', *Med chem*, 5(2), 81–89, (2015).

Paolo Bigini, Valentina Diana, Sara Barbera, Elena Fumagalli, Edoardo Micotti, Leopoldo Sitia, Alessandra Paladini, Cinzia Bisighini, Laura De Grada, Laura Coloca, Laura Colombo, Pina Manca, Patrizia Bossolasco, Francesca Malvestiti, Fabio Fiordaliso, Gia, L.C. ''Longitudinal tracking of human fetal cells labeled with super paramagnetic iron oxide nanoparticles in the brain of mice with motor neuron disease'', *PLoS ONE*, 7(2), 32326–32338, (2012)

Pedro Tartaj , Maria P. Morales , Teresita Gonzalez-Carreño , Sabino Veintemillas-Verdaguer, and C.J.S. ''The iron oxides strike back: From biomedical applications to energy storage devices and photoelectrochemical water splitting'', *Advanced Materials*, 23(44), 5243–5249, (2011).

Qiyi Feng, Yanping Liu, Jian Huang, Ke Chen, J.H.& K.X. ''Uptake, distribution, clearance, and toxicity of iron oxide nanoparticles with different sizes and coatings'', *Scientific Reports*, 8(1), 1–13, (2018).

Rahman, M. ''Magnetic Resonance Imaging and Iron-oxide Nanoparticles in the era of Personalized Medicine'', *Nanotheranostics*, 7(4), 424–449, (2023).

Ramimoghadam, D., Bagheri, S. and Hamid, S.B.A. ''Progress in electrochemical synthesis of magnetic iron oxide nanoparticles'', *Journal of Magnetism and Magnetic Materials*, 368, 207–229, (2014).

Remya, S. Syama, A. Sabareeswaran, P.V. Mohanan,''Toxicity, toxicokinetics and biodistribution of dextran stabilized Iron oxide Nanoparticles for biomedical applications'', *International Journal of Pharmaceutics*, 511(1), 586–598, (2016).

Sae-Yeol-Rim Paik, Jong-Seok Kim, S.J.S. and S.K. ''Characterization, quantification, and determination of the toxicity of iron oxide nanoparticles to the bone marrow cells'', *International Journal of Molecular Sciences*, 16(9), 22243–22257, (2015).

Šafařík, I., Horská, K. and Šafaříková, M. ''Magnetic Nanoparticles for Biomedicine'', *Pharmaceutical Research*, 24(11), 2097–2098, (2011).

Seyed Mohammadali Dadfar, Karolin Roemhild, NataschaI. Drude, Saskia von Stillfried, Ruth Knüchel , Fabian Kiessling, T. ''Iron oxide nanoparticles: Diagnostic, therapeutic and theranostic applications'', *Advanced Drug Delivery Reviews*, 138, 302–325, (2019).

Shariful Islam, Alam Khan, G.M. Shafiur Rahman, Hrithita Aftab, Y.K. ''A comparative study on heat dissipation, morphological and magnetic properties of hyperthermia suitable nanoparticles prepared by co-precipitation and hydrothermal methods'', *Bulletin of Materials Science*, 35(7), 1047–1053, (2012).

Shen Wu, Aizhi Sun, Fuqiang Zhai, Jin Wang, Wenhuan Xu, Qian Zhang, A.A.V. ''Fe3O4 magnetic nanoparticles synthesis from tailings by ultrasonic chemical co-precipitation'', *Materials Letters*, 65(12), 1882–1884, (2011).

Shicheng Yang, Mia Wallach, Apurva Krishna, Raushan Kurmasheva, S.S. ''Recent developments in nanomedicine for pediatric cancer'', *Journal of Clinical Medicine*, 10(7), 1–22, (2021).

Sophie Laurent, Delphine Forge, Marc Port, Alain Roch, Caroline Robic, Luce Vander Elst, and R.N.M. ''Magnetic Iron Oxide Nanoparticles: Synthesis, Stabilization, Vectorization, Physicochemical Characterizations, and Biological Applications'', *Chemical Reviews*, 108(6), 2064–2110, (2010).

Sophie Laurent, Jean-Luc Bridot, L.V.E.& R.N.M. ''Magnetic iron oxide nanoparticles for biomedical applications'', *Future Medicinal Chemistry*, 2(3), 427–449, (2010).

Sun Sheng-Nan, Wei Chao, Zhu Zan-Zan, Hou Yang-Long, Subbu S Venkat, and X.Z.-C. ''Magnetic iron oxide nanoparticles: Synthesis and surface coating techniques for biomedical applications'', *Chinese Physics B*, 23(3), (2014).

Susana Chamorr, Lucía Gutiérrez, María Pilar Vaquero, Dolores Verdoy, Gorka Salas, Yurena Luengo, Agustín Brenes, and F.J.T. ''Safety assessment of chronic oral exposure to iron oxide nanoparticles'', *Nanotechnology*, 26(20), 1–11, (2015).

Tombacz , R. Turcu, V. Socoliuc, L.V. ''Magnetic iron oxide nanoparticles: Recent trends in design and synthesis of magnetoresponsive nanosystems.'', *Biochemical and biophysical research communications*, 468(3), 442–53, (2015).

Vanessa Valdiglesiasa, Natalia Fernández-Bertóleza, Gözde Kilic¸, Carla Costad, Solange Costad, Sonia Fragad, Maria Joao Bessad, Eduardo Pásaroa, João Paulo Teixeirad, B.L. 'Are iron oxide nanoparticles safe? Current knowledge and future perspectives'', *Journal of Trace Elements in Medicine and Biology* , 38, 53–63, (2016).

Vinardell, M. and Mitjans, M. ''Antitumor Activities of Metal Oxide Nanoparticles'', *Nanomaterials*, 5(2), 1004–1021, (2015).

Wei Wu, Zhaohui Wu, Taekyung Yu, C.J. and W.-S.K. ''Recent progress on magnetic iron oxide nanoparticles: Synthesis, surface functional strategies and biomedical applications'', *Science and Technology of Advanced Materials*, 16(2), 1–43, (2015).

Xinfeng Song, Yancong Zhang, Hanwen Sun, Pingxuan Dong, Zhongyu Zhang, and J.L. ''In Vitro Safety Evaluation and In Vivo Imaging Studies of Superparamagnetic Iron Oxide Nanoparticles through Biomimetic Modification'', *Journal of Nanomaterials*, 1–9, (2019).

Yan, Y. Wang, S. He, S. Ku, W. Gu, L.Y. ''Transferrin-conjugated,fluorescein-loaded magnetic nanoparticles for targeted delivery across theblood-brain barrier'', *J. Mater. Sci. Mater. Med. 24*, 2371–2379, (2013).

Yao Y, Zhou Y, Liu L, Xu Y, Chen Q, Wang Y, Wu S, Deng Y, Zhang J, S.A.''Nanoparticle-Based Drug Delivery in Cancer Therapy and Its Role in Overcoming Drug Resistance'', *Frontiers in Molecular Biosciences*, 1–14, (2020).

Ying, E. and Hwang, H.M. ''In vitro evaluation of the cytotoxicity of iron oxide nanoparticles with different coatings and different sizes in A3 human T lymphocytes'', *Science of the Total Environment*, 408(20), 4475–4481, (2010).

Yiu HH, Pickard MR, Olariu CI, Williams SR, Chari DM, R.M. ''Fe 3O 4-PEI-RITC magnetic nanoparticles with imaging and gene transfer capability: Development of a tool for neural cell transplantation therapies'', *Pharmaceutical Research*, 29(5), 1328–1343, (2012).

Zhiyao Ma, Chao Shan, Jialiang Liang, M.T. ''Efficient adsorption of Selenium(IV) from water by hematite modified magnetic nanoparticles'', *Chemosphere* , 193, 134–141, (2018).

Zohaib Khurshid, Muhammad Zafar, Saad Qasim, Sana Shahab, Mustafa Naseem, A.A. ''Advances in nanotechnology for restorative dentistry'', *Materials* , 8(2), 717–731, (2015).