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# Iron Oxide Nanoparticles: Types, Synthesis, Biomedical applications and Scope of Nanoinformatics

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**ABSTRACT: Nanotechnology has gained a tremendous appreciation since it's discovery, finding applications across numerous scientific and technological areas. Nanomedicines and nanoinformatics can enhance delivery efficiency and accelerate research in nanomedicine. By utilizing data-driven approaches, computational modelling, and artificial intelligence, they can drive innovation, improve drug design, and transform healthcare by unlocking its full potential. Nanoparticles are generally classified into metallic and metal oxide nanoparticles. Among these, metal oxide nanoparticles are recognized as a more sophisticated and effective form compared to metallic nanoparticles, particularly iron oxide nanoparticles (IONPs). This review meticulously explores and summarizes different types of IONPs and their methods of synthesis. Beyond their general characteristics, the wide applications of IONPs in biomedical field are also highlighted. Although IONPs are a fascinating and emerging class of NPs, they possess some level of toxicity, which may raise potential concerns. In this review, we provide a comprehensive overview of the characteristics, uses, biodistribution, and toxicity of iron oxide nanoparticles. Considering the emerging interest of nanoinformatics, we have also included its opportunities in development of nanomaterial-based therapeutics.**

**Keywords**: Iron oxide nanoparticles, maghemite, hematite, magnetite, targeted drug delivery, magnetic hyperthermia, photothermal therapy, biodistribution, toxicity, cytotoxicity, nanoinformatics.

## INTRODUCTION

The world has recently witnessed tremendous technological progress in the field of nanoscience. Nanoscience and nanotechnology deal with the study of molecules of size ranging between 1 and 100 nm and their applications (Bayda *et al.,* 2019). From electrical equipment to medicines, nanoparticles are unavoidable in various fields of research. Nanoparticles have a number of properties that distinguish them from bulk materials simply by virtue of their size, such as chemical reactivity, energy absorption, and biological mobility (Murthy, 2007). Nanoparticles are also referred to as 'Zero dimensional' nanomaterials as their dimensions are in the nanoscale (Murthy, 2007). Nanoparticles exhibit numerous applications in the field of medicine of which targeted drug delivery and bioimaging are the most explored. Recent studies show that nanoparticles have been used to improve immunity, adsorption of active oxygen, adjuvant material and virus neutralization (Kotsuchibashi *et al*., 2016). Nanomedicine is an important component of nanotechnology, which is mainly used for medical diagnostics and drug delivery (Panda *et al.,* 2021). The nanoparticles widely used in biomedicine can be classified based on their chemical composition into three main types. These nanoparticles include organic nanoparticles such as polymers and liposomes, inorganic nanoparticles such as metals, metal oxides, quantum dots, and ceramics, and carbon-based nanoparticles. Nanoparticles used in biomedical applications must be non-toxic, water-dispersible, biocompatible, non-immunogenic, and stable in physiological media (Nikzamir *et al.,* 2021). Considering the growing interest in herbal medicine due to the side effects of modern medicine, the application of herbal nanoparticles is becoming a hot topic of investigation. The applications of herbal nanoparticles in fertility control has been recently reviewed by Kumari *et al.* (2023).

## IRON OXIDE NANOPARTICLES

Metal oxide nanoparticles is considered as one of the most emerging nanomaterials in many areas due to their unique physical and chemical properties, such as thermal conductivity and heat transfer (Khalil *et al.,* 2017). Metal oxides, such as zinc oxide (ZnO) and tin oxide ($SnO_2$), are semiconductors and used in electronic devices Iron oxide nanomaterial research provides new opportunities in a variety of sectors, including electronics and environmental science (Malik *et al.*, 2023). Ongoing researches are exploring their possibilities, notably in the development of more efficient and sustainable technology.

Iron oxide nanoparticles are widely researched and most commonly used among metal oxide nanoparticles. Their versatility is due to the unique properties they possess such as chemical stability, non-toxicity, biocompatibility, high saturation magnetisation and high magnetic susceptibility (McNamara & Tofail 2017). These properties aid for the different biomedical applications like bioimaging, hyperthermia, drug delivery, cell labeling and gene delivery (McNamara & Tofail 2017). Due to their nontoxic nature in the biological system, biocompatibility, biodegradability, ease of synthesis, magnetic nature, and semiconductor properties, iron oxide NPs are reported to have promising applications in the biomedical field (Xu *et al.,* 2007). The three most common polymorphic forms of iron oxides in nature are maghemite ($\gamma$-$Fe_2O_3$), hematite ($\alpha$-$Fe_2O_3$) and magnetite ($Fe_3O_4$) (Ali *et al.,* 2016).

### *A. Maghemite ( $\gamma$-$Fe_2O_3$)*

Maghemite NPs represent a promising class of iron oxide nanoparticles which are used extensively for the removal of heavy metals (Dutta *et al.,* 2022). Maghemite nanoparticles exhibit the properties of a photocatalyst and magnetic nanomaterial. These nanoparticles are favored very much in water treatment applications due to their effectiveness in degradation and removal of contaminants (Ali *et al*., 2017). These are used as adsorbents to remove contaminants from water with remarkable adsorption efficiency. The contaminants removed using maghemite includes $Cs^+$, $Se^{4+}$, heavy metal ions, $NO_2^-$, $NO_3^-$, NOM, and several dyes like rose bengal, methylene blue (MB), methyl orange (MO), brilliant cresyl blue, thionine, Janus green B, and Congo red (Ali *et al.,* 2017). Earlier researchers successfully synthesised maghemite nanoparticles and utilized them for the removal of As (V) ions (Dutta *et al.,* 2022).

### *B. Hematite ($\alpha$-$Fe_2O_3$)*

Hematite NPs are one of the most durable forms of iron oxide (Dutta *et al*., 2022). They are the most stable iron oxide in air under ambient conditions (Rufus *et al.,* 2016). Hematite iron oxide nanoparticles are also environment-friendly and have sorption capacity. Hematite NPs are important due to better anti-microbial activity, significant therapeutic properties on the cancer cell, and other biomedical applications (Sajjad *et al.,* 2023). Hematite NPs are weakly ferromagnetic. Hence they can be made useful for nanomedicine by manipulating their magnetic properties (Powell *et al.,* 2021). The applications of hematite nanoparticles include wastewater treatment (Fang *et al.,* 2009), catalysis (Jagadeesh *et al.,* 2013) gas sensors (Fang *et al.,* 2009) and electrodes (Piao *et al.,* 2008).

### *C. Magnetite ($Fe_3O_4$)*

Magnetite ($Fe_3O_4$) is a common magnetic iron oxide, and it has a cubic inverse spinel structure with oxygen forming a FCC closed packing and Fe cations occupying the interstitial tetrahedral sites and octahedral sites (Xu *et al.,* 2007). Magnetite nanoparticles have been widely studied because of their applications in ultrahigh density magnetic storage media, biological labeling, tracking, imaging, detection, and separations, and ferrofluid. Magnetite NPs were successfully synthesised via sol–gel method combined with annealing under vacuum using inexpensive, nontoxic ferric nitrate and ethylene glycol as starting material (Xu *et al*., 2007). Magnetite NPs are thought to be promising for a wide range of applications because of their unique characteristics, including their high saturation magnetization, which makes them easily operated by the magnetic field, and their low toxicity. They are broadly applied and have potential for biomedical applications, such as magnetic drug targeting, DNA/RNA purification, magnetofection, hyperthermia, MRI imaging cell separation etc. (Dudchenko *et al*., 2022).

## SYNTHESIS OF IRON OXIDE NANOPARTICLES

There are two approaches for the manufacturing of nanomaterials: The “top-down” approach, which involves the breaking down of large pieces of material to generate the required nanostructures from them. The “bottom-up” approach, which implies assembling single atoms and molecules into larger nanostructures. The iron oxide nanoparticles are synthesised mainly by 3 different production methods. They are (a) Physical method-It is a type of top down production method. This method includes elaborate procedures which are not always practical and feasible. Physical synthesis of iron NPs from the vapor phase is possible using the EB-PVD (electron beam physical vapor deposition) method (Kurapov *et al.,* 2019). (b) Chemical method- This method is simple, tractable, and efficient, in which the size, composition, and even the shape of the NPs can be managed. (c) Biological method-This method is carried out by microbial incubation. It requires scrupulously sterile conditions for production and is not opted much due to the strict procedures. Among all the three types of methods, the chemical based synthesis methods are most commonly adopted due to low production cost and high yield. Now let us consider the production methods of each of the different types of iron oxide nanoparticles.

*A. Maghemite*

**(i) Physical method.** Maghemite iron oxide nanoparticles can be synthesised by condensation of mixed molecular flows of iron and salt in vacuum electron beam installation. Maghemite nanoparticles were generated by this method and their potential biomedical applications were also proposed (Kurapov *et al*., 2019).

**(ii) Chemical method.** Maghemite is synthesised from different iron-containing waste materials by simple chemical precipitation method using HCl, NaOH, and $Na_2CO_3$, followed by calcination. The two important raw materials for production are slag and mill scaleand scrap and iron dust (Rahman *et al*., 2020). It is also synthesised by using co-precipitation method (Patekari *et al*., 2021). Maghemite nanoparticleswere developed by the chemical co- precipitation method (Nurdin *et al.,* 2014). Superparamagnetic maghemite nanoparticles were prepared using chemical co-precipitation technique (Yoon, 2014). Rod-shaped and maghemite nanoparticles with diameters of 5 nm and lengths of 16 and 17 nm were synthesised by a newly designed sol–gel mediated reaction (Woo & Lee 2004).

**(iii) Biological method.** It was reported that *Bacillus subtilis* SE05 strain can produce highly magnetic iron oxide nanoparticles of the maghemite type ($\gamma$-$Fe_2O_3$). The biosynthesis of single phase maghemite ($\gamma$-$Fe_2O_3$) nanoparticles using an aqueous fruit extract of Ficus carica was also reported (Kumar *et al.,* 2021). *Actinobacter* species were utilised for the sysnthesis of bacterial maghemite nanoparticles (Bharde *et al.,* 2008).

*B. Hematite*

**(i) Physical method.** Electron beam physical vapor deposition method (EB VDM) utilizes an electron gun to vaporize the ingot to the form of a rod. The electron beams are directed towards the ingot by employing a magnetic field. An additional electric field is used to stear the electrons onto the ingot surface. Karami (2016) synthesised Magnetite/Hematite/Iron Nanocomposites by the Low Voltage Arc Discharge in Water in the Presence of External Magnetic Field (Department of Chemistry, Payame Noor University, 19395-4697, Tehran, I.R. of Iran & Karami, 2016). A simple hydrothermal process was done to fabricatehematite ($\alpha$-$Fe_2O_3$) nanostructures with narrow size distribution where it was developed by using PVP as surfactant and NaAc as precipitation agent (Zhu *et al.,* 2012).

**(ii) Chemical method.** Nanoparticles were synthesized via the sol-gel auto-combustion method. The synthesised nanoparticles were confirmed to be hematite nanoparticles using different characterization techniques. ("A Facile Approach for the Synthesis of Porous Hematite and Magnetite Nanoparticles through Sol-Gel Self-Combustion," 2021). Research has been conducted to synthesize $Fe_2O_3$ hematite nanoparticles based on iron sand originating from Talaga Village, Dampelas District, Donggala Regency. Iron sand dissolved in HCL (12 M) and $NH_4OH$ (25%) was then heated at a temperature of 120°C for 19 hours and calcined at a temperature of 800°C for 2 hours. The hematite nanoparticles were successfully synthesised by them using this approach (Mahmudin *et al*., 2023).

**(iii) Biological method -**Hematite was synthesised by the sole use of the extract of guava (*Psidiumguajava*) leaves (Rufus *et al.,* 2016). Floral extracts of *Callistemon viminalis* (bottlebrush) were used to produce pure hematite phase magnetic iron oxide nanoparticles (Hassan *et al.,* 2018). In another study, Hematite ($\alpha$-$Fe_2O_3$) nanoparticles were mycosynthesised using *Aspergillus niger* (Saied *et al.,* 2022).

*C. Magnetite*

**(i) Physical method.** By electron beam physical vapor deposition (EB PVD), magnetite nanoparticles were successfully generated. This method is highly productive and also notable for its versatility at selection of various inorganic and organic matrices for the conservation of metal NPs and their oxides (Kurapov *et al*., 2019).

**(ii) Chemical method.** There are different chemical approaches for the synthesis of magnetite nanoparticles. In the Co-Precipitation method, aqueous solution of ferric chloride and ferrous chloride is added to ammonia solution. The nanoparticles are obtained by a series of precipitation reactions following by drying and then characterization (Massart, 1981). It was reported that the magnetite nanoparticles were synthsised by the method of Partial Oxidation of ferroushydroxide. The nanoparticles were confirmed to be of Magnetite by characterization (Sugimoto & Matijević 1980). The sol–gel method is a wet-chemical process for nanoparticle preparation based on hydrolysis and polycondensation of iron precursors. Dudchenko *et al.* (2022) successfully synthesised Magnetite nanoparticles using the Sol-gel method (Dudchenko *et al.,* 2022). Shaker *et al*. (2013) reported about magnetite nanoparticles prepared using the sol–gel method combined with annealing at temperatures of 200, 300, and 400°C. Nanoparticles were synthesized by a non-chemical approach at different amplitudes and under the influence of an ultrasound (Freitas *et al*., 2015). The samples were analysed using XRD and SEM. Another approach was developed where the nanoparticles with narrow size distribution and united shape, reverse coprecipitation method was done under ultrasound. Using this sono-chemical method they successfully synthesised Magnetite nanoparticles (Aliramaji *et al.,* 2015).

**(iii) Biological method.** By the aqueous solution of ferrous and ferric salts mixed with *Magnetospirillum*, magnetite nanoparticles were synthesised (Reza Ghorbani *et al.,* 2017). *Magnetospirillum* strain AMB-1 was also used by Elblbesy *et al.* (2014) to synthesis Magnetite nanoparticles (Elblbesy *et al.,* 2014). The nanoparticles of average size~47 nm were obtained.Synthesis of magnetite nanoparticles was studied and done using *Magnetotactic* bacteria (MTB) (Lang *et al.*, 2007).

The various methods of synthesis of different types of iron oxide nanoparticles are summarised in Fig. 1.

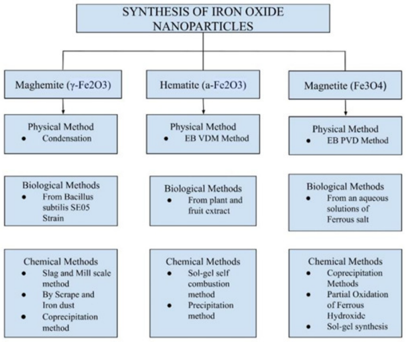


**Fig. 1.** Methods of synthesis of iron oxide nanoparticles.

## BIOMEDICAL APPLICATIONS OF IRON OXIDE NANOPARTICLES

Iron oxide nanoparticles exhibit magnetic properties and possess a significant surface area. They are used in a range of applications, including drug delivery, and are also applicable to many diseases. Furthermore, they are recognized for their minimal toxicity and compatibility with living organisms. The significant biomedical applications of iron oxide nanoparticles are summarized in Fig. 2 and explained in the following section.

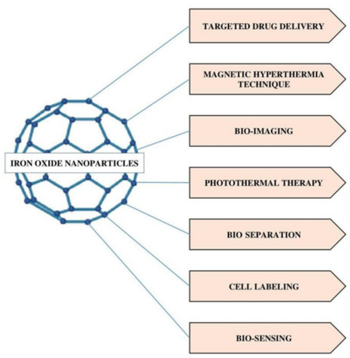


**Fig. 2.** Important biomedical applications of Iron oxide nanoparticles.

### *A. Targeted Drug delivery*

Iron oxide nanoparticles are found to play a significant role in targeted drug delivery. The basic principle behind this application is illustrated in Fig. 3.

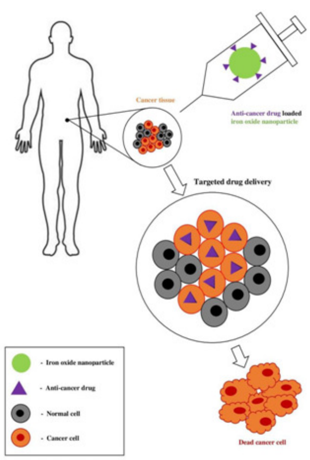


**Fig. 3.** Targeted anti-cancer drug delivery using Iron oxide nanoparticles.

An important approach was utilized by Skorjanc *et al.* (2017) to develop macrocycle-modified iron oxide nanoparticles, aiming to design drug delivery systems specifically utilized to target tumors, administer powerful anti-cancer drugs, and facilitate thermal therapy (Skorjanc *et al.,* 2017). A nanocomposite named Chloramb-CS-IONPs was created by utilizing Chlorambucil as a carrier, with iron oxide NPs acting as cores and chitosan (CS) as the polymeric shell. This nanocomposite was then evaluated on both normal fibroblast cell lines (3T3) and leukemia cancer cell lines (WEHI). The study revealed that approximately 89.9% of the drug was released over around 5000 minutes. Consequently, Chloramb encapsulated in Chloramb-CS-IONPs exhibited enhanced efficiency in comparison to its unbound state (Hussein-Al-Ali *et al.,* 2021). The combination of Carboxymethyl-dextran coated (CMD) iron oxide NPs with anti-microbial peptides has resulted in the creation of a cost-effective and potent drug carrier (Turrina *et al.,* 2022). The engineering of targeted extracellular vesicle delivery systems also involved the use of superparamagnetic IONPs (Zhuo *et al*., 2021). Matuszak *et al*. (2018) synthesised superparamagnetic iron oxide nanoparticles (SPIONs) incorporated with Dexamethasone phosphate (DEXA), which was then tested on an animal model of atherosclerosis to accumulate drugs in specific regions. The results indicated its efficiency to deliver drugs to affected arteries in vivo and speeding inflammatory response (Matuszak *et al.,* 2018). By conjugating SPIONs with an aptamer, the tumor targeting ability was found to be enhanced. Such drug-loaded nanocarriers could be a potential drug delivery system (Sun *et al.,* 2019). Besides drugs, modified iron oxide nanoparticles were investigated for their ability to deliver plasmid DNA (Nikforouz *et al.,* 2021).

### *B. Magnetic Hyperthermia Technique*

Magnetic hyperthermia shows great potential as a method to localize and manage cancer by raising the temperature of body tissue above normal levels, typically between 40 and 45°C. Aminosilane coated iron oxide nanoparticles were studied for their therapeutic applications in Glioblastoma (Rego *et al.,* 2020). Blanco-Andujar *et al.* (2016) suggested the use of IONPs as MRI contrast agents or heating regulators in the magnetic hyperthermia technique (Blanco-Andujar *et al.,* 2016). The IONP stabilized with oleic acid and sodium oleate was designed to potentially offer a therapeutic solution for tumor treatment through magnetic hyperthermia. Moreover, it was found to have minimal local irritant effects and did not affect the structure of internal organs (Kulikov *et al*., 2022). Utilizing a sulfonated ABA-type triblock copolymer, Yang *et al.* (2019) developed electroactive composites with block copolymer-templated iron oxide nanoparticles and TA oligomers for magnetic hyperthermia applications. This involved the template of electroactive TA and $Fe_3O_4$ nanoparticles within the self-assembled micro-structures (Yang *et al.,* 2019). Iron oxide nanoparticles coated with Hydroxyapatite were produced and were then exposed to MG-63 osteosarcoma cells, which showed great hypothermia effects and killed about all 63 osteosarcoma cells within 30 minutes of exposure (Mondal *et al.,* 2017). The addition of magnesium to iron oxide NPs has led to their emergence as promising options for magnetic fluid hyperthermia (MFH) in lung cancer therapy (Nowicka *et al.,* 2023). Similarly, iron oxide NPs doped with rare-earth have also found wide applications in biomedicine like magnetic hyperthermia and MRI techniques (Laha *et al.,* 2021). The studies of Salimi *et al*. (2018) put forward an idea regarding the application of iron oxide nanoparticles in magnetic hyperthermia and MRI. It could be achieved by coating the IONPs with polyamidoamine dendrimer (fourth generation) (Salimi *et al.,* 2018).

*C. Photothermal therapy*

Hybrid nanoparticles formed by the combination of iron oxide nanoparticles with any photo-thermal agents exhibit functions of Near-Infrared (NIR) absorption and magnetism and can be used themselves as photothermal agents. The use of IONPs as contrast agents in MRI depends mainly on their magnetic properties, allowing them to be magnetically targeted (Estelrich & Busquets 2018). Doxorubicin (DOX) incorporated liposomal iron oxide nanoparticles (Lipo-IONP/DOX) were developed, and tested for its role in combined chemo-photothermal cancer therapy (Park *et al*., 2023). Guo *et al*. (2022) synthesised a type of iron oxide nanoparticles that exhibited remarkable photothermal conversion capability and peroxidase-like catalytic properties. These nanoparticles are suitable for making a combined photothermal-enzyme anti-bacterial treatment system. The peroxidase-like catalytic ability resulting in bactericidal effect, which reached almost 100% in the case of *Escherichia coli* and *Staphylococcus aureus*, upon synergistic application of IONPs (Guo *et al.,* 2022). Iron oxide nanoparticle-loaded alginate hydrogels were also developed for the photothermal therapy of colorectal cancer. The synthesised $Fe_3O_4$ NPs, when exposed to the CT26 cancer cells, successfully triggered their absorption by the cancer cells and caused the death of the cells in vitro when subjected to NIR laser irradiation (Ji & Wang 2023). Gupta *et al*. (2023) created super paramagnetic iron oxide nanoparticles as a tool to treat cancer and analysed its photothermal ability and it was concluded that the synthesised SPIONs could be utilized as an efficient photothernal agent (Gupta *et al.,* 2023). Recently, a multifunctional nanosystem was produced using hollow copper iron oxide nanoparticles, having functions as a drug carrier (cisplatin) and a photothermal agent (Feng *et al.,* 2023). Pancreatic cancer is the most severe malignancy. Hence, as a local treatment strategy, Wang *et al*. (2022) developed a platform involving iron oxide NPs, which was loaded with imiquimod and coated with indocyanine green and DSPE-PEG. It was then treated against Panc02-H7 tumors with interventional photothermal therapy (IPTT). The treatment induced immunogenic cell death and thus, the system could improve the therapeutic approaches to pancreatic cancer (Wang *et al.,* 2022).

*D. Bioimaging*

Gadolinum-chelate-based positive contrast agents are the ones that are usually available in markets as MRI contrast agents. At the same time, magnetic iron oxide nanoparticles are found to have better biocompatibility than gadolinium chelates (Shen *et al.,* 2016). Iron oxide nanoparticle-based contrast agents such as Ferumoxide, Ferucarbotran, Ferumoxsil, Ferumoxytol, etc. can be used in liver imaging, oral imaging, gastro-intestinal imaging, and central nervous system imaging, respectively (Geppert & Himly 2021). Magnetic IONPs were found to target over-expressed proteins and biomarkers involved in breast cancer and could be used for its bioimaging and therapy (Halder *et al.,* 2022). A special type of multi-functional iron oxide nanoparticles coated with polyethylenimine was synthesised using Bodipy fluorophore (BOD-MNPs). The imaging capability of this was understood by testing it on cancer cells, and with its unique fluorescence properties, the BOD-MNPs were able to pass through the cell cytoplasm (Topel *et al.,* 2015). Reguera *et al*. (2017) have described in their study the development of Gold-iron oxide Janus magnetic-plasmonic nanoparticles and their role in multimodal imaging (Reguera *et al.,* 2017).

## BIODISTRIBUTION AND TOXICITY OF IRON OXIDE NANOPARTICLES

Past decades have witnessed the growing progress towards the synthesis of nanoparticles and their application in research, industry and medicine. Iron oxide nanoparticles are one of the most vital and fascinating metallic nanoparticles which possess valuable biomedical applications due to their excellent physical properties such as superparamagnetism, stability in aqueous solutions and biocompatibility. However, toxicity concerns prevent the use of iron oxide nanoparticles in clinical treatments. The biodistribution of magnetic nanoparticles in organisms is an important parameter as it helps to reduce the toxicity of nanostructures due to their undesirable distribution in targeted organs or tissue. Magnetic iron oxide nanoparticles can be used for drug delivery, hyperthermia cancer treatments, radiolabelling, magnetic resonance imaging etc. (Khan *et al.,* 2023). However, the variety in nanoparticle size, composition, shape, surface chemistry and state of dispersion may influence their biodistribution and toxic potential (Shubayev *et al.,* 2009).

*A. Biodistribution*

The biodistribution helps to determine whether the target organs have taken up the nanoparticles or accumulated in other tissues which may lead to potential toxicity. The organs that usually uptake nanoparticles are liver, spleen, lymph nodes and brain. Many studies have indicated that the magnetic nanoparticles are primarily captured by the liver and it is the site for biodistribution. Tate *et al*. (2009) studied the biodistribution of two types of magnetite nanoparticles which were coated with hydroxyl-ethyl starch in mice models and the results showed that liver was the primary site of iron accumulation after 72 hours for large sized nanoparticles (Tate *et al.,* 2011).

Another study conducted by Shanehsazzadeh *et al.* (2013) evaluated the biodistribution of dextran coated iron oxide nanoparticles labelled with 99mTc which was intravenously injected in BALB mice. The result showed about 75% of the injected doses were found in the spleen and liver at 15 minutes post injection. The high biodistribution of iron oxide nanoparticles was observed in rabbit liver which was intra arterially or intravenously injected with iron oxide nanoparticles covered with phosphate starch (Tietze *et al*., 2009). Due to the high accumulation of iron oxide nanoparticles in the liver, they are used as liver targeting magnetic resonance imaging contrast agents (Wang *et al.,* 2015; Yazdani *et al.,* 2016). The studies conducted by Maeng et al. (2010) illustrated that superparamagnetic iron oxide nanoparticles is a promising candidate for treating liver cancer and monitoring the progress of cancer using MRI. Recently, a series of studies has been conducted to analyze the biodistribution of iron oxide nanoparticles in different organs including lungs. (Maeng *et al.,* 2010). The biodistribution of superparamagnetic iron oxide nanoparticles was investigated in pig lungs using pEPR technique analysis and confirmed that magnetic nanoparticles localized in alveolar tissue (Edge *et al.,* 2016). The biodistribution of iron oxide nanoparticles involves their capture by reticuloendothelial system which dissolves it into free iron making them available to be used by organisms and hence is a treatment for iron anemia disease (Alphandéry, 2019). In a study, it was illustrated that iron oxide nanoparticles functionalized with dextran caused no adverse effects and exposure to dextran at determined dosage did not impose a toxic effect (Bolandparvaz *et al*., 2020).

The biodistribution of nanoparticles in the body organs are influenced by different factors. Yue *et al.* (2011) studies conclude that positively charged nanoparticles, due to their strong interactions with biological membranes are generally more internalized than negative and neutrally charged nanoparticles (Yue *et al*., 2011). The biodistribution of magnetic nanoparticles coated with negatively charged ethylenediaminetetraacetate (EDT) was studied by Sun *et al.* (2016) and he concluded that they are most likely to cross the blood-brain barrier and enhance the delivery of iron oxide nanoparticles in the brain (Sun et *al.,* 2016). Thus biodistribution of nanoparticles is an important aspect which determines the location and degree of nanoparticles administered in the body and their accumulation in various organs. The undesirable accumulation of these nanoparticles leads to toxicity in tissues.

*B. Toxicity of iron oxide nanoparticles*

Although nanoparticles have a wide range of applications in various biomedical fields including diagnosis, gene delivery, biomarker mapping, drug delivery and target therapy, there is a growing concern about the toxicological potential of nanoparticles and their hazardous effect on health. Toxicity caused by nanoparticles in the cells may lead to impaired mitochondrial function, morphological changes and this may negatively affect the cell viability, metabolism and distort the therapeutic efficiency of the treatment (Ezealigo *et al*., 2021). Iron oxide nanoparticles are found to induce irreversible histopathological modifications in the gill, liver and brain tissue of the fish *Oreochromis mossambicus* even after treatment withdrawal (Vidya & Chitra 2019). Thus the toxicity studies of nanoparticles may help to overcome their adverse effects while treatment of diseases with therapeutic nanoparticles. Many studies have been conducted aiming to discuss the toxicity parameters of iron oxide nanoparticles.

**(i) Plasma membrane toxicity.** The iron oxide nanoparticles exhibit toxicity by inducing profound damage to plasma membranes and associated proteins. The studies conducted by Jeng & Swanson (2006) showed that a maximum concentration of superparamagnetic iron oxide nanoparticles (about $[Fe] \approx 2.5mM$) caused a significant effect upon mitochondrial function (Jeng & Swanson 2006). Similar results were observed in the studies done by Au *et al.* (2007) on astrocytes and thus the authors concluded that iron oxide nanoparticles decreased the cell viability and altered the mitochondrial functions (Au *et al.,* 2007). Stroh *et al.* (2004) highlighted the substantial increase in oxidative stress and protein oxidation caused by citrate-coated iron oxide nanoparticles and the study also concluded that iron was the source to produce the reactive oxygen species (Stroh *et al.,* 2004).

**(ii) Cytotoxicity.** The cytotoxicity of iron oxide nanoparticles is partially explained by the generation of reactive oxygen species (ROS), which induces oxidative stress in cells. This oxidative stress is a major cause of cellular damage and toxicity. The study done by Feng *et al*. (2018) concluded that at low concentration, polyethyleneimine-coated iron oxide nanoparticles exhibited severe cytotoxicity against macrophages and cancer cells while even high concentration of polyethylene glycosylated iron oxide nanoparticles caused no obvious cytotoxicity (Feng *et al.,* 2018). There are a number of methods available to evaluate cytotoxicity. The studies conducted by Decker & Lohmann-Matthes (1988) suggest that LDH release assays are a suitable and potentially preferred method for measuring cellular cytotoxic reactions. They combine the reliability and simplicity of radioisotope release assays with the speed and convenience of avoiding radioactivity (Decker & Lohmann-Matthes 1988).

**(iii) Genotoxicity.** Kaygisiz & Ciğerci (2017) investigated the genotoxic potential of iron oxide nanoparticles (size <50 nm and <100 nm) using somatic mutation and recombination test. It was observed that nanoparticles <100 nm showed no significant genotoxic effect whereas <50 nm nanoparticles showed genotoxicity (Kaygisiz & Ciğerci 2017). The studies by Ghosh *et al.* (2020) demonstrated the synthesis of superparamagnetic iron oxide nanoparticles (SPION) using didodecyl-dimethyl-ammonium-bromide (DMBA) as surfactant by emulsification and the result suggested that SPION-DMAB was least cyto-genotoxic. He also concluded that SPION-DMAB can be further investigated for oral drug delivery to the brain and for imaging cerebral tissue, without the need for any functional ligand or external magnetic field (Ghosh *et al.,* 2020).

## NANO-INFORMATICS

Nano-informatics is a rapidly growing research field that utilizes informatics techniques to gather, process, store, and *retrieve data on nanoparticles, nanomaterials, and nanodevices, with potential applications in healthcare (V Maojo et al., 2012).* Nano-informatics mainly analyze nanobiotechnological data, encompassing properties, toxicity, and interactions with biological units. It fosters collaboration between chemists, physicists, biologists, and data scientists, enhancing innovation. By streamlining data analysis and management, nanoinformatics can significantly speed up research and development processes in nanotechnology. Nanoinformatics involves a range of tools and software that assist researchers in managing, analyzing, and visualizing data related to nanomaterials. Table 1 shows some tools and softwares that are commonly used in this field.

**Table 1: List of tools and softwares commonly used in nanoinformatics.**

| Sr. No. | Tool/server Name | Details |
|---|---|---|
| 1. | Nano HUB<br>An online platform that provides tools and resources for nanotechnology research, including simulation tools and educational resources. | Computational tools for modeling nanostructures, material properties, and nanoscale phenomena (Madhavan *et al.*, 2013). |
| 2. | Materials Project<br>A repository of materials data that allows users to explore materials properties and perform high-throughput calculations. | Provides access to a vast database of computed materials properties, including nanomaterials (Sun *et al.*, 2019; Woods-Robinson *et al.*, 2018). |
| 3. | Nanomaterials Database (NDB)<br>A comprehensive database that contains information on various nanomaterials, including their properties, synthesis methods, and applications. | Facilitates data retrieval and comparison of different nanomaterials (Ji *et al.*, 2021). |
| 4. | Chem Spider<br>A free chemical structure database that provides access to information about chemical compounds, including nanomaterials. | Allows users to search for nanomaterials by structure, name, or properties (Van Noorden, 2012). |
| 5. | Open Quantum Materials Database (OQMD)<br>A database that focuses on quantum mechanical calculations of materials, including nanoscale materials. | Facilitates research by providing data on thermodynamic properties, electronic structure, and more (Kirklin *et al.*, 2015). |
| 6. | Jupyter Notebooks<br>An open-source web application that allows the creation of documents containing live code, equations, visualizations, and narrative text. | Useful for data analysis, visualization, and sharing computational research in nanoinformatics (Perkel, 2018). |
| 7. | Machine Learning Libraries (e.g., scikit-learn, Tensor Flow)<br>Libraries that facilitate the development of machine learning models to analyze and predict properties of nanomaterials. | Provide tools for feature extraction, model training, and evaluation. |
| 8. | VESTA<br>Description: A visualization software for 3D crystal structures, volumetric data, and electronic states. | Useful for visualizing the atomic structure and electronic properties of nanomaterials (Maryamdokht Taimoory *et al.,* 2017). |
| 9. | Nanotexture<br>A software tool for characterizing and simulating the surface topography of nanostructured materials. | Helps in understanding the surface properties and interactions of nanomaterials. |
| 10. | Matlab and Python Libraries<br>General-purpose programming environments that offer libraries for numerical analysis and data visualization. | Widely used for custom analyses, simulations, and modeling in nanoinformatics research. |

The insights gained from nanoinformatics can be applied in various fields, including medicine (e.g., drug delivery systems), electronics (e.g., nanoscale transistors), and environmental science (e.g., pollution remediation). It is suggested that nanoinformatics could accelerate research and development in nanomedicine, similar to the role played by biomedical informatics in genomic and –omics projects (Victor Maojo *et al.*, 2012). Understanding and predicting the cytotoxic effect of nanoparticles at the blood-brain barrier (BBB) is crucial in nanotoxicology and nanomedicine. Computational techniques like molecular docking and dynamics simulations help investigate nanoparticle-cell interactions, predict BBB permeation rates, and evaluate potential harmful effects (Shityakov *et al.*, 2017).

*A. Applications of Nanoinformatics*

Nanoinformatics involves the collection of data from various sources, including experimental studies, simulations, and literature (García-Remesal *et al.*, 2013). It emphasizes the organization, storage, and retrieval of large datasets related to nanoscale materials and phenomena. Computational models are used to predict the behavior and properties of nanomaterials, which can accelerate the discovery and development of new applications. Advanced analytical techniques, including machine learning algorithms, are employed to identify patterns, correlations, and insights from complex datasets. Applications also include assessing the safety and environmental impact of nanomaterials, which is crucial for regulatory purposes.

*B. Scope of nanoinformatics in research on therapeutics based on iron oxide nanoparticles*

Nanoinformatics can accelerate research, drive innovation, and improve delivery efficiency in drug design, delivery systems, and diagnostics. Nanomedicines, loaded with therapeutic active principles, can target inflammation through molecules overexpressed on macrophages or endothelial cells, increased vasculature permeability, or biomimicry. Recent studies shows that application of nanoinformatics in drug development and drug delivery have an impact on healthcare research (Labhasetwar, 2005; Patra *et al.,* 2018). Advancements in biocomputing and nano-technology have led to the discovery of novel biomarkers in personalized medicine, a field that uses genetic/molecular information to predict disease development and clinical outcomes (Alghamdi *et al.*, 2022).

Nanotechnological research is being conducted to entanglement, detect, and operate biomarkers for advanced therapeutics, in response to biomarker-based diagnostic trends. A research by Manzoor *et al*. (2022) demonstrates the potential of green synthesised iron oxide nanoparticles in determining biomarkers and diagnostic fingerprints for early detection and advanced therapeutics (Manzoor *et al.*, 2022). Iron oxide nanoparticles were synthesised using plant extract of *Withaniacoagulans*, bifurcated into pure and oncogenic serum-treated particles for nine cancers. The green $Fe_2O_3$-nanoprobe elucidated 30 common and 25 differential biomarkers, providing a precise range of biomarkers. The metallic probe highlighted the most significant biomarkers, demonstrating advanced robotic nanotechnological techniques for selective biomarker extraction.

In another study, a systems pharmacological approach was employed to understand the reaction of cancer cells to magnetic iron oxide nanoparticles (MNPs) and suggested drug selection for synergetic or additive anti-cancer effects (Zhou *et al.*, 2022). The study found that bare MNPs significantly reduced mRNA expression levels of key genes in cervical cancer cells. This suggests that interactions with anti-cancer drugs should be considered in designing MNP drug delivery systems. This could lead to a systems pharmacology approach, identifying potential molecular reactions and suggesting drug selection for synergetic or additive anti-cancer effects.

Nanoinformatics based approaches have great potential in accelerating research and development in diverse applications of nanomaterials, particularly nanomedicine. Yet the present status of this emerging area has revealed a wide set of different challenges. One of the major issues is related to developing standardized formats for data to ensure interoperability across different platforms and disciplines. Management of heterogenous information encompassing nomenclature, taxonomy and classification of different sets of nanomaterials is an enormous task. The accuracy and reliability of data collected from diverse sources also need to be ensured. Besides, ethical considerations associated with the use of nanomaterials, especially in biomedical applications have to be addressed.

## CONCLUSION

Nanomaterials are defined as materials having a size range of approximately 1 to 100 nm. Metal oxide nanoparticles are a versatile class of nanoparticles and have been emerging as a potential agent in science, especially iron oxide nanoparticles. Here, physical, chemical and biological methods of synthesizing different types of iron oxide nanoparticles were reviewed. Owing to their unique properties and biocompatibility, iron oxide nanoparticles have been employed in various areas of biomedicine, despite their toxicity. Numerous studies are underway that discuss the promising future of Iron oxide nanoparticles. Recently, nanoinformatics has received a lot of interest because it is a fast-evolving discipline with potential applications in nanomaterial based therapeutic methods. This review, hence aims to contribute to the growing body of research that supports the advancements of iron oxide nanoparticles.

## FUTURE SCOPE

As we have seen, iron oxide nanoparticles, with their unique physical and chemical properties, have significant biomedical applications in drug targeting, hyperthermia, disease diagnosis, and cancer treatment. However, their potential toxicity remains controversial due to their high variability in size, surface charge, and coatings. Hence it is the need of the hour that more research needs to be focused on the biocompatibility, bio-distribution, metabolism and bio-clearance of these nanoparticles both *in vitro* and *in vivo*. The combination of imaging, targeting and therapy using one particular nanosystem should be explored further with respect to iron oxide nanoparticles. Some key aspects that need to be addressed also include the functionalisation of the nanoparticle surface with biocompatible coatings, and the possibility to attach functional ligands that can specifically target diseased tissues.

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