



# Iron oxide nanoparticles: synthesis, functionalization, and applications in diagnosis and treatment of cancer

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## Abstract

In recent years, iron oxide nanoparticles have demonstrated great potential in biomedical applications due to their non-toxic role in biological systems. Also, the magnetic and semiconductor properties of iron oxide nanoparticles can lead to multi-functional applications in medicine. These nanoparticles have been developed as antibacterial, antifungal, and anticancer. For cancer treatment and diagnosis, iron oxide nanoparticles have been functionalized with drugs. However, many of those drugs have been related to adverse effects on health. On the other hand, phytochemicals from extracts of plants have been used as an alternative for the functionalization of these nanoparticles preventing negative effects. The main advantage of these nanoparticles is the high biodistribution in the organism compared with other drug delivery systems. The magnetism of iron oxide nanoparticles has been used in cancer treatment and diagnosis, for example, thermoablation, hyperthermia, and contrast media in magnetic resonance imaging. Therefore, this work aimed to discuss the methods for the synthesis of iron oxide nanoparticles, the different kinds of coatings used to functionalize them, and the different applications they have had in cancer treatment and diagnosis.

**Keywords**  $\text{Fe}_3\text{O}_4$  · Nanoparticles · Synthesis · Functionalization · Cancer

## Introduction

Nanotechnology is a science with great potential in the development of useful materials in many fields such as medicine, electronics, physics, and chemistry. According to the European Union Commission (Recommendation 2011/696/EU), a nanomaterial is considered a natural, incidental or manufactured product that contains particles, in an unbound or aggregate/agglomerate state, where 50% or more of the

particles are in the range from 1 to 100 nm (Galocchio et al. 2015; He and Hwang 2016; Kolahalam et al. 2019). The shape and size of nanoparticles are important parameters in the manufacture, processing, and applications due to the high surface area increases reactivity, ion delivery or contact. Also, physical properties such as shape, composition, load, and solubility can change their behavior unpredictably (Galocchio et al. 2015). Recent exploration of nanotechnology in biomedical and pharmaceutical science has resulted in the successful improvement of conventional drug delivery systems (Patra et al. 2018; Chentamara et al. 2019). Nanoparticles can be organized into four material-base categories: carbon-based materials (contain carbon), inorganic-based materials (include metal and oxide metal nanoparticles), organic-based materials (made from organic matter, excluding carbon), and composite-based materials (combined with larger or with bulk-type materials) (Jeevanandam et al. 2018). Inorganic nanoparticles include transition metals and metal oxides (silver, iron, titanium), alkaline earth metals (calcium, magnesium), and nonmetals (selenium, silicates) which have been used in different areas (Martirosyan and Schneider 2014, Rao et al. 2016). Iron oxide nanoparticles

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(IONPs) are inorganic nanoparticles composed of ferromagnetic materials and show an inimitable form of magnetism (Ali et al. 2016). The magnetism of IONPs shows significant advantages such as a low cost of production, environmental safety, great stability, and compatibility. On the other hand, the most frequent biomedical applications include magnetic separation, targeted drug delivery, magnetic resonance imaging (MRI), magnetic fluid hyperthermia and thermoablation and biosensing (Kudr et al. 2017). Another use of IONPs that have been gained attention in therapeutic nanomedicine is either as cancer treatment because they are able to enhance the drug activity in combination therapy (IONPs and chemotherapeutic drugs) or as hyperthermia agents (Vallabani and Singh 2018). However, there are various undesirable side effects of chemotherapeutic drugs. Thus, natural compounds from medicinal plants can be an alternative option in the development of anticancer treatments (Rao et al 2016). In this review, we discuss various methods of synthesis of IONPs, natural functionalization coatings, and applications on cancer diagnosis and treatment.

## Methods for the synthesis of iron oxide nanoparticles

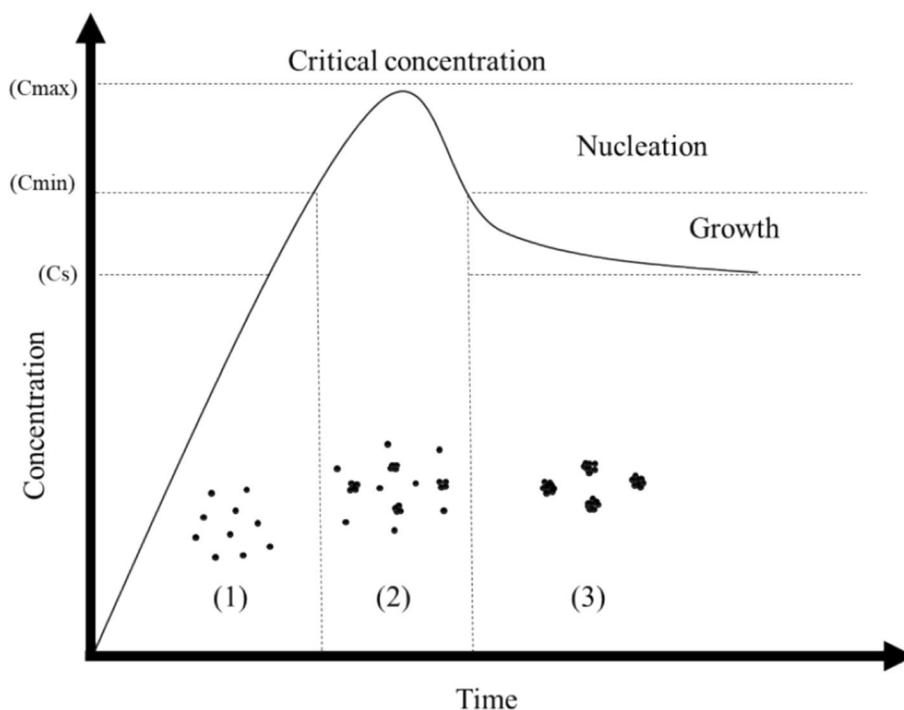
There are two ways to synthesize nanoparticles: Firstly, the 'top-down' method consists of breaking down large pieces of material by wear to generate nanoparticles. Although, the particles obtained have a wide particle size distribution and varied shapes, so this type of synthesis is generally used for

ceramic materials where size and shape are not essential for its application (Biswas et al. 2012).

The other way is known as 'bottom-up'. It consists of the union of atoms or molecules to form larger nanoparticles. According to this methodology, nanoparticles with fewer defects are obtained, achieving more homogeneous chemical composition and a more uniform distribution in size and shape. This type of nanoparticles has been widely used in biomedical applications, where the control in the uniformity of the shape and a narrow particle size distribution are particularly important (Biswas et al. 2012). LaMer and Dinegar (1950) proposed a theory based on the mechanisms of nucleation-growth of sulfur particles, which is divided into three stages (Fig. 1).

In stage 1, the salts remain soluble in a homogeneous system, when the concentration of salts increases (in the case of metallic NPs most likely due to reduction), and it reaches, after time, a minimum concentration at which the nucleation can start ( $C_{min}$ ). As the concentration continues rising, a certain critical supersaturation level ( $C_{max}$ ) is reached, the system becomes heterogeneous, and the molecules form nuclei (Polte 2015). The nuclei are the product of collisions between ions and molecules of the solution in a process known as autonucleation (stage 2). During this stage, the concentration of salts decreases rapidly from  $C_{max}$  to  $C_{min}$  in the solution, due to the formation of clusters, and the rate of nucleation falls immediately to zero. In stage 3, the cluster gradually increases until it reaches a critical size, and the activation energy for structural fluctuation becomes so high that the cluster eventually becomes locked into a

**Fig. 1** Representation of the principle of nanoparticle nucleation due to LaMer's mechanism of (sulfur) nucleation



well-defined structure called seed. Finally, this seed continues growing to form a nanocrystal, through the addition of metal atoms until the concentration of salts in the solution decreases to a solubility concentration of nanocrystals (Cs) (Polte 2015; Geonmonod et al. 2017).

The application of IONPs in biomedical sciences depends on three factors: morphology, size, and surface properties. During the synthesis, the morphology of the IONPs can be affected by several factors, such as the presence of surfactants (e.g., oleylamine or adamantane amine), concentration of the reactants, reaction temperature, or time (Zhang et al. 2006; Xie et al. 2018). The morphology also can affect the blood circulation time, cellular uptake, and biodistribution. Some studies have been focused on the shape of the nanoparticles for anticancer drug delivery (Jindal 2017; Phuoc et al. 2018). However, the effect of morphology on the biodistribution of IONPs has not been extensively studied. For example, Zhou et al. (2012) synthesized IONPs with different shapes as octahedrons, rods, cubes, wires, and hexagonal plates. The lowest viability (about 70%) of the A549 cells was obtained with the nano-hexagonal plates; nevertheless, the effect of morphology on the cell viability has not been clearly probed yet.

The size of the nanoparticles determines their average circulation time, for example, particles with diameters less than 10 nm are removed by renal clearance, while particles with diameter bigger than 200 nm are concentrated in the spleen or absorbed by the phagocytic cells of the body (Chouly et al. 1996). Nanoparticles with sizes between 10 and 200 nm are ideal for biomedical applications because they have longer circulation times, which ease their elimination and increase the effect of permeability and retention in tumor tissues. In this way, IONPs with diameters less than 2 nm are not suitable for medical uses because they may induce toxic effects that can damage intracellular organelles (Xie et al. 2018; Gupta and Wells 2004).

Therefore, particle size is an important property because it influences the chemical and physical properties of the nanoparticles. For example, when the nanoparticles are used for pharmaceutical and biomedical purposes, the magnetic particles must have a narrow size distribution with small average diameter and high magnetization values (Xie et al. 2018). In addition, they must combine high magnetic susceptibility for optimal magnetic enrichment and loss of magnetization after magnetic field removal (Shan et al. 2016).

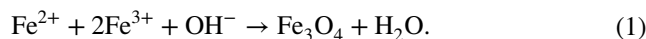
The high surface area of the nanoparticles is related with colloidal stability; meanwhile, high zeta potentials (negative or positive) indicate good dispersion and little agglomeration during storage. Generally, the nanoparticles used in *in vivo* models should avoid the nonspecific adsorption of protein and other biological macromolecules. Also, the IONPs without coating tend to agglomerate due to their high specific surface area and strong inherent magnetic dipole

interactions, facilitating a rapid elimination by reticuloendothelial system (Hu et al. 2018). However, the metabolism of nanoparticles depends on the cell type. On the other hand, the nanoparticles surface charge determines their distribution in the body. Neutral charges interact minimally with the plasma proteins and contribute to the extended circulation time in the body (Reddy et al. 2012). Anionic IONPs efficiently interact with the cells and were internalized by adsorptive endocytosis (Billotey et al. 2003). In contrast, the cell membrane has a slight negative charge and cell uptake is carried out by electrostatic attractions allowing that the IONPs with a positive surface can be taken up at a faster rate (Yew et al. 2018). Hence, the charge and stability of IONPs in the biomedical applications can be improved through surface coating. For example, the particles coated with hydrophilic polymers (polyethylene glycol) can evade reticuloendothelial cells and circulating macrophages, having better therapeutic efficacy (Harris and Chess 2003; Veiseh et al. 2010).

Tombácz et al. (2015) mention 15 bottom-up synthesis procedures for IONPs including coprecipitation, thermal decomposition, microemulsion, hydrothermal, and solvothermal synthesis, among others not included in this review. The IONPs synthesized with these methods allow the control of their size and shape, increasing their stability, solubility, and biocompatibility (Wu et al. 2008). This review presents an overview of the most common methods of synthesis, highlighting the advantages and disadvantages of each method.

## Coprecipitation

This is one of the most used methods in the synthesis of IONPs. Generally, it is carried out by a stoichiometric mixture of ferric and ferrous salts in aqueous solution, followed by the addition of a base (NaOH, KOH, NH<sub>4</sub>OH) at elevated or environmental temperature. IONPs are produced by dehydration of iron hydroxide intermediates (Eq. 1) forming a precipitate. Thus, IONPs contain many OH<sup>-</sup> groups on the surface, favoring a good suspension in aqueous media (Daou et al. 2006; Liang et al. 2006; Fernandes et al. 2017). Another mechanism of formation includes the oxidation of Fe(OH)<sub>2</sub> to FeOOH by oxygen. Fe<sub>3</sub>O<sub>4</sub> is formed by the union of Fe(OH)<sub>2</sub> and FeOOH (Olowe et al. 1989; Refait and Génin 1993).



Some authors have reported that the size, morphology, and composition of the IONPs depend on the type of salt used, reaction temperature, pH, and ionic strength of the medium (Bee et al. 1995; Kim et al. 2001, 2003). The main advantage of the method is the high yield of nanoparticles.

Moreover, the conditions for coprecipitation synthesis are simple and with an easy scale-up possibility. This method has been approved as contrast agent for MRI by Food and Drug Administration (FDA) (Vangijzegem et al. 2018). In contrast, it is difficult to control the particle size distribution due to the agglomeration of the nanoparticles (Lu et al. 2007).

During the synthesis, the concentration of species reaches a critical supersaturation and a brief explosion of the nuclei occurs. In addition, the nuclei grow slowly by diffusion of the solutes (Bitar et al. 2014). The agglomeration can be prevented during the growth stage using surfactants as dodecylbenzene sulfonic acid sodium salt (NaDS), oleic acid, and Tween 80 (Dong-Lin et al. 2006; Wang et al. 2011).

### Thermal decomposition

This method consists of the chemical decomposition of organometallic compounds at a high temperature. In the process, oxidation with organic solvents and surfactants is carried out (Tombácz et al. 2015). The organometallic precursors for thermal decomposition include acetylacetonates, cupferronates, or carbonyls (Lu et al. 2007). Surfactants such as oleic acid, 1-octadecene, or hexadecylamine slow down the nucleation process and favor the formation of spherical nanoparticles with diameters < 30 nm (Sun et al. 2014; Wu et al. 2015a, b).

The type of surfactants, temperature, and reaction time are factors that have an impact on the size and morphology of the nanoparticles, so thermal decomposition allows good control of the size and shape of IONPs (Sheng-Nan et al. 2014). However, the main disadvantage of this method is the use of toxic organic solvents that can chemically bond to the nanoparticles, which limit their use for biological applications (Tombácz et al. 2015).

### Hydrothermal and solvothermal synthesis

This method requires high temperatures (130–250 °C) and high vapor pressures (0.3–4 MPa). For this synthesis, Fe<sup>3+</sup> salts are precursors that are mixed with acetates, urea, and sodium citrate in aqueous solutions or organic solvents. This homogeneous dispersion is transferred into the autoclave and heated at 200 °C for 8–24 h (Hu et al. 2008; Ji et al. 2012; You et al. 2012).

The size and shape of the nanoparticles can be controlled by modifying parameters such as temperature, pressure and reaction time achieving sizes of 10–200 nm. Moreover, this method allows the obtaining of nanoparticles of excellent quality for drug delivery systems (Lima et al. 2015; Shen et al. 2018). However, low yields are obtained in comparison with the method of coprecipitation or thermal decomposition (Frimpong and Hilt 2010; Yadollahpour 2015). Also,

the synthesis time is longer (from hours to days) compared with the microemulsion method, and the IONPs obtained with the hydro or solvothermal method have larger particle diameters, affecting their application in drug delivery systems (Wu et al. 2015a, b; Shen et al. 2018).

### Microemulsion

Microemulsions consist of three components: polar phase (water), nonpolar phase (oil), and surfactant. There are two types of microemulsions: direct (oil dispersed in water, o/w) and reverse (water dispersed in oil, w/o) which have been used for the synthesis of IONPs. In this method, the aqueous phase contains metal salts and other precursors, while the oil phase contains a mixture of different hydrocarbons and olefins (Wu et al. 2015a, b). The precipitation of the particles occurs in nanodrops which act as nanoreactors. In this way, the nucleation and growth of the nanoparticles can be controlled (Malik et al. 2017).

The interface of the nanodrops contains surfactants acting as size filters. Therefore, the size of the IONPs can be controlled by drop size, initial concentration of reagents, and the nature of the surfactant (Zhou et al. 2011; Foroughi et al. 2016). The nanoparticles obtained have homogeneous shapes and sizes that can be easily controlled, in addition to having high magnetic saturation. Besides, low yields are obtained in comparison with the coprecipitation method, and the purification of the nanoparticles is complicated due to the nature of the surfactants (Yadollahpour 2015; Najafi and Nematipour 2017).

### Ultrasound-assisted methods

This method uses ultrasound waves of high intensity, which form microbubbles. In these conditions, bubbles overgrow and collapse releasing energy in short times (heating and cooling rate of > 10<sup>10</sup> K s<sup>-1</sup>) facilitating IONPs synthesis (Ali et al. 2016; Wu et al. 2015a, b). On the other hand, ultrasound waves allow a homogenous mixture of precursors, reduce the growth of crystals and increase the reaction rate. However, the shape and dispersity of the IONPs are not easy to control (Wu et al. 2015a, b).

### Microwave-assisted methods

The shape and size of IONPs can be controlled by microwaves (Ai et al. 2010; Hu et al. 2007). For example, Sreeja and Joy (2007) obtained  $\gamma$ -Fe<sub>2</sub>O<sub>3</sub> nanoparticles with a diameter of 10 nm at 150 °C for 25 min showing the lowest reaction time compared with others. In contrast, the uniform heat of a microwave oven causes shorter crystallization time and homogeneous nucleation (Ali et al. 2016).

## Green synthesis

Green synthesis uses 'bottom-up' techniques to form nanoparticles, which are produced with eco-friendly products. This method consists of mixing precursor salts with a green substrate containing biological compounds. These compounds act as reducing and limiting agents which can stabilize the nanoparticles during the synthesis process (Fig. 2). The concentration of precursor salt, concentration of green substrate, time, temperature, and pH are parameters that can be modified during the synthesis to obtain nanoparticles with different properties and applications (Yew et al. 2018).

For example, El-Kassas et al. (2016) used *Padina pavonica* and *Sargassum acinarium* (seaweeds) aqueous extracts in a coprecipitation method obtaining IONPs with sizes between 10 and 20 nm which were used for lead bioremediation. Furthermore, the leaf extract of *Sesbania grandiflora*

is a good source of phenolic compounds and has been used in the synthesis of iron oxide and zinc nanoparticles with sizes between 25 and 60 nm demonstrating catalytic activity (Rajendran and Sengodan 2017). Bahadur et al. (2017) used lemon juice in the coprecipitation method, obtaining nanoparticles with sizes between 11 and 15 nm.

The IONPs synthesized by this method can be used in biomedical applications due to a coating formed of the biological compounds of the green substrate which is not toxic and biocompatible. Also, the generated IONPs can be linked with drugs, enzymes or proteins that can be targeted to specific tissues, organs, or tumors with the help of an external magnetic field or could be heated in alternating magnetic fields for hyperthermia treatment (Yew et al. 2018).

Table 1 summarizes the advantages and disadvantages of the above-mentioned synthetic methods. The coprecipitation method is the preferred route in biomedical applications.

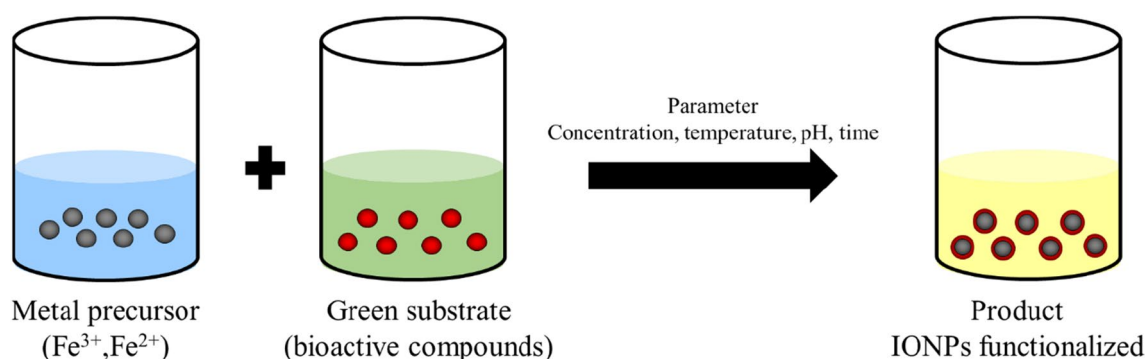


Fig. 2 Green synthesis of IONPs

**Table 1** Advantages and disadvantages of the methods for the synthesis of iron oxide nanoparticles (IONPs)

Synthetic method	Advantages	Disadvantages
Coprecipitation	High production yield of nanoparticles The conditions for synthesis are simple and with an easy scale-up possibility The nanoparticles synthesized with this method have been approved as contrast agent by FDA	The control of the size distribution is difficult to achieve due to the agglomeration of the nanoparticles
Thermal decomposition	The control in the size and morphology is easy to achieve	The use of toxic organic solvents limits their use for biological applications
Hydrothermal and solvothermal synthesis	The shape and size can be easily controlled The IONPs show a high magnetic saturation	Low production yield of IONPs compared with other methods The synthesis time is longer (from hours to days)
Microemulsion	The shape and size can be easily controlled The IONPs show a high magnetic saturation	The purification of IONPs is complicated due to the nature of the surfactants Low production yield of IONPs
Ultrasound-assisted methods	This method reduces the growth of crystals and increases the reaction rate	The shape and size of IONPs are difficult to control
Microwave-assisted methods	The shape and size of IONPs can be controlled The reaction time decreases	Shorter crystallization time and homogeneous nucleation
Green synthesis	The most of green substrate used in this synthesis is not toxic and biocompatible	The negative effects produced by green substrate have not been widely studied

However, other methods (as microemulsion or solvothermal) have been used for the synthesis of IONPs for cancer treatment and diagnosis.

### Stability and functionalization of IONPs

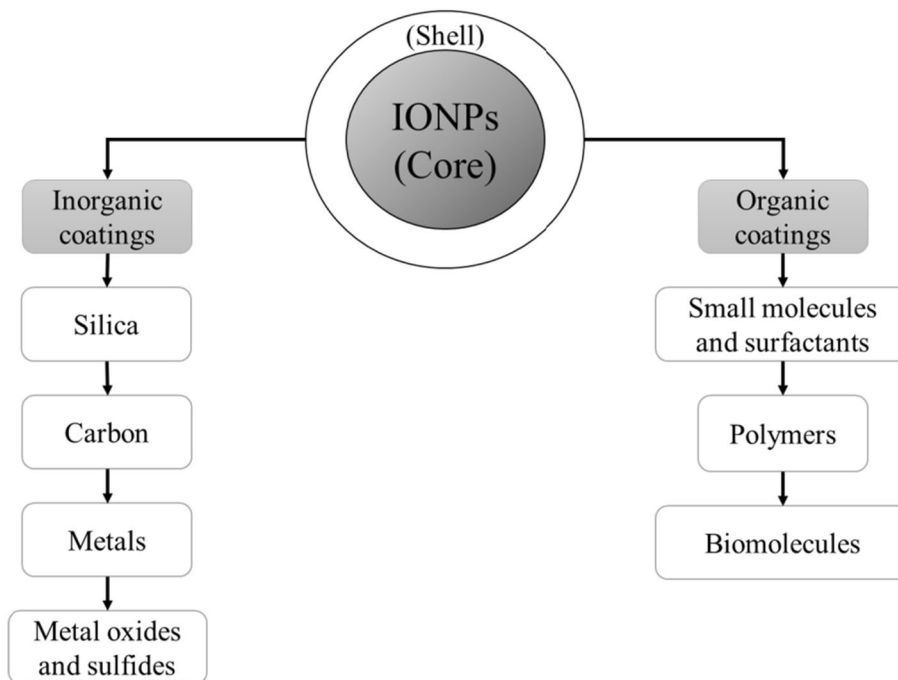
The magnetism of IONPs causes intrinsic instability due to agglomeration, forming large particles. In biological systems, the agglomerated nanoparticles are rapidly eliminated by the endoplasmic reticulum. Nevertheless, agglomeration can increase the content of Fe ions causing toxicity in the organism (Hui et al. 2011). In addition, IONPs are easily oxidizable by the oxygen of the environment which provokes a significant reduction of their magnetism and dispersibility (Wu et al. 2015a, b; Shen et al. 2018). According to this, it is necessary to develop biofunctional coatings in IONPs to improve its dispersibility in water, protect therapeutic agents against degradation, and play a significant role in biokinetics and biodistribution of IONPs in the organism (Ali et al. 2016; Fernandes et al. 2017).

In core–shell nanosystems, the IONPs represent the core, and the shell corresponds to the surface coating for nanoparticle functionalization. For biomedical applications, the core–shell nanosystems can be linked to different classes of drugs which are bound by adsorption, dispersion in the polymer matrix, encapsulation in the nucleus, electrostatic interactions and covalent attachment to the surface (Arias et al. 2018). Moreover, these core–shell systems could be functionalized with natural compounds showing potential activity for cancer diagnosis and treatment. There are two types of functional coatings for IONPs: organic and inorganic (Fig. 3). Table 2 summarizes the advantages of the organic and inorganic coatings in IONPs.

### Organic coatings

For biological applications, organic coatings increase the dispersibility and biocompatibility of IONPs and have been used for specific drug targeting and magnetic separation of cells. Several methods (in situ and post-synthesis) have been developed to produce organic coatings for IONPs (Wu

**Fig. 3** Inorganic and organic coatings of IONPs



**Table 2** Advantages of the methods for the organic and inorganic coatings of iron oxide nanoparticles

Coating	Advantages	References
Inorganic	Prevents the agglomeration and facilitate the functionalization with other molecules Improves the biocompatibility, hydrophilicity, and stability	Luo et al. (2017), Ga et al. (2017)
Organic	Can generate water-soluble, oil-soluble, or amphiphilic nanoparticles, depending on the type of organic molecule or surfactant used Polymers and biomolecules improve biocompatibility and bioavailability	Jiao et al. (2016)

et al. 2015a, b). Organic coatings can be classified into three groups: (1) small molecules and surfactants; (2) macromolecules and polymers; and (3) biological molecules (Ghazanfari et al. 2016).

### Small molecules and surfactants

Surfactants improve the stability, dispersibility, and biocompatibility of IONPs. Also, they can be used as a coating and according to their nature, are divided into three subclasses: oil-soluble surfactants, water-soluble surfactants, and amphiphilic (Ghazanfari et al. 2016).

Oil-soluble surfactants contain hydrophobic groups and are used in oily solutions increasing stability and preventing agglomeration (Morsy 2014). During the synthesis of IONPs, surfactants such as oleic acid and oleamine are used by their C18 chain containing a double bond type *cis* in the middle, which can improve the stabilization of the nanoparticles (Wu et al. 2008). The nanoparticles coated with this kind of materials, can be used in various applications as an MRI contrast agent and as drug transporter in specific drug delivery systems (Ghazanfari et al. 2016; Gupta and Gupta 2005).

Water-soluble surfactants convert hydrophobic nanoparticles into hydrophilic. Silanes are the most used coatings in IONPs which increase dispersibility, stability, and solubility in water (Palma et al. 2007). In addition, silanes can be linked with metal ions, polymers, biomolecules or other biological compounds. 3-Aminopropyltriethoxysilane (APTES), paminophenyltrimethoxysilane (APTS), and mercaptopropyltriethoxysilane (MPTES) are the most common used silanes which increase the water solubility of hydrophobic IONPs and can be linked with groups  $-\text{NH}_2$  and  $-\text{SH}$  (Wu et al. 2015a, b).

For example, Kandasamy et al. (2018) reported the synthesis of hydrophilic IONPs in situ functionalized with short-chained surface coating molecules (with a minimum of two carboxyl functional groups), the nanoparticles synthesized could be used as effective nanomedicines for cancer treatments. Furthermore, Zhao et al. (2016) performed a multilayer structure with  $\text{Fe}_3\text{O}_4$ ,  $\text{WO}_3$ , and (3-aminopropyl) triethoxysilane. IONPs were synthesized through thermal decomposition and were used to deliver and controlled release of VP16 through microwave irradiation.

### Polymers

Polymers like polyethylene glycol (PEG), polyvinyl alcohol (PVA), polymethyl methacrylate (PMMA), and polylactic acid (PLA) have been the most studied coatings. The polymers generate electrostatic forces of repulsion and steric effects avoiding agglomeration of the particles (Fernandes et al. 2017; Ghazanfari et al. 2016). Also, coatings with

intelligent polymers have been performed, which respond to a certain stimulus such as pH, temperature, light, etc. (Zhang et al. 2008). In addition, the development of functionalized IONPs with amphiphilic copolymers is of great interest due to the incorporation of more functional groups that can lead to multiple applications (Zhu and Hayward 2008). However, the presence of polymers can affect the magnetic properties of IONPs in some cases (Wu et al. 2015a, b). Those features could be associated to changes in the particle size distribution, particle interactions or spin canting (Costo et al. 2015).

Natural polymers (dextran, chitosan, gelatin, and starch) are widely used in the synthesis of nanoparticles for cancer treatment. These compounds act as stabilizers during the synthesis procedure to enhance the stability, biocompatibility, and biodegradability (Barrow et al. 2015; Ebrahimi 2016). For example, Avazzadeh et al. (2017) functionalized IONPs with dextran-spermine for the treatment of breast cancer by hyperthermia. The results confirmed the ability of nanoparticles in targeting cancer cells and heating them up to hyperthermia range, while more than 63% of cancer cells were destroyed over a 20-min treatment course. As well, Nguyen (2017) used gelatin for IONPs coating, these nanoparticles were synthesized by the coprecipitation method and functionalized with paclitaxel showing a steady and sustained release profile in vitro up to 5 days. Hence, the paclitaxel loaded in  $\text{Fe}_3\text{O}_4@\text{GEL}$  nanoparticles may serve as stable delivery systems with dual therapeutic effects (hyperthermia combined with chemotherapy) for cancer therapy.

### Biomolecules

The IONPs functionalized with biomolecules (enzymes, antibodies, proteins, biotin, human/bovine albumin, avidin, polypeptides, among others) are highly biocompatible. Generally, the IONPs used in biological applications have been functionalized with surfactants or functional groups such as carboxyl or hydroxyl (Ghazanfari et al. 2016). Also, IONPs can be functionalized through green synthesis (Yew et al. 2018). For example, Wu et al. (2015a, b) used glucose in the coprecipitation method, obtaining IONPs with average sizes of 20 nm, which were used for targeted hyperthermia of cancer cells. Another compound recently used for green synthesis and for the coating of IONPs with sizes of 15–30 nm is nanocellulose from *Aloe vera*, which additionally showed antibacterial activity (Moniri et al. 2018).

### Inorganic coatings

Inorganic materials possess numerous properties such as high electron density and optical absorption (Au and Ag), photoluminescence (CdSe or CdTe), phosphorescence (metal oxides such as  $\text{Y}_2\text{O}_3$ ), and magnetic moment (cobalt or manganese nanoparticles). In biological applications,

inorganic coatings are used to link biological compounds at the surface of IONPs and to increase their antioxidant properties (Kudr et al. 2017; Ghazanfari et al. 2016; Drmota et al. 2012).

### Silica

Silica coatings show high dispersibility, stability, and protection of IONPs in an acidic medium (Wu et al. 2015a, b). Also, silanol groups in the silica layer allow the incorporation of small molecules such as dyes, drugs, or quantum dots. Generally, silica coating is performed by alkaline hydrolysis with tetraorthosilicate (TEOS) in the presence of IONPs (Lieberman et al. 2014). For example, Moorthy et al. (2016) developed IONPs through the solvothermal method and the particles were functionalized with TEOS and aminopolyglycidol which is used for magnetic hyperthermia, drug delivery, and bioimaging analysis. Another reported method for silica coating consisted of the synthesis of IONPs by the solvothermal method and their functionalization with TEOS, which was used as a binding agent for ibuprofen and was tested in vitro for drug delivery (Uribe-Madrid et al. 2015).

### Carbon

Carbon coatings prevent oxidation and corrosion of the magnetic core. In addition, hydrophilic carbon coating improves dispersibility and stability (Bae et al. 2012). Song et al. (2017) synthesized IONPs by coprecipitation which were functionalized with graphene oxide, lactoferrin, and doxorubicin hydrochloride, and these nanoparticles showed high efficacy for targeted delivery of anticancer drugs to brain tumors. Besides, Cui et al. (2017) functionalized IONPs with graphene oxide, oleic acid, folic acid, and chitosan, these nanoparticles were non-toxic to A549 cells and showed excellent biocompatibility.

### Metals

Metal nanoparticles have been used in catalysis, MRI contrast agents, medicine, and cancer diagnosis. These materials can be combined with IONPs showing diverse properties (Wu et al. 2015a, b). Some coatings used are gold, silver, copper, platinum, palladium, among others. In addition, these structures can be modified with different charges or functional groups on the surface of IONPs improving their stability and compatibility (Ghazanfari et al. 2016). For example, Leon-Felix et al. (2018) reported the obtention of IONPs functionalized with poly(ethylenimine) and gold; these particles showed very low cytotoxicity and provided an interesting multifunctional nanoplatform for bimodal application of light and magnetic hyperthermia. Nassireslami and Ajdarzade (2018) used the microemulsion method for the

synthesis of IONPs which were functionalized with gold and an aptamer for targeting breast cancer cells.

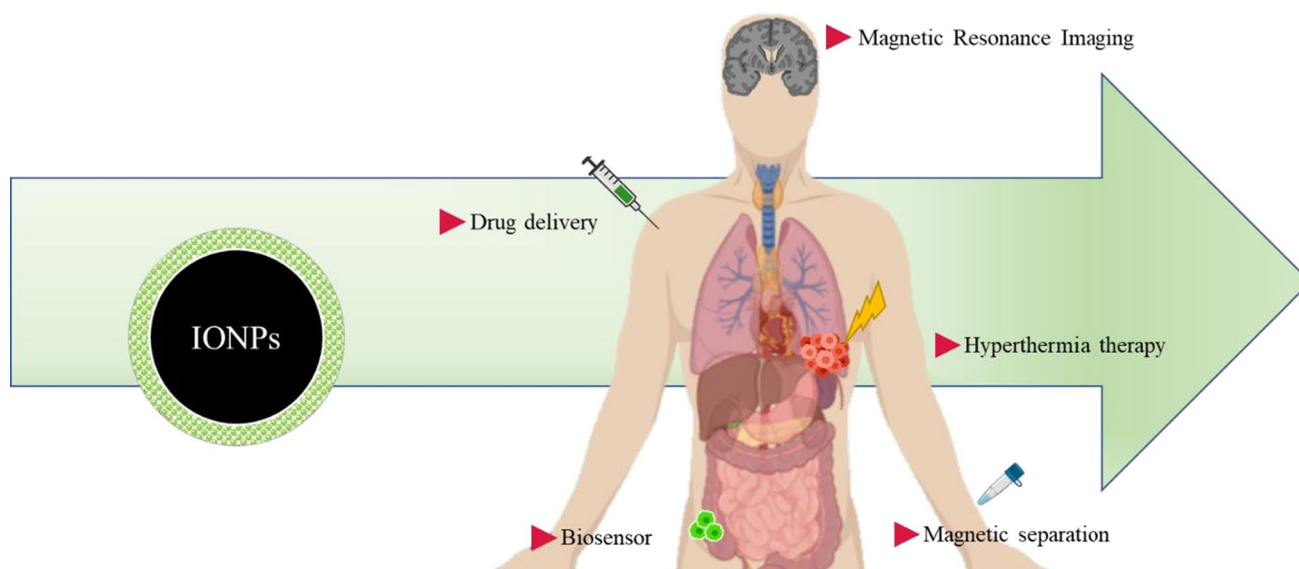
### Metal oxides and sulfides

Metal oxides (ZnO, SnO, TiO<sub>2</sub>, ZrO<sub>2</sub>, and WO<sub>3</sub>) improve stability and increase the generation of heat by IONPs in hyperthermia treatment. In addition, IONPs can be coated with metal sulfides (ZnS, CdS, PbS and Bi<sub>2</sub>S<sub>3</sub>) improving their magnetic and fluorescent properties (Wu et al. 2015a, b; Ghazanfari et al. 2016). As an example, Xu et al. (2010) synthesized IONPs functionalized with silica and CdSe/ZnS by thiol coordination. These particles were successfully utilized to induce apoptosis in pancreatic cancer cells by using radiofrequency electromagnetic radiation.

### Applications

The most used biomedical applications include magnetic separation, targeted drug delivery, magnetic resonance imaging (MRI), magnetic fluid hyperthermia and thermoablation and biosensing (Fig. 4) (Kudr et al. 2017). MRI has a strong influence on the early diagnosis of cancer, and superparamagnetic IONPs are the most representative as a contrast agent for MRI (Zhou and Wei 2017). The small size and large specific surface area of IONPs allow its use as a drug carrier for drug delivery. Thus, the magnetism of IONPs facilitates the location of the lesion through the application of an external magnetic field (Wu and Huang 2017). On the other hand, the magnetism of IONPs allows clinicians to produce a localized thermo-ablative effect leading to the destruction of bacterial biofilms and cancer cells (Williams 2017). As mentioned before, IONPs can be linked with drugs and their biomedical applications have been widely studied. However, natural compounds from plants may also be linked to nanosystems and applied in treatment and diagnosis of cancer which could improve their absorption and elimination in the organism. Additionally, many of these natural products show less toxicity and better tolerance in normal cells compared with chemotherapeutic drugs. But, the use of phytochemicals in humans has not been applied successfully due to the inefficient delivery of promising natural agents to the target site. This could be associated with their poor solubility and chemical stability in the biological environment (Wei et al. 2019). These coating modifications can offer synergic multifunctional applications allowing them to achieve multimodal imaging, and simultaneous diagnosis and therapy. Moreover, the use of IONPs can improve the biodistribution and chemical stability of phytochemicals. Table 3 summarizes some biological applications for IONPs using natural compounds from plants.





**Fig. 4** Biomedical applications of iron oxide nanoparticles

### Magnetic resonance imaging

MRI has been used as a contrast technique in soft tissues, nevertheless, the continuous development of magnetic nanoparticles as contrast agents has made possible the improvement of the quality of the images helping to detect potential diseases at an earlier stage. For example, Malekzadeh et al. (2017) synthesized IONPs by coprecipitation and were functionalized with polymers, folate groups and quercetin (cell receptors). The particles were used as a contrast agent and reduced the growth of HeLa and MDA-MB-231 cells more than IONPs free of quercetin. In addition, these nanoparticles demonstrated a high cytocompatibility (> 80%) with control cells using concentrations of 25–100  $\mu\text{g mL}^{-1}$  demonstrating a good biocompatibility. Furthermore, Ghorbani et al. (2018) synthesized IONPs by coprecipitation, which were functionalized with gold, curcumin (natural anticancer agent), lipoic acid (neuroprotective agent) and glutathione (cell receptor). These nanoparticles could be used as contrast agent due to low cytotoxicity (39%) in normal astrocytes. In contrast, the results indicate a growth reduction of U87MG cells (63%) after 48 h of treatment when a concentration of 100  $\mu\text{g mL}^{-1}$  was used.

### Drug delivery

Functionalized IONPs can be loaded with various drugs, administered to humans by injection into blood capillary and released in a specific area (cancer cells or tumor) increasing the efficiency in the treatment of cancer cells without damaging neighboring healthy cells (Lungu et al. 2019). For example, Ghosh et al. (2015) obtained IONPs through inverse

coprecipitation and used citric acid to link it with diosgenin present in *Dioscorea bulbifera*, these nanoparticles induced apoptosis and prevented the proliferation of breast cancer cells more than IONPs without coating. Also, the incorporation of diosgenin in IONPs inhibited the aggregation and particle growth, thereby increasing the stability. Pham et al. (2016) fabricated IONPs by microemulsion using chitosan and curcumin as coating agents. These particles showed maximum inhibition of A549 cells using 73.03  $\mu\text{g mL}^{-1}$ . Moreover, the curcumin adsorbed to IONPs showed up to 70% of drug release after 2800 min, which could be a good drug delivery carrier for cancer therapy. Barahuie et al. (2016) synthesized IONPs by coprecipitation which were functionalized with chitosan and phytic acid (natural component of seeds and cereals) inhibiting the proliferation of cancer cells in the colon without causing damage to normal fibroblast cells. Besides, the results showed that the percent release of drug from the nanocomposite reached 93% within 56 h when exposed to a pH environment of 4.8 and 86% in 127 h at pH 7.4, demonstrating a good anticancer activity compared with pure phytic acid. On the other hand, Nosrati et al. (2017) used coprecipitation for IONPs synthesis and were coated with bovine serum albumin and curcumin showing a high cytocompatibility ( $\geq 90\%$ ) in HFF-2 cells after 72 h using concentrations of 15–950  $\mu\text{M}$ . Furthermore,  $\text{IC}_{50}$  values of these nanoparticles at 72 h and 96 h were 915 and 275  $\mu\text{M}$  respectively versus those of free curcumin (730 and 300  $\mu\text{M}$ ). Hence, the IONPs coated with bovine serum albumin and curcumin showed an improved cytotoxicity against MCF7 cells.

Essa et al. (2017) used IONPs functionalized with polyphenolic compounds from *Vitis vinifera* developing potent

**Table 3** Application of iron oxide nanoparticles (IONPs) synthesized using different materials for functionalization

Synthesis method	Materials of functionalization	Application of IONPs	References
Coprecipitation	Polymers, folate group, and quercetin	The nanoparticles were used as a contrast agent and showed cytotoxicity in HeLa and MDA-MB-231 cells	Malekzadeh et al. (2017)
	Gold, curcumin, lipoic acid, and glutathione	The nanoparticles demonstrated their application as a contrast agent and showed cytotoxic effects against U87MG cells	Ghorbani et al. (2018)
	Citric acid and diosgenin from <i>Dioscorea bulbifera</i>	The nanoparticles induced apoptosis and prevented the proliferation of breast cancer cells	Ghosh et al. (2015)
	Chitosan and phytic acid	The nanoparticles inhibited the proliferation of cancer cells in the colon	Barahuie et al. (2016)
	Bovine serum albumin and curcumin	The nanoparticles showed cytotoxicity in MCF7 cells	Nosrati et al. (2017)
	<i>O</i> -Carboxyl methyl chitosan, curcumin, and folate	The nanoparticles presented a good distribution in of tumor cells	Huong et al. (2016)
	Alkali lignin from corn cob and resveratrol	The nanoparticles demonstrated anticancer effects and antitumor effect	Dai et al. (2017)
	<i>trans</i> -Resveratrol	The nanoparticles avoided the proliferation of cancerous cells	Sallem et al. (2019)
Green synthesis	Polyphenols from <i>Vitis vinifera</i>	The nanoparticles presented cytotoxic effects against L20B cells	Essa et al. (2017)
	Polyphenols, proteins and reducing sugars from <i>Couroupita guianensis</i>	The nanoparticles demonstrated cytotoxicity in HepG2 cells	Sathishkumar et al. (2017)
	Polyphenols from cinnamon and vanilla	The nanoparticles were used in hyperthermia treatment, affecting BV-2 cells	Ramirez-Nuñez et al. (2017)
	Seed at extract of <i>B. flabellifer</i>	The nanoparticles demonstrated high biocompatibility improving their therapeutic properties	Sandhya and Kalaiselvam (2020)
Solvothermal	Polyethyleneimine, gold, epigallocatechin	The nanoparticles showed efficient for hyperthermia therapy, drug delivery, and accurate MRI	Yin et al. (2017)
Microemulsion	Chitosan and curcumin	The nanoparticles demonstrated inhibition of A549 cells	Pham et al. (2016)

cytotoxic effects against L20B cells at concentrations of 10 and 5 mg L<sup>-1</sup> causing inhibition of 70.8 and 57.5%, respectively. In addition, these nanoparticles showed antiinflammatory, antimitotic and antioxidant activity. Sathishkumar et al. (2017) synthesized IONPs by coprecipitation which were functionalized with *Couroupita guianensis* extract. These nanoparticles proved a cytotoxicity effect at a minimal dosage of 44.5 L µg mL<sup>-1</sup> against HepG2 cells comparatively with the pure extract which used a minimal dosage of 120 µg mL<sup>-1</sup>. Sallem et al. (2019) used coprecipitation for IONPs synthesis and these nanoparticles were coated with *trans*-resveratrol (a natural antioxidant molecule found especially in peanuts, grapes, and wine). These nanoparticles avoided the proliferation of cancerous cells after incubation for 24 h using a concentration of 50 µM. Another application has been reported by Dai et al. (2017). They incorporated IONPs functionalized with resveratrol to nanoparticles of alkali lignin, recovered from corn cob. These nanoparticles

demonstrated anticancer effects on LLC and A549 showing a cell viability < 25% after 72 h at a concentration of 20 mmol L<sup>-1</sup>. Besides, these nanoparticles displayed antitumor effect in LLC tumor/bearing mice. Recently, Sandhya and Kalaiselvam (2020) synthesized IONPs through green synthesis using the seed coat extract of *B. flabellifer*, these nanoparticles exhibited a high cytocompatibility (> 80%) with NIH 3T3 cells at concentrations of 50–500 µg mL<sup>-1</sup> and could increase their biocompatibility, improving their therapeutic properties. Moreover, these nanoparticles showed efficient antimicrobial and antioxidant activity.

### Hyperthermia treatment

Magnetic hyperthermia consists of heat generation through the application of an alternating or external magnetic field on magnetic nanoparticles. In ferromagnetic or ferrimagnetic materials of multiple domains, heat production occurs

through the losses of the magnetic field by hysteresis (Carrey et al. 2011). Hysteresis depends on the strength in an applied magnetic field. Also, the size and nature of the magnetic nanoparticle influence in the hyperthermia properties (Hergt et al. 2008).

Balivada et al. (2010) demonstrated the thermoablative effect caused by IONPs and reported a temperature increase of 11–12 °C in C57/BL6 mice. Additionally, they increased the IONPs concentration (5–25  $\mu\text{g mL}^{-1}$ ) proving that the number of viable tumor cells decreased (approximately from 480,000 to 150,000). Other studies have demonstrated the efficacy of magnetic hyperthermia as an alternative treatment for cancer (Balivada et al. 2010; Yanase et al. 1998a, b; Jordan et al. 2006). In the initial work of Yanase et al. (1998b), cationic liposomes were used, based on magnetization for brain gliomas in F344 rats, decreasing the volume of the tumor (from 30,377 to 2684  $\text{mm}^3$ ) with three rounds of treatment. However, a test group did not respond to the treatment due to metastasis in multiple sites, application of magnetic hyperthermia could be technically more demanding.

Delivery drugs can be combined with hyperthermia, which is the best way to reduce the temperature. Temperature-sensitive pharmaceutical formulations have been extensively investigated and explored in oncology (Mura et al. 2013; Tagami et al. 2011). Furthermore, hyperthermia can be combined with the release of phytochemicals. For example, Huong et al. (2016) used coprecipitation for IONPs synthesis and were coated with folate and curcumin, these nanoparticles allowed a good biodistribution in sarcoma-180 solid tumor-bearing mice, concluding that IONPs functionalized with folate and curcumin could be effective against tumor cells. Also, the nanoparticles at concentration of 0.3  $\text{mg mL}^{-1}$  or higher, enabled to reach a temperature of 42 °C in 10 min for hyperthermia treatment. Ramirez-Nuñez et al. (2017) used green synthesis of IONPs by coprecipitation using separately the polyphenols extracted from cinnamon and vanilla as both, reducing agents and functional coatings. These nanoparticles were used in an in vitro model of hyperthermia, causing an 88% reduction of the BV-2 cells after 30 min. On the other hand, epigallocatechin gallate is a phytochemical that has a strong anticancer effect and has been used in the solvothermal method for the synthesis of IONPs (Yin et al. 2017). These nanoparticles have been efficient for hyperthermia therapy, drug delivery, and accurate MRI in tumor-bearing mice. In addition, their results demonstrated that the major organs as heart, liver, spleen, lung, and kidney, in all experiment groups, showed no significant toxicity compared with the control group.

## IONPs toxicity

Iron ions have different roles in the physiological process such as DNA synthesis, oxygen transportation, mitochondrial respiration, heme synthesis, and metabolic functions at the central nervous system level. In contrast, the toxicity of IONPs involves the generation of reactive oxygen species (ROS) which affects the macromolecules and organelles of the cells (Yarjanli et al., 2017). This process occurs as follows:  $\text{Fe}^{2+}$  ions react with  $\text{H}_2\text{O}_2$  generating ROS (Fenton reaction). Then, the high concentration of ROS causes a cascade of events as the release of more iron ions and detrimental effects on the lysosomal membrane; lipid peroxidation, damage of proteins, break of DNA chains and degradation of bases, mutations, deletions or translocations at the nuclear level. Also, the concentration of iron ions facilitates apoptosis via mitochondria. On the other hand, iron accumulation contributes to neurodegenerative diseases due to protein aggregation such as  $\text{A}\beta$  and  $\alpha$ -synuclein (Yarjanli et al. 2017; Niu et al. 2019). However, the toxicity of IONPs depends on the size, concentration, surface charge, and the functional groups in the coating (Arias et al. 2018; Ansari et al. 2017). As mentioned before, the incorporation of phytochemicals from plants in IONPs can improve their solubility and chemical stability. Also, the functionalized nanoparticles present a high cytotoxicity in cancer cells compared with normal cells. However, toxicity is the main reason hindering the biological application of nanomaterials. For example, Yin et al. (2017) performed a biotoxicity assay in bearing mice which were sacrificed and their major organs, such as the heart, liver, spleen, lungs, kidneys, and tumor were analyzed with H&E (hemotoxylin and eosin) staining. The results demonstrated that the major organs, in all experiment groups, showed no significant toxicity compared with the control group. Nevertheless, Ghorbani et al. (2018) carried out a hemolysis assay where the IONPs functionalized with curcumin developed a lower hemolytic activity compared with the IONPs free of curcumin which can be explained by the negative charge of the surface. Furthermore, they performed a complement and platelet activation assay to evaluate hypersensitivity reactions and the generation of thrombosis. The IONPs functionalized with curcumin are less prone to cause complement activation and impeded platelet activation. Another study has been reported by Dai et al. (2017) showing an extremely low hemolytic activity (<5%) in lignin coated with IONPs and resveratrol which could be associated with the lower capability for membrane damage by the presence of lignin. Moreover, they used an indicator for hypersensitivity response demonstrating no significant change in comparison with the control group. Hence, these nanoparticles have demonstrated to possess good biocompatibility. Despite the numerous applications of

IONPs functionalized with natural compounds from plants, enough information is not available on their potential toxicity and degradation in the organism.

## Conclusions

The synthesis and functionalization of Fe<sub>3</sub>O<sub>4</sub> nanoparticles is a promising first step in ecofriendly-based low-cost synthesis routes. Iron oxide nanoparticles have demonstrated to possess a high potential as adjuvants in cancer therapy and diagnosis. Iron oxide nanoparticles not only can be used as nanodrug carriers for cancer treatment, but also, they can be guided to a specific region of the organism through an external magnetic field, showing a great variety of applications in the biomedical related fields. The great diversity of functionalized Fe<sub>3</sub>O<sub>4</sub> nanoparticles contributes to the development of more selective synthesis and functionalization methods. Despite some booming works about the synthesis of iron oxide nanoparticles, the methods used for their preparation still need to be improved to achieve a better control of their desirable physicochemical and bio-functional properties. In this sense, the functionalization of IONPs is the most crucial stage to avoid toxic effects in biomedical applications, since the magnetic saturation, size, shape, surface charge, colloidal stability, drug loading capacity, and release behavior are features that must be taken into consideration when selecting iron oxide nanoparticles for their applications in diagnosis and treatment of cancer. The incorporation of natural compounds from plants in IONPs has demonstrated to improve the biocompatibility in living organisms and promise a wide potential in cancer diagnosis and treatment. Regardless of recent works have demonstrated excellent results in the obtention of eco-friendly iron oxide nanoparticles, future research of IONPs functionalized with phytochemicals must be focused on their toxicity and degradability through in vivo tests.

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## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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