Chapter 3
Iron Oxide-Based Nanozymes and Their Applications

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Abstract In the past ten years, interest in nanozymes, which are nanomaterials with inherent enzyme-like capabilities, has skyrocketed because of their potential to overcome the drawbacks of conventional enzymes, such as their low stability, high cost, and difficult storage. Iron oxide-based nanozymes, among other forms of nanozymes, have magnetic properties (superparamagnetic), are biocompatible, and are stable. Iron oxide-based nanozymes are frequently used for many biomedical applications because of the aforementioned features. The basic concepts of iron oxide-based nanozymes and their biological applications are the main emphasis of this chapter. Also briefly covered are recent findings and the outlook for iron oxide-based nanozymes.

Keywords Iron oxide · Nanozymes · Biomedical applications · Nanotechnology

3.1 Introduction

The manipulation, study, and comprehension of material properties at the nanoscale level are the focus of nanotechnology. One nanometer (nm) is one billionth of a meter (m). Over the past 20 years, interdisciplinary fields inspired by nanotechnology and nanoscience have made contributions to chemistry, physics, material science, and biomedical sciences [1–5]. The Nanotechnology Revolution aided in the creation of an environment that allowed chemists and other specialists in the fields of physics, biology, and engineering to cooperate until they reached a point of

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collaboration with material and industrial scientists, allowing scientists and specialists in all fields to advance their research quickly [6–8]. Over the last three decades, scientists have focused their research on simulating the functioning and structural features of natural enzymes [9]. The overarching objective was to develop "artificial enzymes" that imitate the fundamental activities of biologically occurring enzymes while also having better features such as cost-effectiveness and stability. Nanozyme research intends to merge features of nanomaterials and take inspiration from biological enzymes to create the artificial enzymes of upcoming generation, which is an emerging topic connecting nanotechnology and biology [9–11].

Biological enzymes are macromolecular catalysts that catalyze natural biochemical processes. Although each enzyme serves a specific job, it has various disadvantages, which limit its use in broad-spectrum applications. To accomplish catalytic tasks, biological enzymes need specified physiological conditions. Some of the key downsides are low strength in extreme environmental conditions of the enzymes and also the large cost of manufacturing, separation, and refinement. As a result, numerous ways have recently been developed as a substitute to natural enzymes, with the production of complexes, molecules, and nanoparticles that mimic their intrinsic catalytic properties [12–14]. Nanozymes are the nanomaterials which are inherited with properties like natural enzyme those have exploded in popularity since the last decade due to the potential to get over the normal enzyme restrictions such as high cost, limited stability, and problematic storage [15]. Nanozymes are the nanoparticles that have the characteristics of an enzyme. Because of the rapid growth and improved knowledge of nanotechnology and nanoscience, nanozymes have the capability to act as direct surrogates for natural enzymes by reproducing and further altering the active centers of biological enzymes. It possesses the same kinetics (e.g., Michaelis–Menten equation) and catalytic mechanism (e.g., ordered, ping-pong, or random reaction) as a natural enzyme. It has inhibitors and activators to control how active it is. The nanozyme's catalytic activity is obtained without the change of any extra natural enzymes or chemical catalysts [16, 17]. The activity of nanozymes is dramatically simulated by typical nanoscale parameters such as shape, size, and surface, which gives a superior technique for modifying its activity. Nanozymes, like normal enzymes, frequently have active centers or electron-transport structures. Nanozyme has enzymatic or catalytic activity due to its active site. Nanozyme has the potential being used like the replacement of the enzyme for human health and surpasses natural enzymes in a variety of areas, including durability, cheap cost, and ease of manufacture. Nanozymes have substantial advantages over biological enzymes, leading to a surge in the development of artificial biocatalysts. These advantages include simple production techniques, smooth surface modification and dependable catalytic performance of nanomaterials [9, 12–14]. In today's nanotechnology, nanozymes are being studied extensively to develop a variety of applications in immunoassays, theranostics, biosensing, disease diagnosis and therapy, oxidative stress protection, cell/tissue development, and pollution removal. Nanozymes have lower specificity and selectivity than biological enzymes, although having more reactivity. This drawback

can be overcome if nanozymes are utilized for catalytic activities involving small molecules (e.g., oxygen radicals), where the steric characteristics of native enzymes is less significant [18–20].

Many metal oxide-based nanomaterials have also been investigated for their ability to replicate the functions of functional enzymes seen in natural defense systems. Metal oxide nanostructures have a lot of charge on their surfaces, which explains why they have such good electron characteristics. Metal oxide-based nanozymes, as a result, show up in the fields of fuel cells, sensing and electrocatalysis. In addition, as potential replacements for natural bioenzymes, they were found to be more stable and resilient under harsh circumstances than natural enzymes. Their uses are additionally broadened by their noteworthy physicochemical qualities (e.g., excellent optical and photothermal exchange abilities and high surface energy), as well as their ease of manufacture and storage [21, 22]. Surprisingly, the physicochemical characteristics and catalytic activities of metal oxide nanoparticles may be tailored without difficulty to meet convenient requirements. Surface modification, for example, has been identified as a possible technique for improving the biocompatibility of these nanozymes. Through proper management of synthetic circumstances, the structural design linked with catalytic efficiency is adaptable. As a result of this ascendency, metal- and metal oxide-related nanozyme research has increasingly expanded beyond the environment to the medicine, food, chemical industry, biomedicine, agriculture, and other industries [12, 19, 21, 22]. Metal oxide nanozymes have long been regarded as potential artificial enzymes because to their high surface energy and surface-to-volume ratio. The most prevalent metal oxide nanozymes, such as Co_3O_4, Mn_3O_4, Fe_3O_4, Mn_2O_3, Fe_2O_3, and CeO_2, have all been shown to exhibit activities like multi-enzymes. They also have a number of unique features, including fluorescence quenching, dielectric, and magnetic properties. Metal oxide-based nanozymes have a cheaper cost and a shorter manufacturing procedure than precious metal nanomaterials [23, 24]. Furthermore, their biopharmaceutical application has expanded due to their less biological toxicity and good accumulation in tissues. Natalio et al. investigated the intrinsic activity of V_2O_5 nanowires like peroxidase enzyme generated by a hydrothermal technique, demonstrating that V_2O_5 nanowires functioned similarly to naturally occurring vanadium haloxidase, that could help to avoid marine biological contamination [25]. CeO_{2-x} nanorods were manufactured by a hydrothermal technique, mimic haloperoxidase enzyme, that is, based on Ce^{4+}/Ce^{3+} redox couples, which was created by Herget et al. [26]. Wang et al. investigated the influence of chloride ions on the suppression and eradication of biofilms by CuO peroxidase using the CuO-Fenton reaction (peroxidase) [27]. Karim et al. discovered that CuO nanorods were manufactured via a solution-based technique that possesses peroxidase activity, and they used visible light as an external "trigger" to modulate the antibacterial activity of the CuO nanorods nanozyme [28]. Iron oxide NPs (IO-NPs), which primarily contain magnetite, i.e., iron(II, III) oxide, Fe_3O_4, and hematite, i.e., iron(III) oxide, Fe_2O_3 NPs, have been the focus of metal oxide research. This is because IO-NPs have the capacity to decrease reactive oxygen species (ROS) [11].

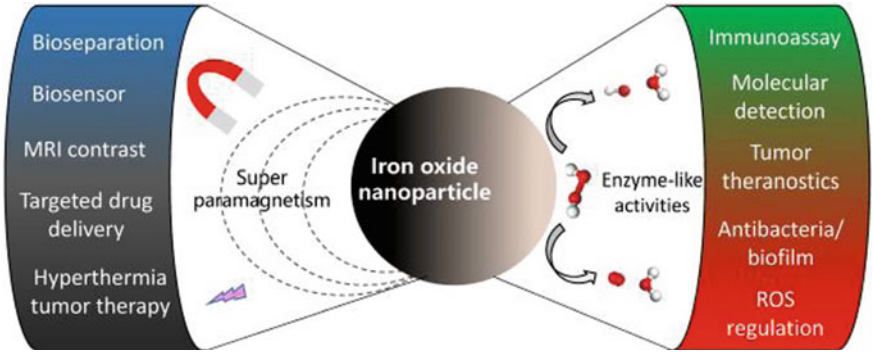

Fig. 3.1 Magnetic properties and enzyme-like activities of iron oxide nanoparticles for various applications [29]

One of the most common nanozymes is iron oxide nanoparticles (IO-NPs). In vivo cell monitoring, magnetic resonance imaging (MRI), hyperthermia, drug or gene delivery, and magnetic targeting are just a few of the biomedical uses for these [29]. The vast range of applications for IO-NPs, including electrochemical applications, data storage, and environmental clean-up, drew a lot of attention. Iron oxide NPs are commonly used in diagnostics (e.g., imaging, detection, or biosensing) due to their inherent magnetic characteristics (superparamagnetic) as well as their biocompatibility and stability. When exposed to an alternating magnetic field, IO-NPs can cause local heat enhancement, which is particularly useful for the reduction of cancer cells, those, unlike healthy cells, cannot survive in the temperature of 42–49 °C [29–31]. To be ready for diagnosis or therapy, cells of interest must be labeled with a rather high number of IO-NPs in each case, raising the issue of toxicity concern. In 2007, ferromagnetic (Fe_3O_4) nanoparticles were revealed to have inherent activity like peroxidase, exhibiting catalytic action comparable to horseradish peroxidase (HRP). Other nanozymes have been investigated using the analytical methods developed for iron oxide nanoenzymes characterization, particularly for kinetics and mechanism experiments to identify catalytic characteristics. Figure 3.1 shows the activities of iron oxide nanomaterials like enzyme with different utilizations.

3.2 Enzymatic Activities of (Iron Oxide Nanozyme) IONzyme

IONzyme is now being used to imitate two enzyme activity from the oxidoreductase family: peroxidase and catalase. While hydrogen peroxide is used by both enzymes as a substrate, only peroxidase produces free radicals that can be used to react with

a hydrogen donor (AH_2), while catalase produces oxygen (Eqs. 3.1 and 3.2). In aerobically respiring species, both peroxidase and catalase are important in avoiding cellular oxidative damage.

$$H_2O_2 + AH_2 \xrightarrow{\text{Peroxidase}} A + 2H_2O \tag{3.1}$$

$$2H_2O_2 \xrightarrow{\text{Catalase}} O_2 + 2H_2O \tag{3.2}$$

(a) **Peroxidase enzyme-like activity**: The first enzyme-like characteristics discovered in IONzyme were the activity like peroxidase enzyme, which catalyzes the standard colorimetric process using chromogenic reagents and hydrogen peroxide (H_2O_2). This characteristic is present in both Fe_3O_4 and Fe_2O_3 nanomaterials; however, the former is generally more active than the latter. Free radicals are produced as an intermediate, by catalyzed reaction of H_2O_2, and those subsequently react with a hydrogen donor (typically chromogenic molecules) to produce H_2O and oxidized donor [17]. The ideal conditions for catalysis of iron oxide nanozyme are the same as HRP, with a temperature range of 37–40 °C and a pH range of 3–6.5 in an acidic buffer. When 3,3′,5,5′-tetramethylbenzidine (TMB) was used as the hydrogen donor, an excessive quantity of H_2O_2 might hold back the colorimetric reaction. The peroxide concentration must be within a certain range for both HRP and iron oxide nanozyme catalysis and to retain activity. O-phenylenediamine (OPD), TMB, 2,2′-azino-bis (3-ethylbenzothiazoline-6-sulfonicacid) (ABTS), and 3,3′-diaminobenzidine (DAB) are just a few of the chromogenic substrates that IONzyme may catalyze. Aside from chromogenic substrates, biomolecules such as polysaccharides, nucleic acids, proteins, and lipids can also be the targets. In biological systems, peroxidases have a variety of important activities, including detoxification of reactive oxygen species (e.g., glutathione peroxidase) and fighting in opposition to infections (e.g., myeloperoxidase). The enzyme peroxidase is frequently utilized in clinical and bioanalytical chemistry, where it is conjugated to an antibody and used to enzymatically catalyze colorimetric substrates for signaling or imaging [10, 21, 22, 29].

(b) **Catalase-like activity**: IONzyme has activity like peroxidase as well as catalase in the decomposition of H_2O_2 into O_2 and H_2O. Under basic and neutral pH (pH 7–10), dimercaptosuccinic acid (DMSA)-coated Fe_3O_4 and Fe_2O_3 nanoparticles converted H_2O_2 to O_2, according to the Gu group. Fe_3O_4 has stronger catalase-like activity than Fe_2O_3, similar to peroxidase-like catalysis. IONzyme has so far been able to conduct the two actions stated above while maintaining correct pH regulation [10, 21, 22, 29].

3.3 Applications of Iron Oxide-Based Nanozyme

3.3.1 Iron-Based Nanozymes for Tumor/Cancer Treatment

Iron-based nanomaterials are some of the most effective nanomedicines. They were originally used in translational research, and the FDA has authorized numerous iron-containing nanoformulations for clinical use. Iron-based nanozymes have often showed a number of therapeutically beneficial features, many of which are particularly significant for tumor treatment [9, 29]. From a physiochemical standpoint, earlier research has shown that after being stored at room temperature, the nanoparticles that are based on iron can be stable for 40 days and also that their catalytic efficacy can be maintained after numerous treatment sessions.

Additionally, iron-based nanozymes have high biocompatibility that helps to the effectiveness and safety of treatment. Furthermore, because of their controlled magnetic characteristics, iron-based nanozymes might be effectively deposited into tumor tissues, increasing the therapeutic index. Furthermore, as compared to natural enzymes, iron-based nanozymes have enhanced resistance to environmental stress for instance acidic or basic conditions and severe temperatures. Additionally, iron-based nanozymes exhibit high morphological uniformity and are simple to manufacture at a low cost. Because of the benefits listed above, iron-based nanozymes have made major contributions to the advancement of nanocatalytic cancer treatment [9–11].

Iron-based nanozymes have the potential to mimic a variety of enzymes in vivo with their varied catalytic activities. This, together with the magnetic receptivity, variable surface chemistry, and superior biocompatibility of nanoparticles based on iron, has led to an increased use of iron-based nanozymes in the detection and treatment of a wide range of tumor indications (Fig. 3.2). Cai et al., for example, revealed the iron core in ferromagnetic H-ferritin nanoparticles has catalytic activity similar to peroxidase and could be employed to stain tumor tissues immunohistochemically. The authors found that xenografted tumor tissues incubated with ferrimagnetic H-ferritin nanoparticles turned brown due to the nanozyme-catalyzed oxidation of 3,3′-diaminobenzidine tetrahydrochloride substrates in the presence of excessive H_2O_2, whereas normal tissues were stained purple by hematoxylin [33]. Meanwhile, catalase-like iron-based nanozymes have been reported to degrade tumor H_2O_2 to create extra oxygen, which might be used to improve ultrasound imaging of the tumor region [34]. In terms of therapeutic applications, current research focuses mostly on the use of iron-based nanozymes as Fenton nanocatalysts or oxygen producers, which will be explored in the section below.

Iron-based nanozymes with catalase-mimicking characteristics have also been investigated for reducing hypoxia-induced resistance to cancer treatment. In a recent work, a hybrid nanosphere containing Fe^{3+} was used to overcome tumor hypoxia by decomposing endogenous H_2O_2. This strategy's viability and prospective therapeutic benefits were proven.

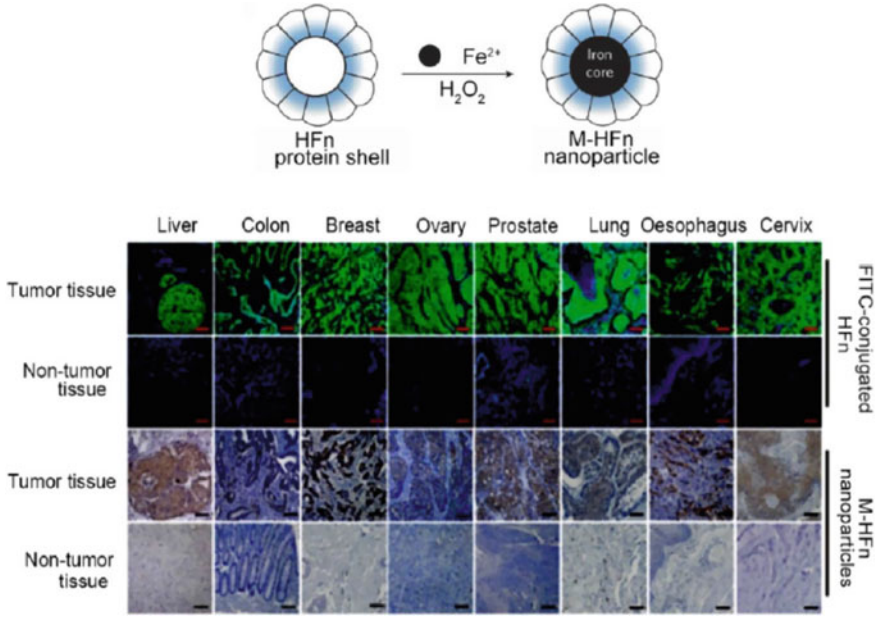

Fig. 3.2 IONzyme activity for tumor using magneto ferritin. Reproduced with permission from the Royal Society of Chemistry [32]

Aside from the iron-based nanozymes' promising antitumor effectiveness, it is also important to look at their possible effects on the recipient host's health in the short and long term. As a result, iron-based nanozymes should be non-toxic to normal tissues, disintegrate in biological settings, and finally be removed from the body when the therapeutic activities are completed. The biocompatibility and biosafety of enzymes and nanozymes are crucial in assuring their continued clinical use. Nonetheless, iron-based nanozymes are a new technology in its early stages of development, and the majority of their interactions with the biological environment are unknown, necessitating ongoing research into their pharmacokinetics, metabolism, absorption, therapeutic sustainability, excretion, distribution, and toxicity at the molecular, cellular, and systemic levels [10, 35].

3.3.2 Cardioprotection

Iron oxide nanoparticles were also examined for their cardioprotective properties. Iron oxide NPs were found to protect hearts in vitro and in vivo against ischemia injury from various studies. Myocardial ischemia can be explained as a lack of blood supply to the heart, which is one of the most common causes of myocardial injury. This causes myocardial hypoxia that can lead to angina pectoris, coronary artery

heart disease, or even a heart attack. There is currently no treatment for myocardial ischemia damage that has been proved to be successful, and current treatment comprises the administration of a variety of pharmacological medications such as free-radical scavengers, antioxidants, calcium channel blockers, and anti-apoptotic agents [14, 19, 21, 23, 25]. Although, one of the most significant difficulties is that pharmacologic medications intend just one method, but myocardial ischemia damage is linked to a number of other pathogenic pathways. The cardioprotective effect of iron oxide NPs was investigated as an alternate strategy. The activity of the iron oxide NPs was compared to that of two pharmaceutical medications often used to treat myocardial ischemia injury: verapamil, a calcium channel blocker, and *Salvia miltiorrhiza* extract, an antioxidant. The researchers used a rat coronary artery ligature model to investigate the cardioprotective effect of 2,3-dimercaptosuccinic acid (DMSA)-modified iron oxide NPs in a variety of tiny sizes [14, 19, 21, 23, 25, 36]. The cardioprotective impact of the iron oxide NPs was greater than that of both *Salvia miltiorrhiza* extract and verapamil, following ischemia reperfusion, as evaluated by left ventricular developed pressure. The cardioprotective effect was shown to be dependent on the size of the iron oxide NPs, but not on their surface charge.

Iron oxide NPs were used to stimulate cardiac mesenchymal stem cells (cardiac MSCs, cMSCs) by Han and colleagues. The MSCs were labeled with superparamagnetic iron oxide NPs by Parivar's team. Superparamagnetic iron oxide NPs are widely employed in MRI for cell tracking and contrast, as well as for cell magnetization in tissue engineering and medication targeting. To produce iron oxide NP-labeled MSCs, polyethylene glycol (PEG)ylated iron oxide NPs were manufactured and applied to the MSCs for 48 h. The iron oxide NP-labeled MSCs were then injected into the heart of a rat model of heart failure. A neodymium magnet was put over the heart for 48 h for the magnet-dependent iron oxide NP-labeled MSCs. In comparison with the unlabeled MSCs and the magnet-independent groups, the magnetic-dependent group had a higher restoration of the injected proportion. Because a larger percentage of iron oxide NPs were kept in the heart, the cardiomyocytes were preserved, and the formation of fibrosis following heart failure was reduced.

3.3.3 Wound Healing

Because of the negative and positive effects of oxygen and H_2O_2 on wound healing, iron oxide NPs that can catalyze H_2O_2 have been investigated for wound-healing applications. It was discovered that incorporating iron oxide NPs into three-dimensional (3D) cellular spheroids stimulated ECM synthesis. It was also feasible to change the composition of iron oxide NP by adjusting its concentration and properties. Magnetic iron oxide NPs (magnetoferritin) boosted the production of all the proteins that make up the ECM, while varying the iron oxide NP concentration had an influence on both collagen IV and elastin formation. Hu and colleagues employed iron oxide NPs in wound dressings manufactured from electrospun poly(vinyl alcohol) (PVA) membranes [37]. Because of its large surface-to-volume ratio as well as

porosity, which allow for significant water absorption and robust oxygen permeability, a polymeric PVA mesh was chosen as the scaffold. By combining spindle-shaped iron oxide NPs with a PVA solution and electrospinning them, they were synthesized and incorporated into the scaffold fibers. The as-prepared fibers were TEM imaged with concentrations of iron oxide NPs that are homogeneously incorporated. The results, as indicated by a colorimetric test and an oxygen-sensitive electrode, suggest that the iron oxide NP-containing PVA fibers had catalytic activity at all concentrations investigated. In the presence of H_2O_2 at harmful amounts, the effect of the iron oxide NPs on the scaffolds was studied in terms of fibroblast proliferation. More than 90% cell survival was observed after incubation with H_2O_2-disclosed nanofibrous dressings containing iron oxide NPs for overnight period, indicating that the catalytic scaffolds provided a superior environment for cell growth. Importantly, cells treated with bare scaffolds showed full apoptosis. The iron pxide NP PVA membranes have potential for wound-healing dressings because of their ability to reduce H_2O_2 concentrations to harmless levels.

3.3.4 Antibacteria and Biofilm Elimination

IONzyme combines with H_2O_2 in the catalytic process to produce free radicals as intermediate products; those are very harmful to bacteria because of targeting proteins, cell membranes, and nucleic acids, causing bacterial dysfunction. H_2O_2 is a typical biocidal chemical that can be used for a variety of cleaning and disinfecting applications, as well as like an antibacterial agent in good hygiene and in medical treatments [9, 14, 18, 38]. The mechanism is also based on the reaction of hydrogen peroxide with cellular constituents, but for resistant bacteria, the effectiveness is generally less. In terms of mechanism of the ping-pong reaction, an iron oxide nanozyme with activity like peroxidase enzyme may aid in the enhancement of antimicrobial properties of H_2O_2. In the previous studies, the enhanced impact was established on methicillin-resistant *Staphylococcus aureus* (MRSA) and *Escherichia coli* (*E. coli*). The antibacterial capability had demonstrated to be effective for wound healing in bacteria-infected wounds, as well as other treatment techniques against multidrug-resistant bacteria [9–11, 14, 18, 29, 38].

Enhancing H_2O_2 catalysis to create radicals also opens up the possibility of eradicating biofilm, a type of bacterium community that aids in the development of drug resistance by preventing antibiotics or other biocides from penetrating the organic matrix used for protection. Through improved oxidative breakdown of biofilm components (oligosaccharides, proteins, and nucleic acids) in the presence of hydrogen peroxide, Fe_3O_4 nanozyme with activity like peroxidase enzyme could amplify the effectiveness of H_2O_2 in breakdown and prevention of biofilm. The Fe_3O_4 nanozyme can break nucleic acids (DNA), proteins, and polysaccharides into minute pieces when combined with H_2O_2. IONzyme or H_2O_2 administered independently, on the other hand, failed to balance the oxidative destruction. The Fe_3O_4 NP-H_2O_2 system's capacity to cleave biomolecules allows it to proficiently break

the matrix of existing biofilm and avoid development of new biofilms, killing both planktonic bacteria and those within the biofilm, resulting in a unique technique for biofilm removal and other uses. This method had previously proved successful in the removal of dental biofilms. In vivo, IONzyme combined with H_2O_2 successfully inhibited the beginning and harshness of tooth caries while protecting normal biological tissues. These findings suggested that nanozymes could be used as a viable alternative treatment for the common biofilm-related disease [9–11, 14, 18, 29, 38].

3.4 Conclusion and Perception

It has been ten years since iron oxide nanoparticles' inherent enzyme-like activity was discovered. As a new generation of enzyme mimics, iron oxide nanozyme's catalytic activity and kinetics have been thoroughly studied to better understand the mechanisms. By attempting to control specific parameters, such as size, dopants, surface modification, morphology, nanostructure, or integration with other nanomaterials, we can then rationally design the appropriate nanozymes for potential implementation. IONzyme is a platform with multifunctionality and adaptability that may be functionalized with additional labels or compounds. It has significantly more stability than conventional enzyme mimetics or natural enzymes. These advantages have made it possible to use iron oxide nanoparticles in a new way that does not rely on magnetism. In clinic and biomedical applications such as cancer imaging, gene transfer, DNA extraction, and cell sorting, magnetic iron oxide materials have long been used. All of these applications make use of the magnetism of these materials. The enzyme-like actions will be useful for pathogen detection and immunoassay, boil removal, cancer detection and therapy, and ROS modulations at various levels for neuroprotection, cell differentiation, and cardioprotection. These nanozymes can also break down influenza virus by inducing lipid peroxidation in the viral envelope. These advantages have made it possible to use iron oxide nanoparticles in a new way that does not rely on magnetism. In clinic and biomedical applications such as cancer imaging, gene transfer, DNA extraction, and cell sorting, magnetic iron oxide materials have long been used. All of these applications make use of the magnetism of these materials. The enzyme-like actions will be useful for pathogen detection and immunoassay, boil removal, cancer detection and therapy, and ROS modulations at various levels for neuroprotection, cell differentiation, and cardioprotection. These nanozymes can also break down influenza virus by inducing lipid peroxidation in the viral envelope. There must be a detailed investigation of the final effect on biological systems that are ROS-sensitive, such as immunological activation, brain development, stem cell proliferation and differentiation, cardiac stress, and cancer growth. Therefore, serious efforts are needed to solve the underlying issues and boost iron oxide nanozyme activity for biological applications in vitro and in vivo.

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