



Review Article

Therapeutic applications of nanozymes and their role in cardiovascular disease

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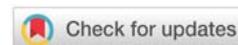
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Abstract

Enzyme mimetic is an increasing pull to overcome the limitations on natural enzymes. Enzyme mimicking is done with the help of nanozymes. Nanozymes contain nonmaterial which have enzyme-like activity; this similar activity attracts the researchers. Nanozymes studies showed that they are exceptional in many aspects, such as robustness to a harsh environment, long term storage, easy mass production, and high stability. In the field of biomedical technology, nanozymes have exhibited advantages to diagnose and treat disease. Nanozymes used to treat many therapeutics affect antiinflammatory, anti-ageing effects, neuroprotection, cytoprotection, dental biofilms, antioxidation, and antithrombotic effects. However, to broaden the applications of nanozymes, it is synergistically important to combine the activity of enzymes with properties of nanoscale such as optics, magnetic, mechanics, and electric. Many types of enzymes have been reported, and their applications in Environmental remediation, therapeutics, and biosensor development. Compare with natural enzymes, current research on applications of nanozymes is tranquil somewhat limited. This uncertain issue will be the next borderline for promotes applications.

Introduction

Enzymes use as a catalyst in biology that converts substrates into products in any biochemical reaction which needs a catalyst. The first enzyme, urease, was said to be a protein in 1926, determined by James B. Since, enzymes well treated to be proteins that allow the enzymes to accomplish high activity as a catalyst. So, protein activity is missed when its exposure occurs at high temperature and high pH. Proteins are also affected by proteases present in the environment moreover natural enzymes have a high cost due to these practical applications of enzymes retard in industry [1].

However, enzyme mimetic is an increasing pull to overcome the limitations; enzyme mimicking is done with the help of nanozymes [2]. Nanozymes contain nonmaterial which have enzyme-like activity; this similar activity attracts the researchers. Nanozymes studies showed that they are extraordinary in many aspects, such as robustness to a harsh environment, long term storage, easy mass production, and high stability [3].

Nanozymes have different structures or sizes because nanomaterials are hard due to a porphyrinic nucleus, and proteins are soft [4]. So the comparison with natural enzymes nanozymes is more stable because the nanomaterials they contain, are inorganic [2]. Nanozymes have inherent properties, and unique catalytic activities due to this nanozymes have great attention towards mimetic the natural enzymes until now 50 kinds of nanoparticles have been found. Catalytic activities of enzymes are Catalase (CAT), Peroxidase (POD), glucose oxidase [5], Superoxide Dismutase (SOD). Nanozymes are mainly divided into carbon-based, noble metal nanozymes, metal oxide nanozymes [1].

Applications of magnetic nanoparticles include cell separation, nucleic acid separation, wastewater treatment, biomedical separation, magnetic target drug delivery, catalysis [4]. However, to broaden the applications of nanozymes, it is synergistically important to combine the activity of enzymes with properties of nanoscale such as optics, magnetic, mechanics, and electric [2]. Many types of enzymes have been reported, and their applications in Environmental remediation, therapeutics, and biosensor development [6].

The many latest developments in the field of nanotechnology have broadened the approach to investigate the novel enzymes. The possible catalytic mechanism for nanozymes has unravelled when combined with computer theoretical calculations, simulation. These studies improve the nanozymes catalytic activities. In biomedical technology, nanozymes have exhibited advantages in diagnosing and treating disease [7].

Therapeutic application of enzymes

Due to eliminating reactive nitrogen species (RNS) or reactive oxygen species (Mulder, Fayad, & biology) [8], nanozymes have been used for latent therapeutic [9]. Some interesting enzyme mimetic applications include CeO₂ as Superoxide Dismutase (SOD) [10]. Their SOD mimicking activities mainly describe ROS effects, which converts the superoxide in H₂O₂ [3]. This section is based on the nanozymes therapeutic effect (Table 1) antiinflammatory, anti-ageing effects, neuroprotection, cytoprotection, dental biofilms, antioxidation, antithrombotic effects, etc.

Antiinflammatory effects

Inflammation plays a role in diabetes, physiology of arthritis, irritable bowel syndrome, heart disease, Alzheimer's disease, illnesses, and Parkinson's disease. The major constituent of the yellow spice turmeric, curcumin derived from the *Curcuma longa*. It is non-toxic and safe and has antiinflammatory properties [11]. A high level of nitric oxide [12] abnormally contributes to chronic inflammation and immunological disorder resulting in organ damage. Cerium oxide nanoceria has characteristics used in nanotherapeutics and decreases the moderator chronic inflammation [13]. Nanoceria can scavenge the reactive oxygen species [8] or free radicals and inhibit the mediators of inflammation from protecting the cell against the inflammatory diseases [4].

Catalase, glutathione peroxidase, and superoxide dismutase 1 (SOD1) are potent scavengers of ROS, in eye diseases, these enzymes are very effective because eye disease is related to oxidative stress. However, With the help of sodium hydroxide, acute corneal inflammation in animals is treated. Eye disease was treated by contingent ordination of eye drops; these drops contain many problems, so due to this reveal that nanoparticles improve the efficacy by drug carrier system or conquered the corneal diffusion barriers [14].

Antioxidant effects

ROS such as H₂O₂, O₂^{•-}, and •OH, are the by-products of metabolism. They can serve as second messengers at a low level

and take part in many signalling processes [15]. Moreover, when the reactive oxide species are over-expressed, they lead to many unfavourable reactions; for example, over-expression of ROS produces oxidative damage to DNA, lipids, and proteins. They also induce cell apoptosis and many other diseases like cancers, atherosclerosis, kidney diseases, arthritis, and neurodegeneration [16]. Antioxidants protect the tissues from damages compel by the free radicals; It also improves the many other damaged tissues. Antioxidants are catalase, glutathione reductase, glutathione peroxidase, peroxiredoxins, and superoxide dismutase. Biological antioxidant required some elements which have no antioxidant activity but needed for the proper functioning of biological antioxidant; these include iron, selenium, manganese, zinc, and copper([17]. The V₂O₅ has glutathione peroxidase (GPx) like antioxidant activity; it protects the cell from oxidative stress [18].

Superoxide Dismutase (SOD) enzyme is needed for antioxidants' defences, maintaining the level of O₂⁻ [4]. According to some new research, the Hollow PB nanozymes (HPBZs) contain multienzyme-like properties such as neuroprotection, and they scavenge the ROS([19] (Figure 1). The over-production of ROS effect biomolecules leads to a wide range of human diseases, and induce tissue injury. Human skin which acts as a protective layer between the external environment and body is prone to pro-oxidant agents. ROS's over-production causes inflammatory and allergic skin disease, for example, psoriasis, urticaria, and atopic dermatitis [20].

So, the Prussian blue nanoparticles have been reported about their antioxidant activity. The PB nanoparticles (PB NPS) a mixed-valence of iron cyanide containing hexacyanoferrate [Fe(CN)₆]²⁺ complex and Fe³⁺ cations [21]. Due to their instability in biological buffers in vivo applications of PB nanoparticles are limited; the stability of these particles has been improved by coating with poly(vinylpyrrolidone), poly(diallyl dimethylammonium chloride), and polyethylene glycol, from all these the chitosan, is best due to its excellent biocompatibility, good stabilization, biosafety, and biodegradability.

Hyperion Oh, et al. developed PB/Chi nanoparticles using many chitosan samples ranging from 3 to 100 kDa to improve the antioxidant activity and stability PB nanoparticles (Figure 2). Chitosan is a polysaccharide that is a permeation enhancer and mucoadhesive that facilitates NP retention in the administration [22]. The improvement in stability was examined by monitor change in the diameter of the nanoparticles and appearance. The antioxidant activities were examined by deoxyribose assays and 2,2-diphenyl 1-1-picrylhydrazyl(DPPH) [23].

Table 1: Comparison of Graphene quantum dots with an inorganic, organic, and natural antimicrobial agent.

Characters	GQDs	Inorganic	Organic	Natural
Anti-bacterial efficiency	Good anti-bacterial efficiency.	Cause leakage of the metal ion.	Complicated process.	Poor anti-bacterial efficiency.
Antibiotic resistance	Not resistance to antibiotics.	Resistance to antibiotics.	Resistance to antibiotics.	Resistance to heat and protease.
Production cost	In vivo low cost of production due to usage of low dose.	The high cost of production and cause environmental pollution.	The high cost of production.	High cost to extract and in vivo usage.
Stability	Highly stability and low biotoxicity [42].	Instable in the biological environment [43].	Not stable.	Practical applications of the natural agent are crucial due to low stability [44].

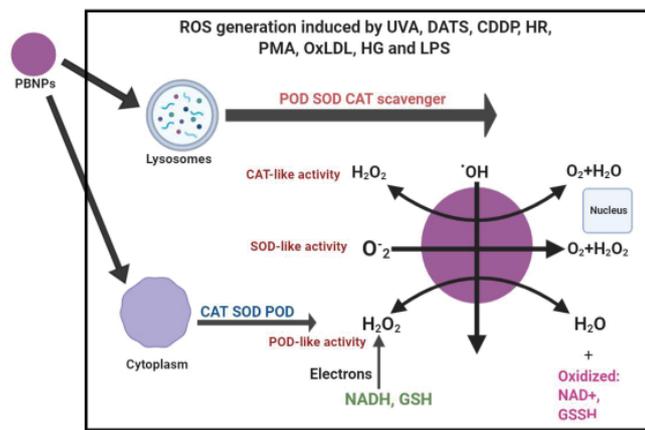


Figure 1: PBNPs with multienzyme-like properties, achieve excellent antioxidant efficiency, and effectively decrease intracellular ROS level.

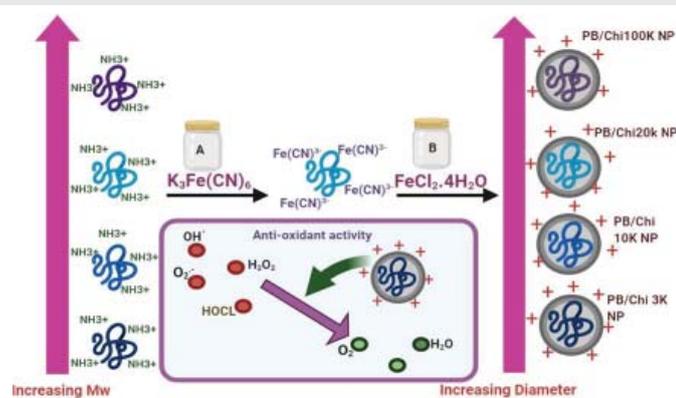


Figure 2: Prussian blue nanoparticles schematic preparation which is stabilized by chitosan with diverse molecular weights.

Neuroprotection

Stroke is the third headmost cause of death which is also called cerebral ischemia. Bioenergetics failure occurs due to the reduction of oxygen and glucose delivery to the brain during a stroke. These conditions lead to stress, blood-brain barriers, and ultimately cell death occurs. Cerium oxide nanoparticles have the potential to treat the stroke. Cerium is a metal that belongs to the lanthanide series of the periodic table. When oxygen is combined with the cerium in a formulation of nanoparticles, they have also found antioxidant properties [24]. Cell line HT22 is the most well stood clonal cell system for analyzing the oxidative stress. The natural pro-oxidant for HT22 cells is the glutamate amino acid when glutamate is present, cysteine consumption is blocked, and oxytocic occurs. Reduction of C_4^+ to C_3^+ and loss of oxygen is retained by creating an oxygen vacancy. This is done with the help of ceria nanoparticles, and due to these reactions, catalytic application possible [25].

Antithrombosis effect

Bacterial infection and thrombus formation are two major harms. These harms lead to complications in biomedical devices such as heart valves, catheters, and vascular grafts. To develop the antimicrobial and antithrombotic is important to

sustain the function of these biomedical devices [26]. Colloidal Mesoporous Silica (CMS) nanoparticles have engrossed enormous consideration as possible injectable drug delivery. In addition to their high Biodegradability and biocompatibility, CMS can selectively customize at their outer and inner surfaces to encapsulate molecules powerfully. They can be specifically functionalized on their outer surface [27]. The delivery of this multiple function CMS in the bloodstream prevents the thrombogenic effects. The coating of ethylene glycol addresses hemolytic behaviour and their fast degradation prevention. Moreover, the additional efforts are critical to delivering these manifold core-shell CMS to the blood and assurance sufficient circulation time to prevent the thrombotic effect. Heparin, anionic polysaccharide and highly sulfated, is best due to its anticoagulant property. Moreover, Heparin is conventionally injected intravenously or subcutaneously [28].

Heparin in free form involves an increased risk of bleeding due to these risks. Many other side effects occur. The example of this situation is this Heparin-induced thrombopenia even as diffusing all over the blood circulation system. Tissue targeted nanoceria the CMS with Heparin must be harmless and injectable into the bloodstream. Heparin and nanoceria prevent the clotting cascade's establishment only in the abrupt vicinity of nanocarriers and have no side effects [29].

Nitric oxide [12] is predictable as an antiplatelet agent. Nitric oxide [12] can prevent thrombus formation. Due to its ability to increase the cyclic Guanosine Monophosphate (cGMP) levels within the platelets, Nitric oxide [12] showed the antiplatelet agents. So, lowering the intracellular Ca^{2+} level required for the common passageway in the coagulation cascade, NO drug agents' release to accomplish the antiplatelet activity in vivo. These in vivo studies attract to mimic the natural role of NO release from the endothelial cells. Endothelial cells are healthy blood vessels [30].

NO was arising from the oxidation of L arginine and catalyzed by the enzyme nitric oxide synthase. Moreover, these enzymes use O_2 as an oxidant and Nicotinamide Adenine Dinucleotide Phosphate (NADPH) as a cofactor. When the cofactor supplies and L arginine concentration are inadequate, the NO reduced form nitroxyl (HNO) produced [30]. Analogous to NO the HNO has an anti-thrombogenic effect. The NO generating catalysts and non-releasing materials have some problems, HNO is the possible solution.

However, there is no report on the local production of HNO efficiently prevent thrombus formation. Some reports showed Graphene hemin glucose oxidase's conjugate use as a catalyst to generate HNO from L arginine and physiologically abundant glucose. These catalysts create a long-lasting antithrombotic covering [31].

Nanozymes role in cytoprotection

Platinum is used as an industrial catalyst in an extensive range. Some older studies about Platinum reported that the Pt NPs serve as both SOD mimics to scavenge H_2O_2 , CAT, and $O_2^{\cdot-}$ [32]. Conventional methods also used poly (acrylic acid) (PAA)

in the research process to improve their biocompatibility. To in situ synthesize Pt nanostructures; Nie, et al. used nanocarrier apoferritin (about) protein shell. These ferritin-platinum nanoparticles were non-toxic, stable with exceptional catalase-like activity; catalyze the breakdown of H_2O_2 , and these nanoparticles are bioactive [32].

The non-cytotoxic properties of Pt NPs have been reported in previous research. All these studies showed that 10^{-4} – 10^3 ng/cm² (7.86×10^{-7} – 7.86 mg/l) of 20–100 nm Pt NPs affected neither the cellular metabolism nor cell death [33]. Moreover, hybrids nanomaterials have been broadly invented. Graphene oxide [33] nanomaterials broadly use in research, due to their high conductivity, absorbing properties, large surface area, and outstanding biocompatibility [34].

However, the hybrid GO-Se nanomaterials have GPx like antioxidant properties for Cytoprotection. In the presence of GSH, the GPx catalyzes the breakdown of H_2O_2 to the harmless product. These nanomaterials catalyze the decomposition of H_2O_2 to the less reactive product. Comparison between Se NPs and GO-Se nanoparticles showed higher GPx mimic catalytic effectiveness. Moreover, GO-Se nanozymes are obsessed with a high capacity to scavenging the reactive oxygen species [35].

Liu and his co-workers constructed enzyme from the self-assembly of polymers with protein; this nanocomposite is used for cytoprotection. Protein (SP1) is a stress-responsive protein and has no sequence homology to other stress proteins. SOD and GPx's catalytic centre assembled into protein (SP1) and polymer nanoparticles (PD5). The electrooptic contact between polymer and protein can self-assemble and form nanowires with SOD and GPx like properties (Figure 3). These nanocomposites scavenge the overexpressed reactive oxygen species and maintain the intracellular balance [36].

Anti-aging effect

Ageing is determined by the combination of environmental factors and genetics. *Caenorhabditis elegans* have identified many genes such as daf-16, Age-1, Sir2, and daf-2. From which the daf-16, daf-2, Age-1 are associate with insulin-dependent signalling. Moreover, these genes are involved in oxidative stress responses and lead to stress resistance and longevity [37].

The redox reaction involves ageing; the detoxification of ROS regulates ageing. The ageing-related diseases are preventing by the help of ROS scavenging enzymes. Quick, et al. [37] reported that $C_{60}[C(COOH)_2]_3^-$ based SOD mimic showed fascinating anti-ageing effects and also better mice cognition ability [37]. Comprehensive studies showed that the nanozymes lower the age-related mitochondrial superoxide and improve the biological functions of mitochondria. Moreover, these biological functions rescued the age-related cognitive destruction due to its presence in mitochondria [38].

However, the drosophila melanogaster has been used to explain biological processes' mechanisms, including ageing, metabolism, and developments. Moreover, drosophila's short life cycle makes a suitable tool to study ageing mechanisms

[39]. Zhang, et al. reported the *Drosophila melanogaster* ageing process (Figure 4).

They examined the effect of Fe_3O_4 NPs on drosophila life span and ageing, examined drosophila on different age stages. Results showed that the aged drosophila has a low climbing ability. The daily uptake of 200µg/mL Fe_3O_4 NPs reduced the ROS level and improved climbing ability [38].

Anti-bacterial effect

Bacteria produce many contagious diseases that have major health issues all over the world. Millions of peoples died due to bacterial related issues; anti-bacterial agents are primarily antibiotics [40]. Moreover, metal-containing inorganic salts, organic agents, and natural anti-bacterial agents are used as anti-bacterial materials. These antimicrobial agents have drawbacks (Table 2) [41]. So it is essential to induce stable, efficient, and novel antimicrobial agents to overcome bacterial diseases. The peroxidase constituent of cytochrome P450, take part in many essential living functions.

Peroxidase catalyzes the H_2O_2 to generate an elevated level of $\cdot OH$ and oxidize abundant organic substrates. The Qu and co-workers productively implement Graphene quantum dots

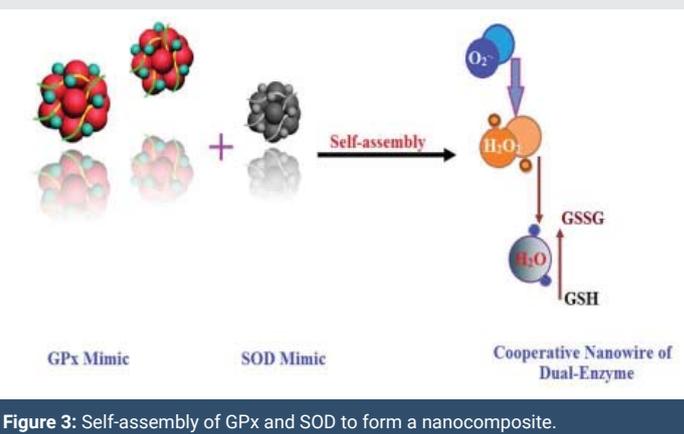


Figure 3: Self-assembly of GPx and SOD to form a nanocomposite.

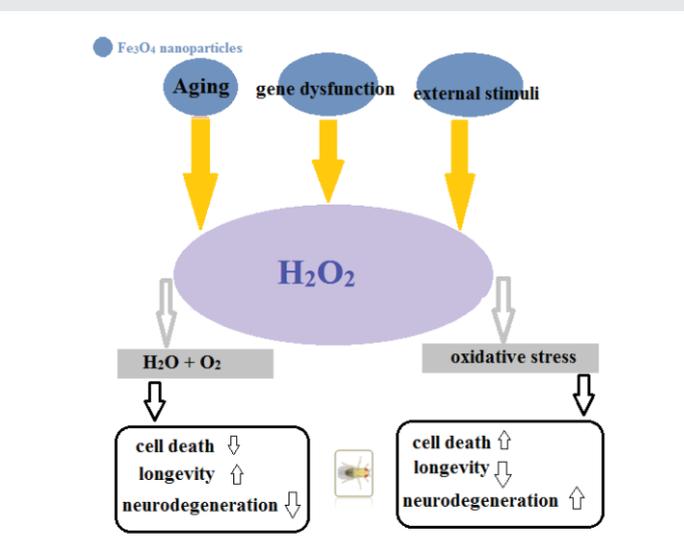


Figure 4: Anti-aging possessions of Fe_3O_4 nanoparticles to ameliorate ROS induced neurodegeneration and holdup drosophila ageing.

Table 2: Applications of nanozymes and their mimetic enzymes.

Enzyme mimic	Nanomaterials	Applications	References
Peroxidase	Iron oxide	ELISA	[67]
Peroxidase	Dietary iron oxide	Anti-ageing, Neurodegeneration	[38]
Catalase	Iron oxide	Tumour detection	[67]
SOD	Cerium oxide	Suppress myocardial inflammatory process	[68]
SOD	Cerium oxide	Retinal degenerative process	[69]
SOD	Cerium oxide	Antioxidant	[4]
	Cerium oxide	Neuroprotection	[70]
SOD	Cerium oxide	Oxygen sensor	[24]
Oxidase	Cerium oxide	Detection	[71]
Catalase	Cerium oxide	hydrogen peroxide sensing	[72]
Oxidase	Zinc oxide	Detection	[73]
Nitric oxide synthase	Grapheme herein	Antithrombosis	[30]
Peroxidase	Graphene herein	Detection	[74]
Glutathione Peroxidase	Graphene oxide-Selenium composites	cytoprotection	[35]
Glutathione Peroxidase	selenium-functionalized graphene oxide	Antioxidant	[75]
Glutathione Peroxidase	Graphene oxide	Biosensing	[35]
Oxidase	Manganese oxide	Immune-detection	[76]
Peroxidase	Manganese oxide	Immune-detection	[76]
Glutathione peroxidase	Trimanganese tetraoxide	Antioxidant	[77]
Glucose oxidase	Gold nanoparticles	Detection	[78]
Peroxidase	Platinum iridium	Immunoassay	[79]
Peroxidase	Ferromagnetic	Cancer therapy	[80]
Sulfite oxidase	Molybdenum trioxide	Cytoprotection	[81]
Peroxidase	Molybdenum disulfide	Cancer therapy	[82]
Glutathione Peroxidase	Vanadium pentaoxide	Antioxidant	[83]
Halo-peroxidase	Vanadium pentaoxide	Anti-bacterial	[84]
Glutathione Peroxidase	Tellurium nanorods	Antioxidant, anticancer	[85-87]

(GQDs) with peroxidase type possessions to the anti-bacterial system. In a deficient concentration of H_2O_2 , the GQDs catalyze the transformation of H_2O_2 to highly oxidized $\cdot OH$ and slaughter the bacteria efficiently. Moreover, the GQDs have an excellent anti-bacterial effect on Gram-positive and Gram-negative bacteria; these GQDs also used for wound disinfection [42].

Dental biofilms

Nanozymes also use to deal with oral diseases associated with biofilms. Bacterial biofilms bacteria that stay on the surface of contact, polysaccharides, secreting proteins, and biomolecules. Biomolecules enfold the bacteria due to these bacteria aggregates. As a result of these biofilms, many human diseases are produced. The most costly and common

biofilms associated with the oral disease are dental cavities and nanozymes to deal with these oral diseases [45]. When bacteria, especially *Streptococcus* mutants, use the food sugar to produce the polysaccharides and focus them on the upper layer of the teeth, the environment will gradually be more acidic due to this cavities biofilms formed because bacteria can be entrenched in the extracellular surface. Hence, it is hard to remove the oral biofilm [46].

Moreover, the acidic environments in the biofilm region can liquesce the analeptic component of teeth resulting in the commencement of dental cavities. Given the exclusive properties of enzymes, Koo's group used Fe_3O_4 nanoparticles with CAT NPS as the peroxidase mimics to prevent oral bacterial biofilm [2,47]. At the low pH environment, the oral biofilm CAT NPs could catalyze the production of $\cdot OH$ to kill the embedded bacteria and mutilate the biofilm matrix. CAT NPS alleviates the ossified of apatite in acidic pH and protects the teeth ideally.

Moreover, the CAT NP/ H_2O_2 system keeps adequately hinder the formation and decadence of cavities, on mucosal tissue with no side effects. They also showed that ferumoxide exhibit properties of peroxidase in a pH reliant manner. These nanoparticles bind under the ultra-structure of biofilm due to this bacterial membrane disturb. They also used rodent models of early childhood caries and ex vivo biofilm; finding showed that acid damage of the enamel surface and contingent applied ferumoxide effectually suppresses biofilm amassing, also prevents the start of tooth cavitation. Ferumoxide NPs serve as an efficient therapy for biofilm-related oral diseases [48].

Nanozymes role in cardiovascular disease

In the United States, over 80 million peoples have one in three deaths recognized for Cardiovascular Disease (CVD). Post myocardial infarction [1] heart failure can cause common deaths due to cardiovascular diseases. Mechanisms showed that in the place of damaged myocardium collagenous scar formation, these scars are non-contractile and lead to ventricular dilation, infarct wall thinning and hypertrophy of the myocardium. If no particular treatment applied and left untreated, this failure progress due to this heart no longer supplies adequate blood to the body, which is distinct as heart failure [49]. Moreover, advanced therapies of CVD and current techniques for early detection are imperfect, and they also have less efficiency in preventing the diseases [8].

Nanotechnology involves the following constituents, human-made nature and the unique characteristics of new material and nanoscale dimensions of the whole system or its vital components. Cardiovascular nanomedicine aims to improve detection and address current CVD and therapy challenges by advancing in vivo and ex vivo biomarkers imaging and detection and improving tissue regeneration and drug delivery. Drugs are delivering with direct injection and nanocarriers [50].

Nanocarriers

Nanocarriers are nanomaterials with an affinity to wrap

nanosized materials to transport, ideally release, and protect them at an addicted location or time. Nanocarrier size ranges from 1-100nm, many types of visitor molecules have been transferred with these nanocarriers, including imaging agents, metal nanoparticles, enzymes, dyes, and drugs [51]. Currently, many nanomaterials have been attempt and legalized in clinical trials: Liposomes [12] and micelles used in diseases as Drug Delivery Systems (DDS). Nanocarriers used in medicine to treat cardiovascular and other types of diseases differ in their chemical properties: nanotubes, polymeric nanoparticles, magnetic nanoparticles, liposomes, quantum dots, and dendrimers.

Liposomes

Liposomes size ranges from (80-300nm) they are lipid bilayer structure due to this use in medicine, and gene delivery. Liposomes are lipophilic and can pass target tissues/cell membranes [52]. These spherical vesicles have been most extensively investigated in nanomedicine with reapproval due to small toxicity for in vivo experiments. They have superior biocompatibility because liposome consists of phospholipids to form bilayer inside aqueous phase [53]. To protect the agents from degradation, they can also incorporate hydrophobic agents inward the lipid bilayer and hydrophilic therapeutic agents inside the aqueous place. The liposome's advantages, such as high stability in biological environments, high agent-loading efficiency, controllable release kinetics, the biodistribution of theragnostic agents, and biocompatibility provide liposome with efficient pharmacokinetics [54]. By the process of encapsulation, the drug is fused in the liposomes. Moreover, liposomes are employed as coordinators to deliver particles under the skin layers due to this frequency of administration reduce [55].

Micelles

Micelles consist of amphiphilic artificial molecules. To form monolayer micelles self-gather in aqueous solution with a hydrophobic phase, they incorporate hydrophobic agents. The micelles' size ranges from 10-100nm, and the inner space is more compassed than of liposomes [53]. These nanocarriers possessed of stimuli perceptive amphiphilic chunk copolymer are of pursuit due to their aptitude utilization in the field of discipline drug delivery [56].

Polymeric nanoparticles

Nanomedicine defines as the device of therapeutics and/or diagnostics on the nanoscale. Nanoscale gives benefits due to a huge degree of concurrent transfer and the prevention, treatment, and diagnosis of diseases in the biological systems [57]. Therapeutics based on polymeric nanoparticles are developed to advance the treatment and diagnosis of an extensive range of diseases. Leading in polymerization has implemented the engineering of leaded multifunctional polymeric NPs with accurate control, size, fictionalization, shape, and surface charge [58].

Advantage of these multifunctional polymeric NPs, where

the rendition of multiple functional groups from nanoparticle manufacture empowers binding capabilities examined to linear polymers and higher cell recognition. Moreover, these polymers allow the encapsulation of cargo molecules that contain the drug and released at the targeted sites. In biosensing and photodynamic therapies fabrication of polymer, nanoparticles provide new avenues [58].

Poly(ethylene glycol) (PEG) is a hydrophilic, biocompatible, biologically inert polymer that has been permitted by the U.S. Food Drug Administration (FDA) for use in a wide range of application. The number and length of PEG cuffs per NPs have been shown to fabricate significant deviation in circulation time in blood vs clearance of organs by eliminating polymeric NPs [57]. Flourishing data supports the idea that NPS loaded coated drugs onto an angioplasty balloon surface is an assuring approach to moderately enhance and protract drug delivery to the wall of arteries [59]. Nanoparticles are made from poly (lactic-co-glycolic acid) (PLGA) which is a biodegradable polymer that has been used as a vehicle of drug delivery for continuous releases of both hydrophilic and hydrophobic drugs [22].

Carbon nanotubes: In nanotechnology, carbon nanotube has become the leading edge due to its unique thermal, mechanical and electrical properties. Their low weight and high mechanical strength combined with their stability and electron conductivity prepared them valuable materials for biomedical applications [60].

Moreover, single-walled carbon nanotube (SWCNT) has an exclusive 1-layer cylindrical structure that repose of a graphene sheet and nanometer-size diameter the length of several hundreds of nanometers. These single-walled carbon nanotubes are hydrophobic in aqueous media. They are used in life sciences and nanotechnology, carbon nanotube used as gene and drug delivery to the cells [61].

Nanoparticles local injection for myocardial infarction

Enormous inflammatory responses distinguish by the enrollment of macrophages and neutrophils to the flubbed myocardium. These sequential responses result in the curative of infarction. Enrollment leukocytes stash several proteinases such as protease, cathepsin B, and matrix metalloproteinases, to expedite the clearance away of necrotic debris. By the deposition of remodelling and new tissues, efficient repair of the myocardium is scantily completed. If this healing is imperfect, it may ultimately lead to the cleft of the heart failure and infarction [49].

The nanoparticles which are used in the study by Chang, et al. insulin growth factor (IGF-1) was complexed to poly(lactic-co-glycolic acid) (PLGA) by electro statistically employing polyethyleneimine (PEI) to established nanoparticles. These particles' effect was checked by injecting these particles into the border zone following myocardial infarction in mice. The PEI/PLGA combination was also more powerful in lowering left ventricular systolic/diastolic, reducing infarct area, thickening the infarct wall [50].

A Gene level approach examined by somasuntharam, et al. [62] brings Nox2-nicotinamide adenine dinucleotide phosphate (NADPH) oxidase small interfering RNA (siRNA) in polyketide situate nanoparticles. Nox2 is a known source of ROS and catalytic subunit of NADPH. Nox2 prevents cardiomyocytes apoptosis and improves cardiac function due to the complete knockout of Nox2 [62].

Atherosclerosis

Atherosclerosis is an analytical progression that involves the gathering of cholesterol underneath the intima of arteries. These progressions are pursued by local commencement of the immune system, deposition of connective tissues, and vascular smooth muscle cells [63]. Moreover, atherosclerotic plaque proceeds from the early atheromatous lesion. When the atheromatous plaque burst thromboembolic ischemia formed. These plaques are thin capped vulnerable through immune responses and inflammation and infiltration of macrophages with intraplaque haemorrhage, neovascular expansion of the vasa vasorum, and necrotic core enlargement [64]. Evidence showed that the ROS has a double role: oxidative stress as a harmful culprit and maintaining physiological vascular homeostasis as a signalling messenger. Dysfunction occurs when the ROS level beats the maximum limit due to this disease stat formed [65].

Atherosclerosis is a lipid and dietary accession disorder, in lesion formation lipid play a role they cannot report for all atherosclerosis corporations. Atherosclerosis begins with endothelial damage, and apolipoprotein B has attractions for the basal membrane exposed in the place, where the endothelium is damaged [12].

Angiogenic expansion of the vasa vasorum in the adventitia is the key feature of the atherosclerotic process; within atherosclerotic plaques, the extensive neovascular proliferation is prominent within lesions and linked with unstable stroke, myocardial infarction, and angina. To inhibit the proliferation of the vasa vasorum and quantifying angiogenesis research used rabbit model, they combined drug delivery and molecular imaging with targeted NPs. They used the drug fumagillin with an integrin targeted paramagnetic NPS $\alpha_v\beta_3$ [66].

Moreover, the cardiac magnetic resonance with $\alpha_v\beta_3$ targeted paramagnetic NPs used noninvasively showed that only 1-minute dose of $\alpha_v\beta_3$ with targeted fumagillin NPS lowered the angiogenesis of aortic for 3 weeks [64]. Many studies hypothesized that $\alpha_v\beta_3$ with targeted NPs serve as an efficient nanomedicine tool for drug delivery, monitoring atherosclerosis, and noninvasive characterization [66]. The application of nanozyme and their mimetic enzymes are given in Table 2.

Conclusion

Since the discovery of Fe₃O₄ nanoparticles as peroxidase mimics, nanozymes have attracted much attention. As natural enzyme mimics, nanozymes possess many advantages: low cost, easy preparation, excellent stability, and good durability. They have been widely applied in sensing, environmental

treatment, anti-bacterial, cancer therapy, antioxidation, etc. This review summarized the classification, catalytic mechanism, activity regulation, and recent research progress of nanozymes in these fields in detail. Although nanozymes overcome many disadvantages of natural enzymes, several exciting challenges remain. Natural enzymes are widely used in fields, including medicine, food, industry, agriculture, environment, biotechnology, etc. Compared with natural enzymes, current research on applications of nanozymes are still rather limited. These unsolved issues will be the next frontier for further applications.

Authors' contributions

Conceived and designed the experiments: Naima Nashat, and Zeshan Haider, Wrote the paper: Naima Nashat, and Zeshan Haider. Finally, finalized the final review paper by Zeshan Haider.

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