Nanotechnology Perceptions
ISSN 1660-6795
www.nano-ntp.com

Nanozyme-Hydrogel Composites: Innovations in Drug Delivery and Tissue Engineering

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Nanozymes, a novel class of inorganic nanoparticles, mimic natural enzymatic functions and exhibit catalytic activities, making them promising tools in biomedical applications. The combination of nanozymes with hydrogels has led to the development of nanozyme-hydrogel composites, offering enhanced capabilities in drug delivery and tissue engineering. These composites leverage the catalytic efficiency of nanozymes and the biocompatibility of hydrogels to facilitate targeted drug delivery, controlled release, and tissue regeneration. By protecting nanozymes from burst release and improving their stability, these composites minimize toxicity and enhance therapeutic outcomes. Additionally, they contribute to antimicrobial activity, oxidative stress regulation, and improved cellular interactions, making them valuable in wound healing, anticancer therapies, and regenerative medicine. This review explores the synthesis, functional properties, and biomedical applications of nanozyme-hydrogel composites, highlighting their potential to revolutionize modern healthcare.

Keywords: Nanozymes, Hydrogels, Drug Delivery, Tissue Engineering, Catalytic Activity, Biomedical Applications.

1. Introduction

Nanozymes, a burgeoning class of inorganic nanoparticles, exhibit a remarkable capacity to mimic the catalytic behavior of natural enzymes, particularly in facilitating redox reactions [1]. This enzyme-like activity stems from their unique composition, which artfully merges the

inherent characteristics of nanomaterials with specific catalytic functionalities [2]. The resulting synergy endows nanozymes with exceptional attributes, including heightened catalytic activity, robust stability, and an inherent multifunctionality, making them attractive candidates for a wide array of applications spanning environmental science, technology, and biomedicine [3],[4]. In the realm of environmental science, nanozymes have demonstrated their utility in both qualitative and quantitative detection of various ions, molecules, and organic compounds, offering sensitive and reliable methods for environmental monitoring [5]. Furthermore, they exhibit the capacity to degrade a diverse range of organic pollutants, thus contributing to environmental remediation efforts, and effectively combat multi-drug resistant bacteria, addressing a critical challenge in public health [6]. Moving into the biomedical arena, nanozymes present themselves as promising alternatives to traditional natural enzymes, primarily due to their inherent biocompatibility and the ability to fine-tune their enzymatic activities for long-lasting effects [2]. Their versatility is showcased in a wide range of applications, notably in antimicrobial functions, where they instigate oxidative damage to bacterial membranes and biofilms by mimicking oxidoreductases, leading to the generation of reactive oxygen species (ROS), which are detrimental to bacterial survival [7]. Additionally, nanozymes can cleave glycosidic, amide, and phosphate bonds within biofilms via hydrolase-like activity, effectively disrupting the biofilm structure and reducing the likelihood of bacterial resistance[8]. A notable example is SAzymes, which have been developed for broad-spectrum antiviral and antifungal applications, leveraging their surface properties and tunable catalytic activities[3]. Beyond their antimicrobial capabilities, nanozymes also function as antioxidants, offering therapeutic potential for redox-regulated diseases by acting as analogs of endogenous antioxidant enzymes, thereby regulating intracellular homeostasis[6],[2]. For instance, Ceria nanoparticles (NPs), known for their CAT- and SOD-like activities, have shown promise in preventing hepatic ischemia-reperfusion injury and suppressing inflammatory reactions[9]. Their utility extends to food safety, where nanozymes are employed in biosensing and immunoassays to detect contaminants, ensuring the safety and quality of the food supply[4]. Complementing nanozymes, hydrogels represent another class of materials with significant biomedical potential[5]. Hydrogels are characterized by their unique network structure, enabling them to absorb and retain substantial quantities of water[10]. This inherent property, coupled with their biological functions, makes them well-suited for serving as structural scaffolds in various applications[1]. In drug delivery, hydrogels are employed to administer therapeutic agents for a multitude of diseases[7]. Their structure allows for the incorporation of hydrophilic drugs into hydrophilic hydrogel matrices through hydrogen bonding and electrostatic interactions, offering a means to control drug release kinetics[11]. Moreover, hydrogels can be modified with hydrophobic domains or amphiphilic molecules to enhance the encapsulation efficiency of hydrophobic drugs, expanding their applicability to a wider range of therapeutic compounds[6],[7]. In the realm of tissue engineering, hydrogels play a crucial role in promoting tissue repair, offering a conducive environment for cell growth and tissue regeneration[12]. The convergence of nanozymes and hydrogels has led to the development of nanozyme-hydrogel composites, which synergistically combine the advantageous properties of both components, using the nanozyme as a catalytic core and the hydrogel as a structural scaffold[13]. These composites offer several benefits, including the ability to shield nanozymes from burst release during catalytic production, thereby reducing potential toxicity, and the capacity to concentrate nanozymes in

targeted lesions, enhancing their therapeutic efficacy[14],[5]. Furthermore, they can catalyze the binding of specific substrates, leading to the impairment of drug-penetrating barriers and the remodeling of the pathological microenvironment, thus facilitating drug delivery and improving treatment outcomes[3]. The combination of nanozymes and hydrogels results in enhanced properties for both drug delivery and tissue engineering[15]. In drug delivery, the hydrogel component acts as a protective barrier, enabling the sustained release of nanozymes, preventing their aggregation and precipitation, and facilitating targeted delivery to specific sites[16]. Moreover, the composite materials can remodel the microenvironment, enhancing drug penetration and efficacy[12]. In tissue engineering, nanozyme-hydrogel composites promote tissue regeneration and repair through their antimicrobial and antioxidant activities, as well as their inherent biocompatibility[17]. These composites can be fabricated using either covalent or non-covalent immobilization techniques[3]. Covalent immobilization provides high stability and reduces enzyme leaching, but it involves a complex preparation process that may reduce nanozyme activity[14]. Non-covalent immobilization, on the other hand, is simpler and preserves the original nanozyme activity, but it exhibits lower stability and potential nanozyme leaching[18]. The development of nanozyme-hydrogel composites is gaining increasing attention due to their potential in various biomedical applications[19]. By combining the catalytic efficiency of nanozymes with the stability and biocompatibility of hydrogels, these composites offer enhanced drug delivery, promote tissue engineering, and expand therapeutic possibilities in areas such as anti-inflammatory, antibacterial, anticancer, and tissue repair[20],[8]. Hydrogels are now widely used in drug delivery, wound healing, tissue engineering, and cell transplantation, with structures similar to extracellular tissue matrices that play a vital role in tissue formation[21]. Hydrogels are widely used biomaterials in the delivery of therapeutic agents, including drugs, genes, proteins, etc., as well as tissue engineering[22]. Hydrogels can protect cells and sensitive drugs such as peptides, proteins, oligonucleotides, and DNA inside them, preventing their association with enzymes and ROS[20]. Hydrogels work well in delivering nutrients and growth factors to cells and removing the products of cellular processes from them [4]. Cell adhesive ligands can be easily attached to them[16]. Highly hydrated hydrogels mimic the physical and chemical environment of ECM; especially, injectable hydrogels have a microstructure similar to ECM, creating good physical integration[23]. Hydrogels also support cell proliferation due to their porous network[1]. The advantage of using hydrogels in drug delivery mostly refers to regulating the processes' kinetics[5]. For example, the network porosity can be easily adjusted to control the speed of drug penetration into the surrounding tissues[24]. In addition, it is possible to deliver both hydrophilic and hydrophobic drugs with these materials[13]. Hydrogels are attractive materials for the controlled release of therapeutics because of their capacity to embed biologically active agents in their water-swollen network[25]. In situ forming hydrogel systems are injectable fluids that can be introduced into any tissue, organ, or body cavity in a minimally invasive manner[14]. Hydrogels provide controlled dissolution, protect the labile drug from degradation, and control the release of various actives, including small-molecule drugs, macromolecules, and cells[26]. Hydrogel dressings absorb liquid well and can create a moist environment for tissue regeneration, and the slip elastic state of the hydrogel can effectively avoid secondary injury caused by wound adhesion, making them an excellent choice for medical dressings[27],[12],[14]. Injectable hydrogels provide a better survival environment for transplanted cells, and can be infused into the myocardium via

catheter for minimally invasive treatment, making them an important component of cardiac tissue engineering[16]. Hydrogel materials are widely used in tissue engineering because of their good biocompatibility and biodegradability[28]. Hydrogels are known for their high water retention capacity and biocompatibility and have become essential materials in tissue engineering and drug delivery[7]. Hydrogels with responsive performance have a broad range of potential applications in biological tissue engineering, including drug delivery[13].

Table :1 Applications of nanozyme-hydrogel composites.

S.NO.	Therapeutic Agent	Experimental Systems (Cells/Animals)	Nanozyme-Hydrogel Composition	Mode of Action	Observed Outcomes	refernces
1	Cerium Oxide (CeO2)	C57BL/6 rats	CCNZ1:Alg1.5 Matrix	Reducing Reactive Oxygen Species (ROS)	Rodents receiving the treatment showed a 5% greater weight gain compared to those treated with 5-aminosalicylic acid, following administration of three doses.	[34]
2	AIPH	4T1 cells/BALB/c mice	Iron Sulfide + Agarose Gel	Photothermal Therapy (PTT), Free Radical Action, Glutathione (GSH) Reduction	Tumor size in the treated group was significantly smaller, measuring just 1/9th of the size observed in the control group.	[65]
3	CpG ODN	CT26 cells/BALB/c mice	Modified CQD@Pd SAN with APS	Immune System Activation, ROS Scavenging	Complete suppression of tumor development was achieved, with the highest proportion of CD4+ and CD8+ T cells within the tumor area compared to all studied groups.	[51]
4	Doxorubicin	B16F10 cells/BALB/C nude mice	PFD + SD Complex	Targeted Drug Delivery & PTT	Virtually no tumor tissue remained in the treated group, contrasting sharply with the control group, which had tumors measuring 800 mm3.	[32]
5	Layered Double Hydroxide (LDO)	4T1 cells/BALB/c mice	Cobalt-Manganese-Iron LDO with Gelatin-Hydroxyphenyl	Synergistic Therapy (ST), PTT, Chemodynamic Therapy (CDT)	The mass of tumors in the treatment group was approximately one-seventh of that found in the untreated control group.	[21]
6	Mesenchymal Stem Cells (MSC)	Sprague-Dawley (SD) rats	Ceria Nanoparticles + Chitosan	Enhanced MSC Autophagy, ROS Diminution	Rats receiving the treatment showed a 6.2-fold improvement in hindlimb coordination compared to the control cohort.	[49]

7	Not Applicable (N/A)	Diabetic rats	Complex Hydrogel with ODex/gC/MoS2@Au@BSA	ROS Reduction, Oxygen Supply	Wound closure in the experimental group reached nearly 90%, whereas minimal healing occurred in the control animals.	[19]
8	Chondroitin Sulfate (CS)	SW135/BL6J/C57 mice	Manganese Oxide@CS	Attenuation of ROS Stress	Maintenance of both the thickness and integrity of the cartilage surface was observed post-injection.	[66]
9	Ce6	4T1 cells/BALB/c mice	Prussian Blue + Agarose Matrix	PTT, Sonodynamic Therapy (SDT), Oxygen Release	A tumor growth inhibition rate of 90% was achieved when compared against the control, and 80% relative to treatment with Prussian Blue alone.	[39]
10	microRNA (miRNA)	Sprague–Dawley (SD) rats	PCN-miR/Col + Agarose Scaffold	Modulation of Wound Environment	Wound dimensions in the treated group were reduced to approximately half the size of those in the control group.	[28]
11	Hydrogen Peroxide (H2O2)	MRSA/AREC/Kunming mice	Iron Phosphate Hydrogel	ROS Mitigation	A bactericidal effect of 98.21% against MRSA and 96.12% against AREC was recorded.	[61]
12	Not Applicable (N/A)	HGF/ SD Rats	PDMO Hydrogel	Inhibition of ROS, Antimicrobial Properties	Near complete antibacterial action was demonstrated by the PDMO hydrogel.	[13]
13	Copper Selenide (Cu2Se)	Cal-27/ BALB/c mice	Copper Selenide + SNP + Alginate	PTT and Gene Therapy (GT)	Near eradication of oral squamous cell carcinoma was accomplished.	[8]
14	Zeolitic Imidazolate Framework-8 (ZIF-8)	SD rats	Alginate-ZIF-8	ROS Reduction	Improves heart performance, reduces heart restructuring, and promotes blood vessel growth.	[42]

2. Components:

2.1. Nanozymes

Nanozymes, defined as nanomaterials with intrinsic enzymatic properties, have emerged as a transformative area of study, bridging nanotechnology, chemistry, biomedicine, and other interdisciplinary fields[29]. These nanomaterials, capable of mimicking natural enzymes, have garnered recognition as one of the top ten emerging technologies in chemistry[30]. With over 1200 distinct types reported, nanozymes are being explored across various applications, from environmental monitoring to biomedical diagnostics and therapeutics, showcasing their

versatility and potential to replace natural enzymes[14],[31]. Nanozymes can be largely separated into two types. Type 1 nanozymes refer to immobilized catalysts or enzymes on nanomaterials, which were dominant in the first decade since 2004 [32]. Type 2 nanozymes, which rely on the surface catalytic properties of inorganic nanomaterials, are the dominating type in the past decade[31].

A key aspect of nanozymes lies in their catalytic performances and mechanisms, which significantly influence their physicochemical characteristics, such as stability, specificity, and sensitivity, all vital for a wide range of biomedical applications[29]. Nanozymes effectively simulate the activities of oxidoreductases, including peroxidase (POD), catalase (CAT), oxidase (OXD), and superoxide dismutase (SOD), whereas a smaller subset exhibits catalytic capabilities akin to hydrolases and other enzyme classes[33]. The antimicrobial mechanisms of nanozymes can be categorized into two primary mechanisms: (1) oxidative damage to bacterial membranes and biofilms through the mimicking oxidoreductases to produce ROS, including O2 ·–, ·OH, 1O 2, HOO·, hypochlorous acid, and nitrogen radicals, and (2) the cleavage of phosphate, amide, and glycosidic bonds in biofilms via hydrolase-like activity[15],[16],[34]. These distinctive mechanisms significantly reduce the probability of bacterial resistance, presenting a promising avenue for enhancing antibacterial efficacy[11].

Nanozymes are becoming formidable alternatives to natural enzymes, owing to their unique advantages, particularly the long-lasting and adjustable enzymatic activities, as well as their favorable biocompatibility[35]. Recent advancements in nanozyme technology have facilitated sophisticated biomedical applications, encompassing areas such as sensing and imaging, microbial infections, inflammation, tumors, neurodegenerative diseases, and other medical conditions[36],[18]. In addition to their enzymatic activities, the unique physicochemical properties of nanozymes offer additional possibilities for synergistic antimicrobial treatments[9]. Properties such as the plasmonic effect, photocatalysis, porosity, and surface modifications can enhance photothermal therapy, photodynamic therapy, and drug delivery, thereby significantly improving antibacterial performance[37]. On the other hand, various nanozymes, including SAzymes, have been developed for broad-spectrum antiviral and antifungal applications due to their tunable catalytic and surface properties[29]. Compared with bacteria and viruses, enhancing antifungal efficacy represents a significant challenge, mainly due to the unique structural characteristics of fungi, such as their thicker cell walls and hyphal formations[23],[16]. In addition to significant progress in anti-infection applications, nanozymes also play a crucial role in treating several redox-regulated diseases in which ROS plays a primary and critical role in intracellular signaling[38].

To fully realize the potential of nanozymes, addressing challenges such as their tendency to precipitate and aggregate, as well as issues related to adhesion deterioration in composite materials, is crucial[39]. Strategies to enhance enzyme activity, ensure monomer structural stability, and improve substrate selectivity are also essential for advancing the field[40]. Nanozymes represent a promising frontier in biomedicine, offering a versatile platform for addressing a wide range of diagnostic and therapeutic challenges[37]. Nanozymes represent a category of nano-biomaterial artificial enzymes distinguished by their remarkable catalytic potency, stability, cost-effectiveness[41].

2.2. Hydrogels

Hydrogels, especially those designed with mucoadhesive properties, represent a significant advancement in both drug delivery and tissue engineering, offering a distinctive combination of characteristics that make them exceptionally well-suited for a diverse array of biomedical applications[42]. Characterized by their capacity to absorb and retain substantial quantities of water within their three-dimensional network structures, they effectively mimic the natural environment of bodily tissues, providing a biocompatible matrix ideally suited for both drug encapsulation and cell growth[16],[36],[43]. Several critical factors determine their effectiveness in therapeutic applications: the stability of hydrogels against erosion, their mucoadhesive properties, their capacity for sustained drug release, and their injectability into deep tissues[44]. The structural integrity of hydrogels in a physiological setting is of paramount importance to their overall function, and they must be capable of resisting degradation and erosion to ensure a controlled and predictable release of any encapsulated drug, while also providing ongoing support for tissue regeneration over extended periods[45]. Various factors influence the stability of hydrogels, including the specific type of polymer utilized in their creation, the overall degree of crosslinking, and the presence of enzymes or other degrading agents in the surrounding environment[42]. To improve their stability, researchers often employ crosslinking techniques to create a more robust and resilient network structure[27]. Mucoadhesion, which is the ability of a material to effectively adhere to a mucous membrane, is another essential property[18],[46]. By delivering drugs directly to the site of action, mucoadhesive hydrogels prolong the residence time of the drug and improve its bioavailability, which is particularly beneficial for drugs that are poorly absorbed or rapidly metabolized by the body[22],[47]. The mucoadhesive properties of hydrogels are generally achieved through the incorporation of polymers with adhesive groups, such as carboxylic acid or hydroxyl groups, which can interact with the mucus layer through various mechanisms, including hydrogen bonding, electrostatic interactions, or physical entanglement[48]. Another key advantage of hydrogels as drug delivery systems is their capacity to provide a sustained release of the drugs they carry. Researchers can control the drug's diffusion through the hydrogel matrix, or the degradation of the hydrogel itself, allowing them to achieve a desired release profile that optimizes therapeutic efficacy and minimizes potential side effects[10],[49]. Adjusting the hydrogel's composition, crosslinking density, and porosity enables them to tailor the drug release rate precisely[50]. The ability to inject hydrogels into deep tissues through minimally invasive procedures is also highly desirable for targeted drug delivery and various tissue engineering applications[51]. Typically, injectable hydrogels are formulated as viscous liquids that can be easily administered via a syringe or catheter[52]. Once injected, the hydrogel undergoes a phase transition to form a solid or semi-solid gel, providing support to the surrounding tissue and releasing the encapsulated drug over a period of time[49]. In the context of nanozyme-hydrogel composites, the hydrogel component serves as a protective barrier, facilitating the sustained release of the nanozymes, while the nanozymes themselves can contribute to the adherence of the hydrogel[8]. This synergistic combination of properties makes nanozyme-hydrogel composites promising candidates for a diverse range of biomedical applications, including drug delivery, tissue engineering, and regenerative medicine[53].

2.3. Nanozyme-hydrogel Composite:

Nanozyme-hydrogel composites represent a sophisticated advancement in drug delivery, artfully combining the strengths of both nanozymes and hydrogels to create synergistic therapeutic platforms[54]. These composites inherit the beneficial attributes of each component, presenting a multifaceted approach to drug delivery and biomedical applications[55]. The nanozyme component provides high enzyme activity, monomer structural stability, and high substrate selectivity, enabling catalytic reactions that can be harnessed for therapeutic purposes[56]. The hydrogel, acting as a structural scaffold, contributes stability against erosion, muco-adhesion, sustainable drug release, and injectability in deep tissue, and this combination addresses individual limitations, such as the tendency of nanozymes to aggregate and precipitate and the weak muco-penetration and delicate structure of hydrogels[42],[56],[57]. One of the most significant advantages of nanozyme-hydrogel composites is their capacity for controllable spatio-temporal drug release[31]. By carefully designing the composite material, drug release can be precisely orchestrated in both space and time, a level of control that is crucial for maximizing therapeutic efficacy while minimizing off-target effects and systemic toxicity[19]. For instance, drugs can be released specifically at a disease site, such as a tumor or an inflamed tissue, and the release rate can be modulated to maintain therapeutic drug concentrations over an extended period[33],[58]. The hydrogel component acts as a protective barrier, facilitating the sustained release of nanozymes and encapsulated drugs, and this protective function is particularly important for preserving the activity and stability of nanozymes, which can be susceptible to degradation or inactivation in biological environments[59]. Moreover, nanozyme-hydrogel composites excel in microenvironment remodeling[60]. The unique catalytic properties of nanozymes can be leveraged to manipulate the local microenvironment, creating conditions that favor drug activity and therapeutic outcomes[61]. For example, nanozymes can catalyze the production of reactive oxygen species (ROS) to induce oxidative stress in cancer cells or modulate the redox balance to promote tissue regeneration; this ability to remodel the microenvironment is a powerful tool for enhancing drug penetration, overcoming drug resistance, and promoting tissue healing[17],[20]. The inherent nature of nanozyme-hydrogel composites enables them to be highly compatible with various drugs[62]. Drugs can be loaded into the composite system by directly embedding them in nanozymes or hydrogels[63]. Drugs can be incorporated with nanozymes and subsequently introduced into a hydrogel solution through blending or encapsulation[64]. Hydrophilic drugs are readily incorporated into hydrophilic hydrogel matrices due to their compatibility with the aqueous environment, and the hydrogel's network structure allows the drugs to be evenly distributed throughout the matrix via hydrogen bonding and electrostatic interactions[53],[59]. To overcome this, hydrogels can be modified with hydrophobic domains or amphiphilic molecules that enhance the encapsulation efficiency of hydrophobic drugs[65]. Nanozyme-hydrogel composites hold immense promise for a wide array of biomedical applications, and their controllable drug release, microenvironment remodeling capabilities, and compatibility with various drugs make them well-suited for treating cancer, infections, inflammatory diseases, and injuries[23],[66]. They can be designed to respond to specific stimuli, such as pH, temperature, light, or magnetic fields, enabling targeted and on-demand drug delivery[67]. Their versatility and biocompatibility position them as a cutting-edge platform for advancing personalized medicine and improving patient outcomes[68].

3. Preparation Methods for Nanozyme-Hydrogel Composites:

Nanozyme-hydrogel composites can be prepared by either covalently immobilizing nanozymes within the hydrogel matrix for high stability, or non-covalently immobilizing them for a simpler preparation that preserves the nanozyme's original activity[60]. Other methods involve incorporating nanozymes into hydrogel microspheres to enhance catalytic efficiency and enable targeted delivery[55].

3.1. Nanozymes covalently immobilized within a hydrogel matrix:

Nanozyme-hydrogel composites, promising materials in biomedicine, can be synthesized through different preparation methods, each with its own set of advantages and disadvantages[63]. One prominent method involves covalently immobilizing nanozymes within a hydrogel matrix, resulting in a highly stable construct with reduced enzyme leaching and prolonged nanozyme activity[22]. In this approach, nanozymes are chemically bonded to the hydrogel network, ensuring that they remain firmly anchored within the matrix[37]. This strong interaction prevents the nanozymes from detaching or diffusing out of the hydrogel, leading to enhanced stability and sustained catalytic activity over extended periods[64]. The covalent linkage also protects the nanozymes from degradation or inactivation in biological environments, further contributing to their longevity[10]. However, the covalent immobilization method typically involves a complex preparation process that may require specific chemical modifications of both the nanozymes and the hydrogel[64]. These modifications can be challenging to implement and may involve multiple steps, increasing the overall complexity and cost of the synthesis[16]. Additionally, the chemical reactions used to create the covalent bonds can potentially alter the structure or properties of the nanozymes, potentially reducing their catalytic activity[56]. Despite these challenges, covalent immobilization remains a popular choice for applications where high stability and long-lasting activity are paramount[55]. An alternative approach involves non-covalently immobilizing nanozymes within a hydrogel matrix[44]. In this method, nanozymes are physically entrapped within the hydrogel network without the formation of direct chemical bonds[31]. This can be achieved by simply mixing the nanozymes with the hydrogel precursor solution before gelation[29]. As the hydrogel forms, the nanozymes become enmeshed within the matrix, held in place by physical constraints[55]. Non-covalent immobilization offers several advantages, including a relatively simple preparation process that preserves the original nanozyme activity[27]. Because no chemical modifications are required, the nanozymes retain their inherent catalytic properties. This method is also applicable to various hydrogels, providing flexibility in material selection[66]. However, non-covalent immobilization typically results in lower stability compared to covalent immobilization[32]. The nanozymes may leach out of the hydrogel over time, particularly in biological environments, leading to potential instability and reduced therapeutic efficacy[54]. In addition to these two primary methods, other techniques have been developed to create nanozyme-hydrogel composites[52]. For instance, nanozymes can be incorporated into hydrogel microspheres, increasing the surface area and enhancing catalytic efficiency[67]. These microspheres can also facilitate targeted delivery within the body and provide effective controlled drug release[54]. However, this approach may involve a complex preparation process and requires precise control of microsphere size and morphology[50]. Proper biocompatibility and non-toxicity should also be taken into consideration[31],[73]. The properties of the nanozymes should be compatible with those of

the hydrogel[41]. The drug should not chemically react with the composite and should be uniformly distributed within the hydrogel, allowing for stable and controlled release. Time effect needs to be considered as well[51].

3.2. Nanozymes non-covalently immobilized within a hydrogel matrix:

Nanozymes non-covalently immobilized within a hydrogel matrix present an alternative strategy for creating these composite materials, offering a distinct set of advantages and disadvantages compared to covalent immobilization[25]. This approach involves physically entrapping the nanozymes within the hydrogel network without forming direct chemical bonds[49]. Typically, this is achieved by mixing the nanozymes with the hydrogel precursor solution before gelation, resulting in the nanozymes becoming enmeshed within the matrix as the hydrogel forms[61]. One of the primary advantages of this method is its relatively simple preparation, as it doesn't require complex chemical modifications of either the nanozymes or the hydrogel, thus reducing the time, cost, and technical expertise needed for synthesis[32]. Furthermore, non-covalent immobilization is advantageous because it preserves the original nanozyme activity, ensuring that their inherent catalytic properties remain intact, which is particularly important for nanozymes with delicate structures or sensitive active sites that could be compromised by covalent modification[49],[51]. The versatility of this approach is another key benefit, as it is applicable to various hydrogels, providing flexibility in tailoring the composite's properties for specific applications[66]. Despite these advantages, non-covalent immobilization suffers from lower stability compared to covalent immobilization[34]. Without chemical bonds anchoring them in place, the nanozymes are more prone to leaching out of the hydrogel matrix over time, and this leaching can be exacerbated by the swelling and degradation of the hydrogel in biological environments, leading to a gradual loss of nanozyme activity and potential instability[45]. The potential instability in biological environments is another significant concern, because the release of nanozymes from the hydrogel could lead to unintended interactions with surrounding tissues or cells, potentially causing adverse effects, and the leached nanozymes may aggregate or lose their catalytic activity in the complex biological milieu, reducing their therapeutic efficacy[52],[58],[63]. To mitigate these limitations, researchers have explored various strategies to enhance the stability of non-covalently immobilized nanozymes[52]. These include using hydrogels with denser network structures to physically constrain the nanozymes, incorporating charged polymers to promote electrostatic interactions between the nanozymes and the hydrogel, or employing stimuli-responsive hydrogels that can encapsulate the nanozymes upon exposure to specific triggers[49]. Non-covalently immobilized nanozyme-hydrogel composites have found applications in various fields, including drug delivery, tissue engineering, and biosensing[18],[21]. In drug delivery, the hydrogel matrix can provide sustained release of the encapsulated nanozymes, allowing for prolonged therapeutic effects[25]. In tissue engineering, the composites can promote cell adhesion and proliferation, facilitating tissue regeneration[27]. In biosensing, the nanozymes can act as catalytic labels for detecting specific analytes[71]. The properties of the nanozymes should be compatible with those of the hydrogel, and the drug should not chemically react with the composite and should be uniformly distributed within the hydrogel, allowing for stable and controlled release[21].

3.3. Nanozyme-functionalized hydrogel microsphere:

Nanozyme-functionalized hydrogel microspheres represent a sophisticated approach in biomedical engineering, merging the catalytic prowess of nanozymes with the advantageous properties of hydrogel microspheres to create multifunctional platforms for drug delivery, tissue engineering, and diagnostics[11],[41]. These microspheres, typically ranging from one to several hundred micrometers in diameter, are composed of a three-dimensional network of cross-linked hydrophilic polymers, providing a biocompatible and highly hydrated environment for nanozyme encapsulation and activity[66]. The integration of nanozymes into these microspheres endows them with unique capabilities, offering a multitude of benefits for various biomedical applications[29]. One of the primary advantages of nanozyme-functionalized hydrogel microspheres is the increased surface area they provide, leading to enhanced catalytic efficiency[33]. By dispersing nanozymes throughout the microsphere matrix, a larger proportion of the nanozymes are exposed to the surrounding environment, facilitating their interaction with substrates and amplifying their catalytic activity[38]. This is particularly beneficial in applications where high reaction rates are desired, such as in biosensing or therapeutic interventions[27]. Moreover, the microsphere structure prevents the aggregation of bacterial cells, which can effectively prevent the invasion of harmful bacteria[64]. These microspheres also facilitate targeted delivery within the body, enabling precise spatial and temporal control over drug release and therapeutic action[45]. The microspheres can be engineered to respond to specific stimuli, such as pH, temperature, light, or magnetic fields, allowing for on-demand release of their nanozyme payload at the desired location, minimizing off-target effects and maximizing therapeutic efficacy, which reduces the risk of side effects and improves patient outcomes[26],[51],[65]. Effective controlled drug release is another significant advantage of nanozyme-functionalized hydrogel microspheres[62]. The hydrogel matrix acts as a reservoir for drugs, and the release rate can be carefully tuned by adjusting the microsphere's composition, crosslinking density, and porosity, which allows for sustained release of the drug over an extended period, maintaining therapeutic concentrations at the target site and reducing the need for frequent administrations[27],[30]. Despite these benefits, nanozyme-functionalized hydrogel microspheres also present several challenges[39]. The preparation process can be complex, often involving multiple steps and requiring precise control over reaction conditions, thus making it difficult to achieve consistent and reproducible results, which hinders their widespread adoption[70]. Precise control of microsphere size and morphology is also crucial for achieving optimal performance, as variations in size and shape can affect drug loading, release kinetics, and targeting efficiency, leading to inconsistent therapeutic outcomes[64]. Techniques such as microfluidics, emulsion polymerization, and 3D printing are employed to fabricate hydrogel microspheres with uniform size and defined structures[60]. Potential aggregation of microspheres affecting drug release represents another concern[29],[19]. Microsphere aggregation can reduce the available surface area for drug release, leading to slower and less efficient drug delivery, and it can also affect the microsphere's ability to target specific tissues or cells, compromising its therapeutic efficacy[37]. To address this issue, researchers often employ surface modification techniques to prevent microsphere aggregation and improve their dispersibility in biological media[45]. Furthermore, the properties of the nanozymes should be compatible with those of the hydrogel, and the drug should not chemically react with the composite and should be uniformly distributed within the hydrogel,

allowing for stable and controlled release[42]. Also, proper biocompatibility and non-toxicity should also be taken into consideration[18]. Nanozyme-functionalized hydrogel microspheres represent a promising platform for a wide range of biomedical applications, and by carefully optimizing their preparation methods and addressing the associated challenges, these microspheres hold great potential for revolutionizing drug delivery, tissue engineering, and diagnostics, paving the way for more effective and personalized healthcare solution[27],[28].

4. Drug Delivery:

Nanozyme-hydrogel composites represent a significant stride in the evolution of drug delivery systems, offering a synergistic blend of nanozymes' catalytic prowess and hydrogels' biocompatible, structural advantages[41]. These composites inherit the biological functions of both hydrogels and nanozymes, where the nanozyme serves as the catalytic core and the hydrogel forms the structural scaffold[71]. This innovative combination allows for improved drug loading, controlled release mechanisms, targeted delivery strategies, and the potential for microenvironment remodeling[20]. The inherent nature of nanozyme-hydrogel composites enables them to be highly compatible with various drugs, making them a versatile platform for drug delivery, and this compatibility stems from the ability to load drugs directly into either the nanozymes or the hydrogel matrix or by incorporating drugs with nanozymes and subsequently introducing them into a hydrogel solution through blending or encapsulation[58]. Several strategies can be employed to load drugs into nanozyme-hydrogel composite systems: embedding drugs directly in nanozymes or hydrogels, involving incorporating the drug directly into the nanozyme structure or the hydrogel matrix, achieved through surface adsorption, encapsulation within the nanozyme structure, or chemical conjugation for nanozymes, and physical entrapment within the polymer network during hydrogel formation for hydrogels; and incorporating drugs with nanozymes and encapsulating them in hydrogels, where the drug is first associated with the nanozyme, often through non-covalent interactions or chemical linking, before being encapsulated within the hydrogel matrix, allowing for synergistic delivery of both the drug and the nanozyme, potentially enhancing therapeutic efficacy[30]. Many nanozyme-hydrogel composites are designed as injectable hydrogels, which exist in a sol state at room temperature and can undergo conversion into a solid gel state in situ upon encountering the physiological environment[32]. This sol-gel transition is triggered by various stimuli, including temperature, pH, ionic strength, or light, and injectable hydrogels offer several advantages, including minimal invasiveness, precise placement at the desired site, and the ability to conform to complex tissue geometries[29]. Several factors influence drug encapsulation and release from nanozyme-hydrogel composites, including hydrophilic and hydrophobic interactions, as the hydrophilicity or hydrophobicity of the drug, nanozyme, and hydrogel components plays a crucial role in drug encapsulation and release; drug compatibility, as the compatibility of the drug with the nanozyme and hydrogel components is crucial for maintaining drug stability and activity; and the time effect, as the release of drugs from nanozyme-hydrogel composites is a time-dependent process, with the release rate influenced by various factors, including the hydrogel's degradation rate, drug diffusion coefficient, and the presence of stimuli-responsive elements[63]. The combination of nanozymes and hydrogels enables controlled spatiotemporal drug release and microenvironment remodeling, thereby augmenting therapeutic efficacy[11]. The hydrogel

component acts as a protective barrier, facilitating the sustained release of nanozymes[27]. Various hydrogel formulations have been developed to precisely target drugs to specific disease sites, such as the spinal cord, the eye, and the skin, and these formulations enable controlled spatiotemporal drug release, minimizing side effects on normal tissues[44],[49]. Moreover, the composite can concentrate nanozymes in targeted lesions and catalyze the binding of a specific group of substrates, resulting in pathological microenvironment remodeling and drug-penetrating barrier impairment[62]. The composite also shields nanozymes to prevent burst release during catalytic production and reduce related toxicity, while the hydrogel component facilitates the sustained release of nanozymes, and the nanozymes themselves contribute to the adherence of the hydrogel[73]. Activable multimodal nanozyme-hydrogel composites release their loaded drugs under sonic or photothermal stimulation[1]. Near-infrared (NIR) irradiation and sonication induce melting of the hydrogel, accelerating the release of sonosensitizers and nanozymes into targeted lesions[12],[55]. Nanozyme-hydrogel composites possess a unique combination of advantages, including high enzyme activity, monomer structural stability, and high substrate selectivity; stability against erosion, muco-adhesion, and sustainable drug release, injectability in deep tissue; controllable spatio-temporal drug release, microenvironment remodeling, higher compatibility with various drugs, and all advantages inherited from nanozymes and hydrogels; and increased surface area enhances catalytic efficiency, facilitates targeted delivery within the body, and effective controlled drug release[3]. Currently, the application of these composites has been extended to antibacterial, anti-inflammatory, anticancer, and tissue repair applications[54]. The enhanced performance of the nanozyme-hydrogel composite makes it a promising platform for drug delivery[22].

5. Applications:

Nanozyme-hydrogel composites are revolutionizing biomedicine with applications in antibacterial, anti-inflammatory, and anticancer therapies, alongside promoting effective tissue repair[28]. Their unique properties allow for targeted drug delivery, microenvironment remodeling, and enhanced therapeutic efficacy[59],[37]. These advanced materials hold significant potential for improving treatments and patient outcomes across diverse medical fields[9].

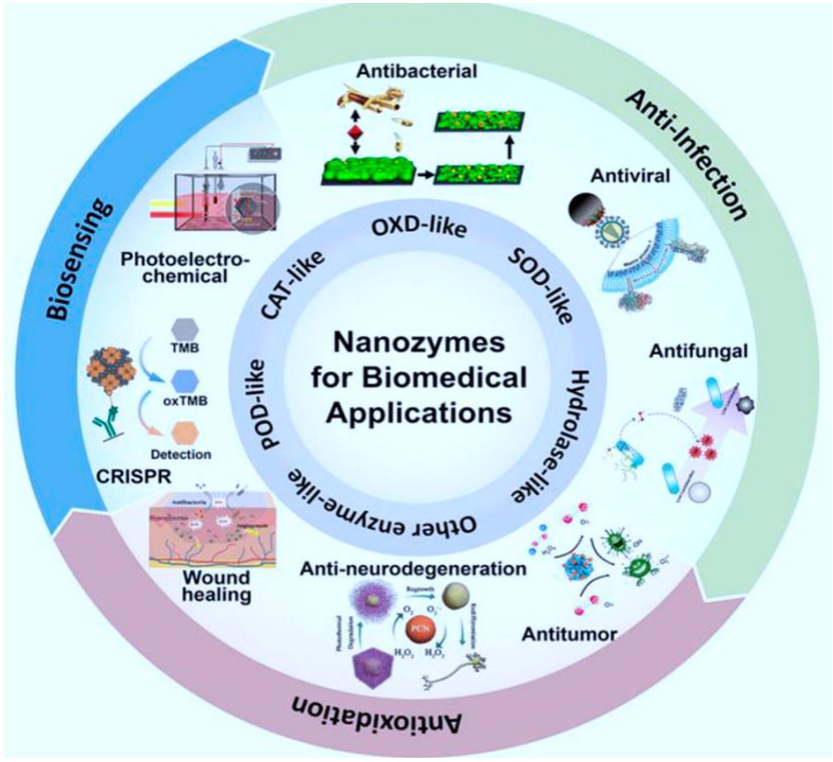

Fig. 1 Schematic illustration of nanozymes for biomedical applications.

5.1. Antibacterial:

Nanozyme-hydrogel composites are emerging as promising candidates in the fight against bacterial infections, showcasing broad-spectrum antibacterial activity both in vitro and in vivo [40]. The growing problem of antibiotic resistance has spurred the development of new antibacterial strategies, and nanozymes, with their unique physical and chemical properties, high stability, adjustable catalytic activity, and good biocompatibility, offer a compelling alternative[61]. By integrating nanozymes into hydrogels, these composites can effectively target and combat bacterial infections through multiple mechanisms, acting as versatile delivery systems that can be modulated in size, surface modification and active centers to kill different bacteria[52]. The antibacterial mechanism of nanozymes primarily involves the production of reactive oxygen species (ROS), which can damage bacterial cell membranes and destroy essential cellular substances[16]. Nanozymes catalyze the generation of ROS, such as superoxide anion, hydroxyl radicals, and singlet oxygen, leading to oxidative stress in bacterial cells that disrupts cell function and ultimately leads to bacterial death. Beyond ROS production, nanozymes can also exhibit contact sterilization, metal ion antimicrobial activity, and photothermal antimicrobial effects, further enhancing their antibacterial capabilities, enabling them to kill bacteria and treat wound infections with broad spectrum and high durability, which is superior for tackling the challenge of antibiotic resistance[49]. Hydrogels provide a supportive matrix for nanozymes, offering several advantages for antibacterial applications. The hydrogel network can protect the nanozymes from degradation and maintain their stability in biological environments[5]. Additionally, hydrogels can promote sustained

drug release, allowing for prolonged antibacterial activity at the infection site, and the combination of nanozymes and hydrogels can also enhance biocompatibility, reduce toxicity, and improve the overall therapeutic efficacy of the antibacterial treatment[30]. One notable application of nanozyme-hydrogel composites is in wound healing, as bacterial infections can significantly impair tissue regeneration and delay wound closure[51]. Nanozyme-hydrogel dressings can inhibit bacterial growth, reduce inflammation, and promote tissue repair, and multifunctional nanozyme hydrogels have been developed with antibacterial, antioxidative, and photothermal-induced nitric oxide-releasing properties to promote the healing of infected wounds, integrating photothermal properties, photo-thermally induced nitric oxide release, antibacterial activity, catalase activity, and antioxidative properties into a single platform, and a novel type of versatile nanozyme encapsulated in a thermo-sensitive hydrogel exhibited significant therapeutic effects in a mouse model of acute wound infections and displayed high biocompatibility[36]. Silver nanoparticles decorated with sodium nitroprusside-doped Prussian blue nanoparticles have been used as a multifunctional nanozyme in a thermo-sensitive hydrogel, demonstrating sustained release characteristics, high photothermal conversion efficiency, photo-induced nitric oxide release, and antibacterial activity, and in vitro and in vivo studies have shown that this composite hydrogel holds significant potential for treating infected wounds, since the proliferation of microorganisms in wounds can inhibit tissue regeneration, resulting in delayed wound healing and potentially leading to severe complications, such as sepsis[31]. In addition to wound healing, nanozyme-hydrogel composites have potential applications in treating various bacterial infections, including those caused by multi-drug resistant bacteria, and by targeting multiple bacterial mechanisms and enhancing therapeutic efficacy, these composites offer a promising strategy for combating the growing threat of antibiotic resistance[53].

5.2. Anti-inflammatory:

Nanozyme-hydrogel composites are demonstrating promising anti-inflammatory applications by leveraging their unique ability to modulate the inflammatory response at targeted sites[14]. These composites combine the benefits of both nanozymes, known for their catalytic activity and reactive oxygen species (ROS) scavenging capabilities, and hydrogels, which provide a biocompatible and injectable matrix for localized delivery; their multifaceted therapeutic effects include scavenging ROS and modulating other inflammatory mediators[42],[33]. One key mechanism by which nanozyme-hydrogel composites exert their anti-inflammatory effects is through the scavenging of ROS. In inflammatory conditions, there is often an overproduction of ROS, which can contribute to tissue damage and perpetuate the inflammatory cycle[29]. Nanozymes, particularly those with catalase or superoxide dismutase-like activity, can catalyze the breakdown of ROS, reducing oxidative stress and inflammation, and when these nanozymes are incorporated into a hydrogel matrix, they can be delivered directly to the inflamed tissue, providing a sustained and localized antioxidant effect[36]. A nanozyme-reinforced hydrogel with stem cells can effectively suppress inflammatory cytokines and improve prosthetic interface osseointegration in rheumatoid arthritis (RA) by scavenging endogenously over-expressed ROS and synergistically producing dissolved oxygen, thus augmenting osteogenic activities of stem cells and acting as a desirable stem cell delivery vehicle for improving prosthetic interface osseointegration in RA[31]. Beyond ROS scavenging, nanozyme-hydrogel composites can also modulate the broader inflammatory

response by influencing the behavior of immune cells and the production of inflammatory cytokines[50]. The composite can concentrate nanozymes in targeted lesions and catalyze the binding of a specific group of substrates, resulting in pathological microenvironment remodeling and drug-penetrating barrier impairment. Studies have shown that nanozyme-hydrogel composites can transform M1 macrophages, suppressing the levels of TNF-α, IL-1β, IL-6, and PGE2, while also exhibiting a similar tendency in the expression levels of these immunological cytokines in the synovial fluid[27]. The injectable nature of many hydrogel formulations further enhances their appeal for anti-inflammatory applications, as they can be easily administered through minimally invasive procedures, allowing for precise and targeted delivery of the nanozymes to deep tissues and joints[35]. This is particularly advantageous in conditions such as arthritis, where inflammation is often localized within specific joints, and the use of nanozyme hydrogel composite dressings is also helpful in bactericidal and anti-inflammatory applications[55]. In addition to their direct anti-inflammatory effects, nanozyme-hydrogel composites can also promote tissue repair and regeneration[47]. By reducing inflammation and oxidative stress, these composites create a more favorable environment for cells to proliferate and rebuild damaged tissues, as demonstrated by nanozyme-reinforced hydrogels with stem cells effectively suppressing inflammatory cytokines and improving prosthetic interface osseointegration, as well as in vivo wound healing results demonstrating accelerated healing of skin wounds in a mouse full-thickness defect[15],[48]. The design of nanozyme-hydrogel composites allows for the delivery of stem cells to protect implanted cells from ROS and hypoxia-mediated death and osteogenic limitation, having a broad impact on bone regeneration and osseointegration[69].

5.3. Anti-cancer:

Nanozyme-hydrogel composites are increasingly important in anticancer therapy because they can remodel the tumor microenvironment, facilitate site-specific drug release, and improve the efficacy of traditional treatment methods[18],[53]. These composites combine the catalytic activity of nanozymes with the stability and biocompatibility of hydrogels, offering a multifaceted approach to fighting cancer[65]. One key strategy in anticancer applications involves using nanozymes to address tumor hypoxia, a condition where cancer cells are deprived of oxygen, making them resistant to conventional therapies[27],[43]. Nanozymes, particularly those mimicking catalase (CAT), superoxide dismutase (SOD), oxidase (OXD), and peroxidase (POD), can generate oxygen within the tumor microenvironment, increasing the effectiveness of oxygen-dependent therapies like photodynamic therapy (PDT)[46]. By enhancing or depleting ROS levels, nanozymes can directly kill cancer cells or indirectly enhance the efficacy of other treatments[39]. Nanozyme-hydrogel composites can respond to characteristic factors within the tumor microenvironment to achieve site-specific drug release, which is essential for enhancing therapeutic efficacy in targeted organs and mitigating side effects in normal tissues[39]. Injectable hydrogels facilitate precise and targeted drug delivery, transitioning from a sol state at room temperature to a solid gel state upon encountering the physiological environment, which allows for the concentration of encapsulated drugs onto the tissue to which they adhere, achieving site-specific drug release[71],[35]. The inherent nature of nanozyme-hydrogel composites enables them to be highly compatible with various drugs[49]. Drugs can be loaded into a composite system by directly embedding them in nanozymes or hydrogels, or by incorporating them with nanozymes and subsequently

introducing them into a hydrogel solution through blending or encapsulation[27]. The choice of loading method depends on the desired relationship between sustained drug release and nanozyme activity[45]. Hydrophilic drugs are readily incorporated into hydrophilic hydrogel matrices because of their compatibility with the aqueous environment, while hydrophobic drugs can be accommodated by modifying hydrogels with hydrophobic domains or amphiphilic molecules[28]. Nanozymes can be tweaked to boost their catalytic performance, integrating them into complex enzyme networks similar to those in biological systems and adjusting functions like altering tumor metabolism, reshaping the tumor environment, and enhancing drug delivery[51]. The application of specially designed nanozymes extends to pan-cancer treatment, from catalytic therapy to improved traditional methods like chemotherapy, radiotherapy, and sonodynamic therapy, including the use of biomimetic design strategies to replicate the key characteristics of natural enzymes, including active structures, catalytic processes, and the ability to adapt to the tumor environment[24],[65]. Furthermore, emerging therapeutic modalities like photodynamic therapy (PDT) have progressively garnered attention within the realm of anti-tumor therapy. Nanozyme-hydrogel composites can also behave as nanocarriers, permitting the regulation and enhancement of the circulating duration of anticancer drugs[45]. Stimuli-responsive nanozyme-hydrogel composites can be injected into the breast tumor site with precise localization, allowing for dual stimulation involving ultrasound and near-infrared light to enhance therapeutic effects[61]. The application of peroxidase mimetic nanozymes is also being explored in catalytic cancer therapy, alongside chemotherapy, phototherapy, sonodynamic therapy, radiation, and immunotherapy[51].

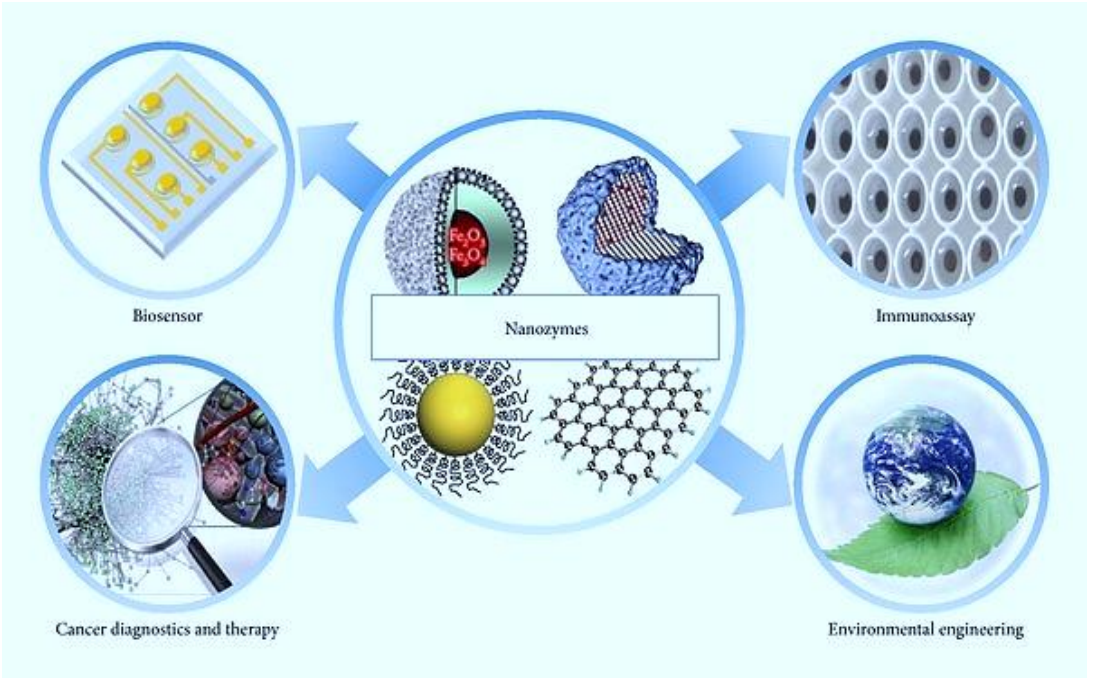

Fig. 2 Applications of Nanozymes in Biosensors, Immunoassays, Cancer Diagnostics, and Environmental Engineering.

5.4. Tissue repair:

Nanozyme-hydrogel composites are emerging as promising materials for tissue repair because of their ability to create a conducive environment for cell growth, tissue regeneration, and controlled delivery of therapeutic agents[36],[48]. Hydrogels, with their inherent biocompatibility and capacity to retain large amounts of water, closely mimic the natural extracellular matrix (ECM), providing a structural scaffold for cells to adhere, proliferate, and differentiate[51]. The incorporation of nanozymes into these hydrogels further enhances their therapeutic potential by introducing catalytic activity and responsiveness to the local tissue microenvironment[27]. In the context of tissue repair, nanozymes can play a crucial role in modulating oxidative stress and inflammation, two key factors that often impede the healing process[62]. Nanozymes with antioxidant properties, such as those mimicking superoxide dismutase (SOD) or catalase, can scavenge excessive reactive oxygen species (ROS) at the wound site, reducing oxidative damage to cells and promoting tissue regeneration[21]. Furthermore, nanozymes can be designed to catalyze the production of oxygen, alleviating hypoxia, which is another common challenge in damaged tissues[15],[63]. The hydrogel component of the composite provides a moist environment that is conducive to cell migration and proliferation, and it also acts as a physical barrier, protecting the wound from infection and dehydration[44]. Moreover, the hydrogel can be functionalized with cell adhesion molecules or growth factors to further enhance cell attachment and tissue regeneration, and by controlling the degradation rate of the hydrogel, the release of these therapeutic agents can be sustained over time, providing a prolonged stimulus for tissue repair[62]. Nanozyme-hydrogel composites have shown promise in various tissue repair applications, including wound healing, bone regeneration, and cartilage repair[33],[47]. In wound healing, these composites can accelerate the closure of chronic wounds by promoting angiogenesis, collagen deposition, and epithelialization, and the nanozymes can also help to prevent infection by killing bacteria and reducing inflammation[51]. In bone regeneration, nanozyme-hydrogel composites can enhance the osseointegration of implants and promote bone formation in large bone defects[55],67]. The nanozymes can stimulate osteoblast differentiation and mineralization, while the hydrogel provides a scaffold for new bone tissue to grow[72],[65]. In cartilage repair, these composites can promote chondrocyte proliferation and matrix synthesis, leading to the regeneration of damaged cartilage tissue[60]. Furthermore, nanozyme-hydrogel composites can be designed to respond to specific stimuli present in the damaged tissue, such as changes in pH, temperature, or enzyme activity, allowing for on-demand release of therapeutic agents or activation of catalytic activity, providing a targeted and controlled approach to tissue repair[68],[62]. The use of stem cells in conjunction with nanozyme-hydrogel composites is also gaining momentum in tissue engineering[44]. Stem cells can be encapsulated within the hydrogel matrix and delivered to the damaged tissue, where they can differentiate into specialized cells and contribute to tissue regeneration[32],[61]. The nanozymes can protect the stem cells from oxidative stress and hypoxia, enhancing their survival and therapeutic efficacy, and the nanozyme-reinforced hydrogel with stem cells can effectively suppress inflammatory cytokines and improve prosthetic interface osseointegration[65]. As research progresses, nanozyme-hydrogel composites are poised to play an increasingly important role in tissue repair, offering new hope for patients with chronic wounds, bone defects, and cartilage damage[70]. Their ability to modulate the tissue microenvironment, promote cell growth, and deliver therapeutic agents in a controlled manner makes them a versatile and powerful tool for

regenerative medicine, ultimately holding immense potential for revolutionizing tissue repair strategies and improving patient outcomes[73],[61].

6. Conclusion

Nanozyme-hydrogel composites represent a promising advancement in biomedical applications due to their unique combination of enzymatic mimicry, catalytic efficiency, and biocompatibility. These composites have demonstrated significant potential in drug delivery, tissue engineering, antimicrobial therapy, and oxidative stress regulation. By improving the stability, controlled release, and bioactivity of nanozymes, hydrogel-based systems offer a versatile platform for enhancing therapeutic efficacy while minimizing toxicity. Despite their remarkable advantages, challenges such as long-term stability, biodegradability, and large-scale production need to be addressed for their clinical translation. Future research should focus on optimizing their design, exploring novel functionalization strategies, and evaluating their in vivo performance. Overall, nanozyme-hydrogel composites hold great promise for revolutionizing modern healthcare by offering innovative solutions for targeted and sustained therapeutic applications.

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