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REVIEW

The Role and Mechanism of Nanozymes in Burn Wound Healing

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Abstract: The treatment of burn wounds is a complex and lengthy process, including infection control, inflammation modulation, tissue regeneration, and scar management. Although significant progress has been achieved, numerous clinical challenges persist, especially the increased bacterial resistance, the risk of wound sepsis, and the issue of serious hypertrophic scar. In recent years, nanozymes have emerged as a hotspot in materials research and increasingly been applied to promote burn wound healing. Possessing multiple enzyme-like activities, nanozymes can integrate antibacterial, anti-inflammatory, and pro-angiogenic effects, among others. Meanwhile, nanozymes offer advantages such as less prone to inducing drug resistance, high stability, and simple preparation, which indicate broad application prospects compared with antibiotics, natural enzymes, and traditional nanomaterials. This review provides a comprehensive overview of the pathophysiology involved in burn wounds and introduces nanozymes exhibiting a variety of enzyme-like activities including oxidase (OXD), peroxidase (POD), superoxide dismutase (SOD), catalase (CAT), haloperoxidase (HPO), nitrite reductase (NiRs), and hydrolase. The potential mechanisms by which nanozymes promote burn wound healing are summarized and elucidated from the aspects of antibacteria, anti-oxidative stress, anti-inflammation, pro-angiogenesis, and anti-scarring. Finally, we discuss the limitations of the current study and offer an outlook for future research, hoping to pave the way for the next generation nanozymes in the treatment of burn wounds.

Keywords: nanozyme, burn wound, antibacterial activity, oxidative stress, inflammation, pro-angiogenesis

Introduction

Burns are tissue injuries caused by heat, cold, chemicals, radiation, or electricity, and the majority of burns are thermal burns resulting from hot liquids, solids, or flames. The WHO estimates that approximately 180,000 people die from burns each year, with the vast majority of these deaths occurring in low- and middle-income countries.[1] The key pathological factors affecting the prognosis of burn wounds include infection, oxidative stress, chronic inflammation, impaired angiogenesis, and pathological scarring.

The goals of burn wound management include preventing infection, removing necrotic tissue, controlling pain, minimizing scarring, and restoring function.[2] To achieve these objectives, clinicians employ a comprehensive approach involving antibiotics, growth factors, negative pressure wound therapy, biological therapies, and other modalities.[3] Despite these interventions, post-burn complications such as infection, multiple organ dysfunction, and hypertrophic scarring continue to pose significant threats to the life quality of patients. Although antibiotics can control burn wound infections to some extent, their overuse contributes to increased bacterial resistance.[4] Growth factor-based therapies promote angiogenesis and accelerate burn wound healing, yet their short half-life and poor stability pose challenges for clinical application.[5] Compared to traditional dressings, disposable negative pressure drainage protective materials reduce hospital stay duration, wound healing time, and infection rates.[6] However, it relies on mechanical devices and the high cost makes them inaccessible to many patients. Emerging biological therapies, such as platelet-rich plasma, stem cells, and extracellular vesicles, demonstrate promising regenerative potential in preclinical studies. But their clinical application is limited by poor stability and complex preparation processes.[7]

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In recent years, nanozymes have emerged as a hotspot in materials research[8] and increasingly been applied to promote burn wound healing.[9] In the treatment of bacterial infected wounds, the bactericidal mechanism that catalyzes the production of reactive oxygen species (ROS) can prevent the emergence of drug-resistant bacteria.[10] Due to their potent ROS-scavenging properties, certain nanozymes can reduce oxidative stress and alleviate inflammation.[11] Benefiting from their multiple enzyme-like activities and potential to release bioactive ions, nanozymes can integrate antibacterial, anti-inflammatory, pro-angiogenic, and anti-scarring effects. When incorporated into the dressing matrix through physical embedding, self-assembly, or chemical cross-linking, nanozymes enable drug delivery and condition-responsive mechanisms, significantly enhancing overall wound healing efficacy.[12] Meanwhile, nanozymes offer advantages in controllability, high stability, biosafety and simple preparation, which indicate broad application prospects for catalytic therapy in wound management.[9]

Plenty of reviews have focused on the enzyme-like catalytic properties of nanozymes and their applications in wound healing, while limited attention given to burn wound treatment. This review aims to provide a comprehensive summary of the roles played by nanozymes with different enzyme-like properties in the pathophysiology scenarios of burn injuries. The pathophysiology of burn wounds is introduced firstly, followed by the discussion of the diverse enzyme-like activities and catalytic mechanisms of nanozymes. Moreover, the potential mechanisms by which nanozymes promote burn wound healing are summarized and elucidated from the aspects of anti-bacteria, anti-oxidative stress, anti-inflammation, pro-angiogenesis, anti-scarring, and so on, hoping to pave the way for the next generation nanozymes in the treatment of burn wounds.

Pathophysiology of Burn Wounds

Unlike lacerations or contusions, burn wounds exhibit minimal bleeding immediately after injury. Despite negligible red blood cell extravasation, substantial plasma-like fluid leaks from blood vessels to the skin surface during the early burn phase. This disrupts the body's internal homeostasis and may even trigger burn shock. Extensive damage of the skin barrier and the presence of necrotic tissue in deep burn wounds predispose the burn wound to infection. This condition potentially leads to severe complications such as sepsis, further impeding the wound healing process.[13] Additionally, impaired angiogenesis, oxidative stress, chronic inflammation, and pathological scarring are also major pathological factors affecting the prognosis of burn wounds. The following section first introduces the depth, zones, and healing process of burn wounds to elucidate potential therapeutic targets for nanozymes in burn wound management.

The Depth of Burn Wound

Based on the depth of burns and clinical manifestations, burn wounds are classified into three degrees (Figure 1A).[14] First-degree burns involve only a portion of the epidermal layer, presenting with redness and pain. Superficial second-degree burns affect the entire epidermis and part of the papillary layer, with partial damage to the germinal layer, resulting in pain, blisters, and exudation. Deep second-degree burns extend below the dermal papillary layer, leaving only a small portion of the dermis and skin appendages. Third degree burns, also known as eschar burns, generally refer to full-thickness burns, which can extend deep to muscles, bones, and internal organs. Some literature or guidelines refer to burns that extend to muscles, bones, and internal organs as fourth-degree burns.[2,7,15]

From a clinical therapeutic perspective, the healing of burn wounds is a complex and lengthy process. Typically, first-degree burn wounds heal spontaneously within 3–7 days. Superficial second-degree and some deep second-degree burn wounds often rely on wound care, due to the presence of blisters and exudate which carries an increased risk of infection. Third-degree and some deep second-degree burns, in which the presence of coagulated necrotic tissue increases the risk of infection, usually require early debridement and/or escharotomy followed by autologous skin grafting. Postoperative wounds, including donor sites and graft sites, also require careful wound management.[13]

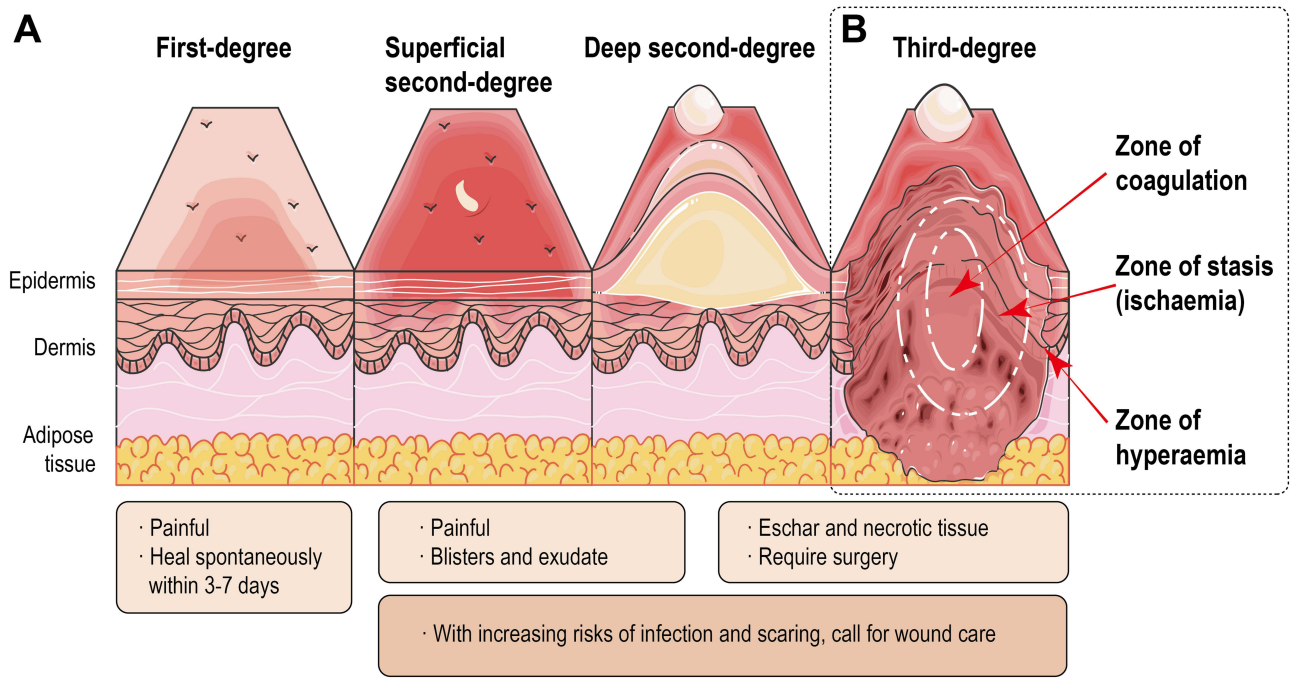

Figure 1 Schematic illustration for burn wounds. (**A**) Characteristics and therapeutic principles of different burn depths. (**B**) Zones of burn wound.

Zones of Burn Wound

Burn wounds exhibit three characteristic pathological zones (Figure 1B): the zone of coagulation, located at the wound center and characterized by tissue coagulative necrosis; the zone of stasis or ischemia, characterized by reduced perfusion but is potentially salvageable; the zone of hyperemia, located at the outermost layer of the wound and characterized by inflammatory vasodilation and congestive edema.[2] The zone of stasis adjoins the zone of coagulation. Due to peripheral vascular damage, this area experiences insufficient or even stagnant blood perfusion. Without intervention, ischemia and hypoxia will lead to tissue necrosis within 48 hours. Conversely, timely and positive intervention may reverse tissue necrosis, making this zone the primary target for wound-healing agents.

Cell necrosis in burn wounds is not only associated with tissue ischemia or hypoxia and bacterial infection, but also closely linked to excessive activation of ROS and oxidative stress. Systemic or topical administration of antioxidants can reduce tissue necrosis, thereby promoting burn wound healing. Animal experimental studies have confirmed that intraperitoneal injection and oral administration of the antioxidant N-acetylcysteine exert salvage effects on the zone of stasis.[16] Furthermore, immersion treatment of burn wounds with the antioxidant cerium nitrate can prevent progressive necrosis in the zone of stasis.[17]

Burn Wound Healing Process

The healing process of burn wounds can be broadly divided into four phases: hemostasis, inflammation, granulation tissue hyperplasia, and remodeling (Figure 2).[15,18]

Hemostasis

The hemostasis phase occurs within 10 minutes after burn injury, as the body rapidly initiates an immediate physiological response to minimize injury. This phase involves phenomena such as platelet aggregation, immune activation, blood coagulation, and complement system activation. The blood clot containing vitronectin, fibronectin, fibrin, and thrombospondins provide a temporary matrix scaffold for the migration of leukocytes, fibroblasts, keratinocytes, and endothelial cells, which in turn produce and release growth factors that accumulate at the wound site.[15]

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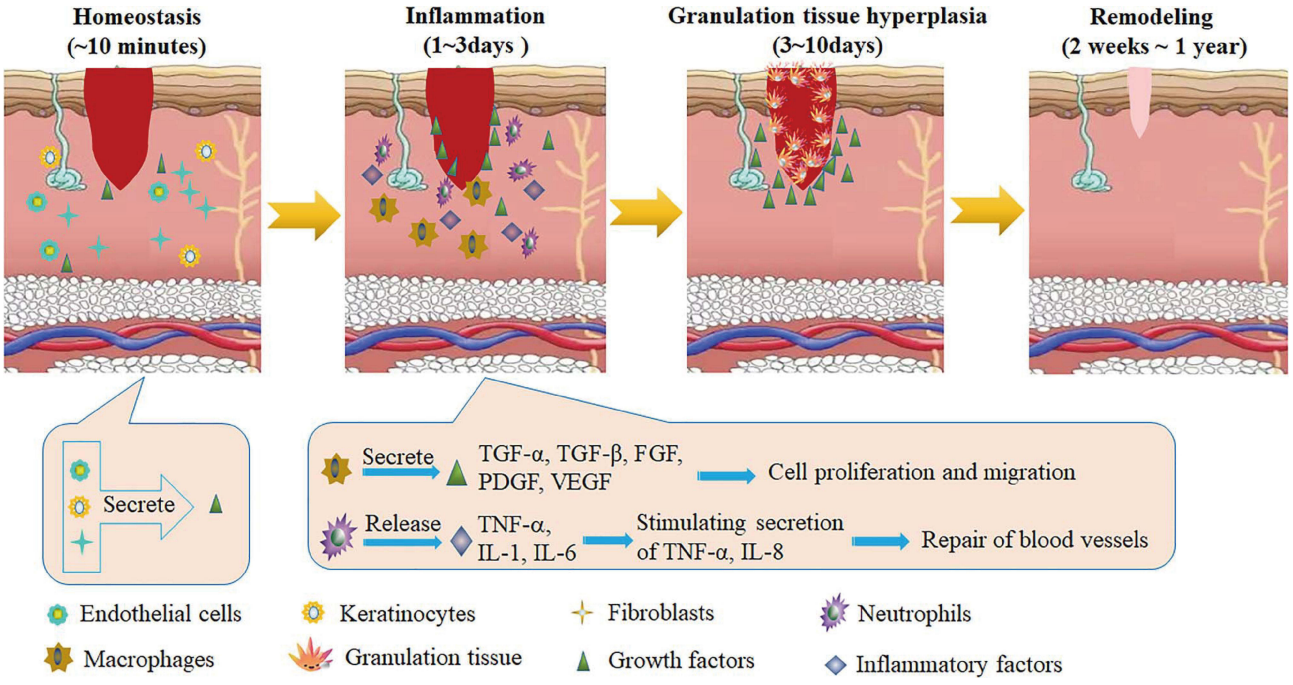

Figure 2 Four phases of burn wound healing process.
Abbreviations: TGF, transforming growth factor; FGF, fibroblast growth factor; PDGF, platelet-derived growth factor; VEGF, vascular endothelial growth factor; TNF, tumor necrosis factor; IL, interleukin. Reproduced from Huang R, Hu J, Qian W, Chen L, Zhang D. Recent advances in nanotherapeutics for the treatment of burn wounds. *Burns Trauma*. 2021;9:tkab026. Creative commons.[18]

Inflammation

The inflammation phase occurs 1–3 days after burn injury and is characterized by rapid activation of the immune system. Following the burn damage, local vasodilation occurs, and meanwhile neutrophils and monocytes are recruited to the wound site by chemotactic factors. Neutrophils arrive at the wound site within minutes to hours after the burn injury. They release inflammatory mediators such as tumor necrosis factor (TNF)-α, interleukin (IL)-1, and IL-6, which activate the inflammatory response and stimulate the secretion of vascular endothelial growth factor (VEGF) and IL-8 to promote angiogenesis. Additionally, monocytes differentiate into activated macrophages that clear debris and pathogens. Meanwhile, they produce various growth factors—including transforming growth factor (TGF)-α, TGF-β, fibroblast growth factor (FGF), platelet-derived growth factor (PDGF), and VEGF—to stimulate cell proliferation and migration.[18,19]

Granulation Tissue Hyperplasia

The granulation tissue hyperplasia phase occurs 3–10 days after the infliction of burn wound and is characterized by the proliferation of fibroblasts, keratinocytes, and endothelial cells. At the end of the inflammatory phase, mesenchymal stem cells differentiate into fibroblasts, which synthesize extracellular matrix (ECM) components such as collagen to form the granulation tissue scaffold. Keratinocytes proliferate and migrate to the wound site, promoting angiogenesis and restoring the epidermal barrier through re-epithelialization. Growth factors such as VEGF, PDGF, FGF-2, and granulocyte-macrophage colony-stimulating factor (GM-CSF) activate endothelial cells, initiating angiogenesis to supply nutrients and oxygen to healing tissues. These processes synergistically interact, which ultimately lead to the formation of granulation tissue through the collaborative action of new blood vessels, fibroblasts, granulocytes, and macrophages, thereby promoting wound closure and restoration of skin function.[18] Currently, topical growth factor therapies based on PDGF-BB, FGF-2, GM-CSF, and VEGF-A are widely applied in burn wound treatment and have demonstrated significant efficacy.[5]

Remodeling

The remodeling phase lasts from 2–3 weeks to 1 year after burn damage. As granulation tissue matures, the ECM undergoes remodeling under the influence of growth factors, matrix metalloproteinases (MMPs, a class of proteolytic enzymes), and tissue inhibitors of metalloproteinases (TIMPs), which results in increased tensile strength. Under the influence of TGF-β and other factors, fibroblasts transform into myofibroblasts. Myofibroblasts express α-smooth muscle actin (α-SMA), facilitating wound contraction to reduce wound area.[20] However, excessive remodeling might lead to the formation of hypertrophic scars or keloids, compromising function and aesthetics.[2]

Burn wound healing is a dynamic process in which four phases usually overlap. Wound exudation persists for 2–3 days and early fluid resuscitation is typically required to maintain internal homeostasis. Infection often accompanies the entire healing process of burn wounds, due to the absence of the skin barrier, the presence of abundant exudate and necrotic tissue.[13] Therefore, anti-infective therapy is crucial in the management of burn wounds.

In acute wounds, macrophages exhibit pro-inflammatory activity (M1 type), infiltrating the site after injury to clear bacteria and necrotic cells. As wound repair commences, macrophages polarize to an anti-inflammatory or pro-healing phenotype (M2 type) that promotes the migration and proliferation of fibroblasts, keratinocytes, and endothelial cells to restore the dermis, epidermis, and vasculature respectively.[21] Dysfunction of inflammatory cells occurs during burn wound healing. Huang et al demonstrated that peripheral blood neutrophil function is impaired in burn shock patients.[22] This impairment manifests as severely compromised chemotaxis, alongside abnormal bactericidal capacity characterized by reduced production of ROS and diminished phagocytic killing. In chronic wounds such as deep burn wounds, the persistent presence of pro-inflammatory macrophages that fail to transition to an anti-inflammatory phenotype may impair tissue repair. During burn wound management, interventions modulating neutrophil and macrophage function may facilitate wound healing.

During the early remodeling phase, macrophages release MMPs to degrade the temporary ECM and subsequently undergo apoptosis, enabling the skin to revert to its original state.[21] Although certain burn wounds may achieve closure with therapeutic intervention, in most cases the structural and functional integrity cannot be fully restored, ultimately resulting in scar tissue that replaces normal skin. Complete skin repair requires not only wound closure, but more critically, the inhibition of pathological scarring and the restoration of normal skin function.

Catalytic Mechanisms of Nanozymes

Enzymes are proteins that exhibit high specificity and highly efficient catalytic activity toward their substrates. Additionally, certain RNA molecules (known as ribozymes) also possess catalytic activity. However, natural enzymes are susceptible to denaturation under high temperatures, strong acids, or strong bases, thereby losing their catalytic capabilities. In 2004, Professor Scrimin and his team coined the term "nanozymes" for nanomaterials characterized by simple synthesis and outstanding catalytic performance.[23] At this stage, the definition of nanozymes referred solely to the immobilization of enzymes or catalysts on nanomaterial surfaces. In 2007, Professor Yan and her team discovered that Fe_3O_4 magnetic nanoparticles exhibited intrinsic peroxidase (POD)-like activity.[24] This discovery challenged the conventional understanding that nanomaterials require modification to exhibit catalytic functions and pioneered a new research frontier for nanozymes. Thus, the definition of nanozymes has evolved. "Nanozymes" now encompass not only enzymes or catalysts immobilized on nanomaterials but also specifically refer to nanomaterials that possess intrinsic catalytic properties.[25]

Over the past two decades, researchers have developed nanozymes with diverse catalytic functions. In biomedical applications, most nanozymes mimic the activity of oxidoreductases, while a minority exhibit catalytic capabilities similar to hydrolases or other classes of enzymes.[26] Nanozymes with oxidoreductase activity can be broadly categorized into two types: (1) pro-oxidant nanozymes that generate ROS (including hydrogen peroxide (H_2O_2), hydroxyl radicals (·OH), superoxide anions ($\cdot O_2^-$), singlet oxygen ($^1O_2$), etc), such as POD- and oxidase (OXD)-like nanozymes; (2) antioxidant nanozymes that scavenge ROS, such as catalase (CAT)- and superoxide dismutase (SOD)-like nanozymes.[27] Due to their exceptional biocatalytic performance and high stability, nanozymes have been employed to treat a range of diseases, including cancer,[28] inflammatory bowel disease,[29] Parkinson's disease,[30] acute kidney injury,[31] glaucoma,[32] and so on. Overall, pro-oxidant nanozymes are utilized for anti-cancer and anti-infective purposes, as the ROS they generate can eliminate pathogens and cancer cells. Antioxidant nanozymes are employed in inflammatory diseases such as acute kidney injury, inflammatory bowel disease, Parkinson's disease, and glaucoma,

owing to their potent ROS scavenging capability. Nanozymes such as haloperoxidase (HPO), nitrite reductase (NiRs), and hydrolases have been extensively studied in promoting wound healing due to their antibacterial, anti-biofilm, and pro-angiogenic effects. Next, we focus on elucidating the catalytic mechanisms of several nanozymes closely associated with burn wound healing (Figure 3).

Pro-Oxidant Nanozymes

OXD-Like Nanozymes

OXD-like nanozymes can catalyze the oxidation of substrates by reducing O_2. Depending on the number of electrons transferred, the reduction products of oxidation can be $\cdot O_2^-$, H_2O_2, or H_2O.[33] Comotti et al demonstrated that Au nanoparticles can form dioxygen intermediates: Au^+-O_2^- or Au^{2+}-O_2^{2-}.[34] These act as electron bridges transferring electrons from glucose to O_2, catalyzing H_2O conversion to H_2O_2, exhibiting glucose oxidase-like activity. Lin et al demonstrated that MoO_3 nanoparticles exhibit OXD-like activity.[35] They can catalyze the activation of dissolved oxygen in the solution to generate ROS such as $\cdot O_2^-$, thereby oxidizing colorless 2,2′-azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) into a green product. Zhang et al employed a hydrothermal method to synthesize a zirconium porphyrin-based MOF.[36] The presence of oxygen vacancies enhances oxygen absorption and activation, generating more reactive $\cdot O_2^-$ and exhibiting OXD-like activity. Additionally, nanozymes containing Ag,[37] Cu,[38] Fe,[39] Pd,[40] and Ir[41] have also been found to exhibit OXD-like activity. Currently, most OXD-like nanozymes are primarily used in detection and colorimetric analysis.[42]

POD-Like Nanozymes

POD-like nanozymes can convert H_2O_2 to $\cdot OH$.[43] This reaction transforms the less reactive H_2O_2 into the more reactive $\cdot OH$. Fe_3O_4 magnetic nanoparticles were the first reported nanozymes exhibiting POD-like activity.[24] Their catalytic performance is similar to that of horseradish peroxidase (HRP). With H_2O_2, they can catalyze common peroxidase substrates like 3,3,5,5-tetramethylbenzidine (TMB), diazotized aniline (DAB), and o-phenylenediamine (OPD) to produce a detectable color change. Currently, various Fe_3O_4-containing nanozymes have been developed and applied in antimicrobial therapy for wound treatment, such as Fe_3O_4/ZnO_2 electrospun nanofibers,[44] Ag-Fe_3O_4 nanofibrous microspheres,[45] and Fe_3O_4@MoS_2 core-shell nanozymes.[46] Additionally, nanozymes containing Au,[47] Pt,[48] Ru,[49] Ir,[50]

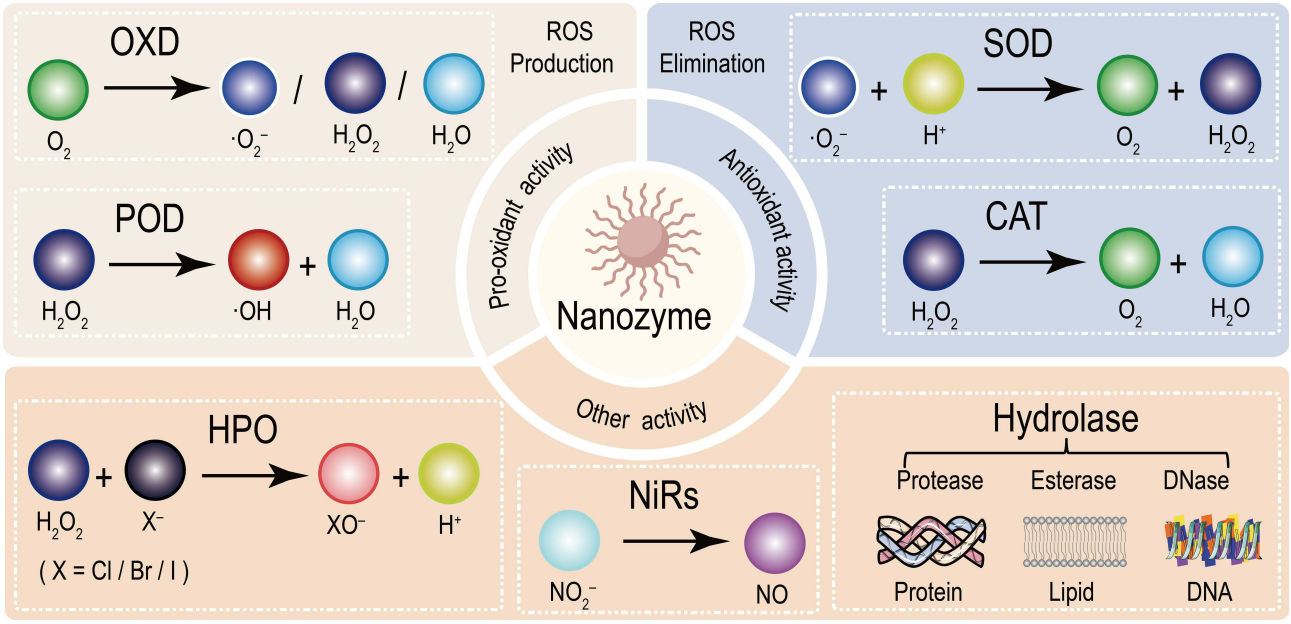

Figure 3 Catalytic mechanisms of nanozymes.
Abbreviations: OXD, oxidase; POD, peroxidase; SOD, superoxide dismutase; CAT, catalase; HPO, Haloperoxidase; NiRs, nitrite reductase; DNase, deoxyribonuclease; ROS, reactive oxygen species.

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Pd,[51] CuO,[52] and Co_3O_4[53] have been found to exhibit POD-like activity. Besides, carbon-based nanozymes such as single-walled carbon nanotubes, graphene oxide, and carbon nanodots have also demonstrated POD-like activity.[28]

Metal polyphenol self-assembled nanodots and single-atom nanozymes represent two emerging types of biomimetic catalytic materials in recent years. Zhu et al fabricated metal-polyphenol self-assembled nanodots (Fe@BDP NDs).[54] In the weakly acidic tumor microenvironment, Fe@BDP NDs exhibit superior Fenton reaction activity, catalyzing the conversion of overloaded H_2O_2 into highly toxic ·OH within tumor cells. Zheng et al developed a potassium single-atom nanozyme (K-SAN) with a K-N active site.[55] K-SAN exhibits remarkable POD-like activity, converting excess H_2O_2 into ·OH, thereby inducing lethal lipid peroxidation. Under 808 nm laser irradiation, the catalytic activity of K-SAN was enhanced, significantly inhibiting tumor growth in vivo. Xu et al reported a zinc-based zeolitic-imidazolate-framework (ZIF-8)-derived carbon nanomaterial containing atomically dispersed zinc atoms.[56] This single-atom nanozyme features an unsaturated Zn-N_4 site, exhibiting superior POD-like activity and potent antibacterial activity against *Pseudomonas aeruginosa*.

Antioxidant Nanozymes

SOD-Like Nanozymes

SOD-like nanozymes can catalyze the disproportionation of $\cdot O_2^-$ to produce O_2 and H_2O_2.[33] $\cdot O_2^-$ serves as a precursor for various ROS and plays a crucial role in oxidative stress and immune regulation.[57] This reaction helps reduce superoxide levels, thereby alleviating oxidative stress and inflammatory responses. Geethika et al designed a SOD-mimetic $CeVO_3$ nanozyme that optimally regulates $\cdot O_2^-$ levels in endothelial cells under oxidative stress conditions while enhancing endogenous nitric oxide (NO) levels by preventing peroxynitrite anion ($ONOO^-$) formation.[58] Long et al developed a formulation of Prussian blue nanozyme coated with polydextrose-sorbitol carboxymethyl ether (PBNz@PSC), exhibiting enhanced SOD-like activity due to its polysaccharide properties.[59] PBNz@PSC demonstrated outstanding ROS scavenging capacity, driving macrophage polarization from M1 to M2 and reducing IL-1β, IL-6, and TNF-α levels to counteract inflammation.

Li et al designed a microglial membrane-wrapped single-atom nanozyme (PtRhIr/Ru SAN@M) by anchoring a single atom of Ruthenium onto ultrasmall, medium-entropy PtRhIr alloys.[60] It exhibits superior SOD-like and CAT-like activities, enabled by electronically modulated active sites. Ye et al developed an ultra-small platinum single-atom nanozyme (Pt/SAE) with multiple antioxidant enzyme activities.[31] Pt/SAE not only mimics the activity of SOD and CAT, converting $\cdot O_2^-$ into H_2O and O_2, but also demonstrates remarkable ·OH scavenging capacity, thereby reducing pro-inflammatory macrophage levels and preventing inflammation.

CAT-Like Nanozymes

CAT-like nanozymes can decompose H_2O_2 into H_2O and O_2, preventing ROS accumulation and protecting cells from oxidative stress damage.[27] Zhang et al developed the NAM@CeMOF-2 nanozyme system, which effectively eliminates H_2O_2 and mitigates oxidative stress.[32] Hu et al integrated hematite nanozymes into a polyvinyl alcohol membrane.[61] Acting as a catalyst with CAT-like activity, this nanozyme efficiently converts H_2O_2 into O_2, promoting fibroblast growth and facilitating wound healing. Kim et al developed Aurozyme, a nanomedicine comprised of Au nanoparticles and glycyrrhizin with a glycol chitosan coating layer.[62] The amine-rich environment provided by glycol chitosan converts harmful POD-like activity of Au nanoparticles into beneficial CAT-like activity. Aurozyme can also oxidize ·OH derived from Au nanoparticles to produce H_2O and O_2, effectively scavenging ROS, reactive nitrogen species (RNS), and damage-associated molecular patterns (DAMPs). This reduces macrophage M1 polarization and exhibits anti-inflammatory effects at the lesion site.

Notably, various nanomaterials, including Au, Ag, Pt, CeO_2, Co_3O_4, MoS_2, CuS, and RuO_2, have been demonstrated to possess multiple nanozyme activities.[63] They commonly exhibit POD-, CAT-, and SOD-like activities, endowing them with broad application potential in biomedicine.

Other Nanozymes

HPO-Like Nanozymes

HPO-like nanozymes, a subclass of POD-like nanozymes, can catalyze halide ions (Br^-, Cl^- or I^-) to generate hypohalous acid in the presence of H_2O_2. Nanozymes containing V_2O_5,[64,65] Ce,[66] and Mo[67] have been found to exhibit HPO-like activity. For

instance, Natalio et al experimentally demonstrated that V_2O_5 nanowires possess activity similar to natural vanadium haloperoxidase (V-HPO).[65] In the presence of Br^- and H_2O_2, these nanowires can catalyze the oxidation of Br^- to hypobromous acid (HBrO), forming $^1O_2$ with potent antibacterial activity that inhibits biofilm formation. Wang et al synthesized a bimetallic sulfide containing nickel and molybdenum (L-$NiMoS_2$), exhibiting outstanding HPO-like activity.[67] In the presence of H_2O_2, it can catalyze the oxidation of Br^- into the bactericidal agents HBrO, demonstrating exceptional antibacterial capability.

NiRs-Like Nanozymes

NiRs-like nanozymes which typically feature active sites composed of metal atoms (such as Cu, Fe, or Mo) can convert nitrite (NO_2^-) to NO.[68] Diverse NiRs-like nanozymes have been developed for antimicrobial applications, including Cu-MOFs, Cu-nitrogen complexes, Fe single-atom catalysts, MoS_2 nanosheets, and so on. Wang et al developed a copper-based MOF (Cu-BDC) exhibiting high electrocatalytic activity for NO_2^- reduction to NO and excellent antibacterial efficacy, achieving a 999% bacterial kill rate when applied to catheter antibacterial treatment.[69] Feng et al developed a NiRs-like nanozyme (NFLA/CuS NHs) by in situ growth of ultrasmall copper sulfide clusters (CuS) on the surface of a nanofibrillar lysozyme assembly (NFLA).[70] Benefiting from the structure with CuS cluster as active center and NFLA as skeleton, NFLA/CuS NHs efficiently catalyze the reduction of nitrite to NO. The initial high-concentration NO release attacks bacteria, while the subsequent low-concentration NO release significantly promotes cell migration and angiogenesis.

Hydrolase-Like Nanozymes

Hydrolase-like nanozymes can catalyze the hydrolysis of ester bonds, peptide bonds, and glycosidic bonds. Based on their substrate specificity, they can be classified into esterase-, protease-, nuclease-, and phosphatase-like nanozymes. Fang et al synthesized a UiO-type metal organic framework-based nanomaterial incorporated with single-atom Cu (UiO-67-Cu-N), exhibiting deoxyribonuclease (DNase)-like activity.[71] UiO-67-Cu-N effectively catalyzes DNA cleavage, thereby inhibiting horizontal gene transfer of antibiotic-resistant genes and eliminating bacterial antibiotic resistance. Guo et al synthesized multi-functional nanozymes manganese selenide nanoflowers (MnSe NFs) exhibiting phosphodiesterase-, OXD-, and POD-like activities.[72] MnSe NFs demonstrated potent anti-biofilm activity against *Staphylococcus aureus* and *Pseudomonas aeruginosa*, achieving antibacterial rates exceeding 99.999%.

To date, over 1,000 types of nanozymes have been developed.[73] Nanozymes can be broadly categorized into metal-based nanozymes, metal oxide-based nanozymes, carbon-based nanozymes, MOF-based nanozymes, and so on.[33] Compared to natural enzymes, nanozymes not only exhibit highly efficient catalytic performance but also feature superior stability, low production costs, extended shelf life, and ease of synthesis and modification.[26] Additionally, nanozymes exhibit distinctive physicochemical properties, such as photothermal capabilities and photodynamic effects.[33] These properties render their behavior remotely controllable through external triggers like lasers, ultrasound, and even heat. Du et al prepared a 2H-MoS_2 nanozyme with excellent near-infrared (NIR) absorption and catalytic performance, which rapidly removes bacteria in subcutaneous infected tissues.[74] The synergistic effect of 2H-MoS_2 nanozyme with photothermal therapy exhibits enhanced bactericidal efficacy while preventing thermal damage to normal tissues.

Furthermore, some nanozymes exhibit specific environmental responsiveness; and their activity can be precisely regulated by various stimuli (including pH, H_2O_2, glutathione (GSH) and so on).[75] As previously described, burn wounds are commonly characterized by ischemia, hypoxia, bacterial infection, and ROS activation. When applied to burn wounds, nanozymes demonstrate significant potential in burn wound management by modulating the wound microenvironment through specific stimulus-responsive mechanisms. For instance, Wang et al prepared $CuCo_2O_4$ nanoflowers with multiple enzymatic activities The OXD-like and POD-like activities of $CuCo_2O_4$ (generating $\cdot OH$ and $\cdot O_2^-$ for antibacterial and anti-biofilm) increase as pH decreases, which is ideal for the neutral pH environment of burn-infected wounds.[76] Meanwhile, the glutathione peroxidase-like activity of $CuCo_2O_4$ can reduce the overexpression of GSH in the wound microenvironment, thereby enhancing the antibacterial effect of $\cdot OH$ and $\cdot O_2^-$.

Mechanisms of Nanozymes in Promoting Burn Wound Healing

In recent years, research on the application of nanozymes in burn wound management has advanced. In general, pro-oxidant nanozymes can catalyze the generation of ROS to kill bacteria, while antioxidant nanozymes demonstrate

excellent ROS scavenging capabilities, thereby reducing oxidative stress and inflammatory responses in burn wounds. In the following sections, we discuss the mechanisms by which they promote burn wound healing, focusing on their antibacterial, anti-oxidative stress, anti-inflammatory, pro-angiogenic, and anti-scarring effects (Figure 4 and Table 1).

Antibacterial Effect

Following a burn injury, the skin barrier at the burn site is compromised, making it vulnerable to bacterial infection. Without intervention, bacterial infection not only prolongs wound healing process, but also may lead to severe complications, such as sepsis and multiple organ failure.[94,95] Therefore, antibacterial intervention is crucial for effective wound recovery. While traditional systemic or topical antibiotic therapies effectively control infection to some extent, the rise of antibiotic resistance poses significant challenges for burn wound treatment.[96,97] Nanomaterials with enzyme-like activities (such as Ag nanoparticles and ZnO nanoparticles) have gained widespread application in treating wound infections due to their potent broad-spectrum antibacterial properties.[98] Moreover, as a class of antimicrobial agents that do not readily induce resistance, nanozymes offer a promising alternative for combating burn wound infections. The antibacterial mechanisms of nanozymes primarily involve the following aspects.

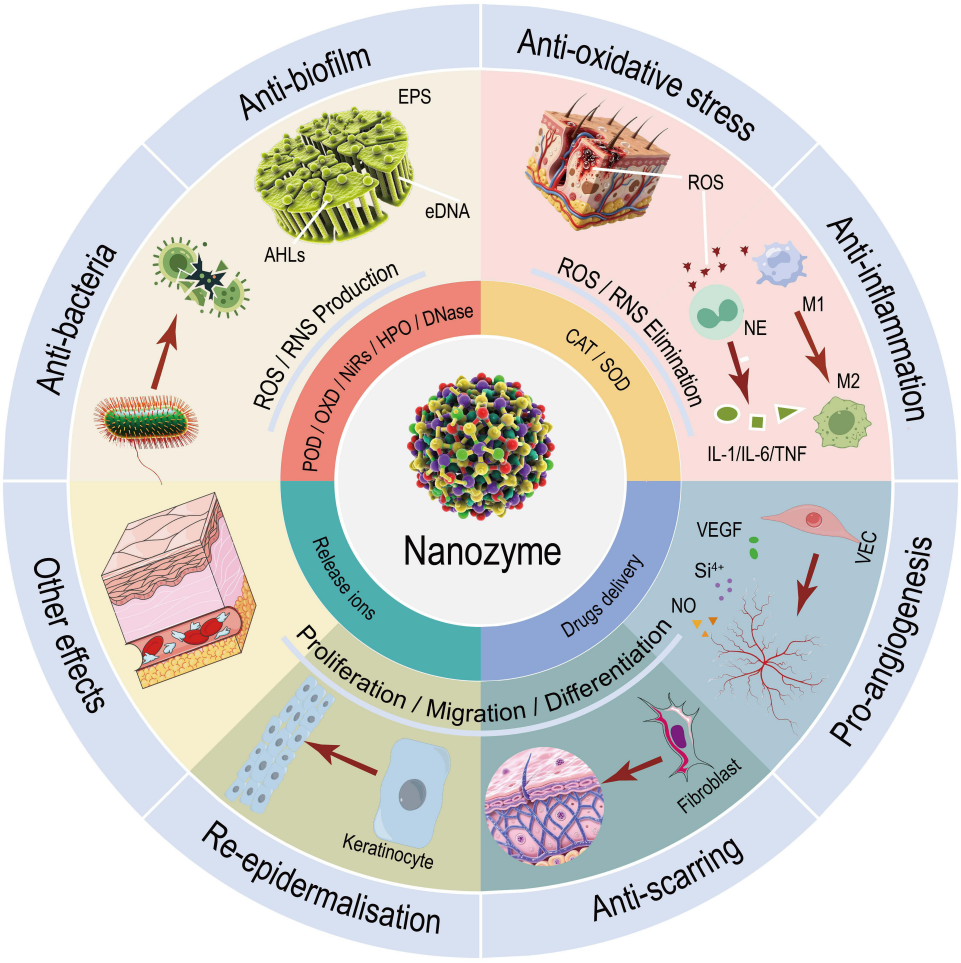

Figure 4 Schematic illustration of Nanozymes for the treatment of burn wounds.
Abbreviations: ROS, reactive oxygen species; RNS, reactive nitrogen species; OXD, oxidase; POD, peroxidase; SOD, superoxide dismutase; CAT, catalase; HPO, Haloperoxidase; NiRs, nitrite reductase; DNase, deoxyribonuclease; TNF, tumor necrosis factor; IL, interleukin; VEGF, vascular endothelial growth factor; NE, neutrophils; M1, M1-type macrophage; M2, M2-type macrophage; VEC, vascular endothelial cell.

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Table 1 Applications of Nanozyme Systems for Treatment of Burn Wounds

Function	Nanozyme System	Enzyme-like Activity	Specific Mechanism	Ref
Anti-bacteria	MoS_2 nanosheets	NiRs	• Catalyze the conversion of NO_2^- to NO • Demonstrate antibacterial activity • Induces effector cells to release neutrophil extracellular traps	[77]
	Ag-Fe_3O_4-NMs	POD	• Catalyze H_2O_2 decomposition to generate ·OH • The synergistic action between Ag^+ and ·OH	[45]
	PV@HCMS	POD	• Generates ·OH via NIR enhanced Fenton-like reactions	[78]
Anti-Biofilms	$CuCo_2S_4$ nanozymes	POD	• Convert H_2O_2 into ·OH	[79]
	Mn-N_4/SAE	POD and glutathione oxidase	• NIR significantly enhanced nanozyme activity	[80]
	DNA nanomedicine	OXD and POD	• Generation of potent oxidative radicals • Break down biofilms • Target drug-resistant bacteria	[81]
	MOF/Ce	DNase and POD	• Hydrolyze eDNA to disrupt established biofilms • Eliminate biofilm-associated bacteria in the presence of H_2O_2	[82]
	AuAgCu@DNase	DNase	• Immobilize DNase on nanomaterials • Hydrolyzes eDNA within bacterial biofilms	[83]
	Ce-MOF	HPO	• Catalyze halide ions to generate hypohalous acids, which oxidize and halogenate AHLs	[66]
Anti-oxidative stress	MS-CeO_2	SOD and CAT	• Reduces intracellular ROS	[84]
	Ag nanoparticles	Antioxidant	• Immobilize *Rhodiola rosea* biomolecule on nanoparticles • Demonstrate significant DPPH and H_2O_2 scavenging activities • Inhibit both Gram-positive and Gram-negative bacteria	[85]
	MSR microneedle	SOD and CAT	• Ruthenium clusters exhibit excellent ROS scavenging capacity • Magnesium and silicate ions enhance cell proliferation, migration, and angiogenesis	[11]
Anti-inflammation	F@Gala	POD, SOD, and CAT	• Environment responsive and NIR responsive • Galangin regulates macrophage polarization	[86]
	PB@Algs-H	POD, CAT, and SOD	• Scavenge excess ROS and suppress inflammation • Triggers the M1 to M2 macrophage polarization with sulfated alginate	[87]
	MI-MPDA	OXD, CAT	• Eliminates biofilms by O_2 generation and $^1O_2$ production • Alleviates oxidative stress and associated inflammation by ROS scavenging	[88]
Pro-angiogenesis	Pt@PSi NPs	POD	• Anti-bacteria by NIR photothermal activity and POD-like activity • Release Si^{4+} promoting angiogenesis	[46]
	CeO_2 hydrogels	SOD and CAT	• CeO_2 activate HIF-1α and upregulate VEGF expression by modulating ROS levels	[89]
	CQDs-NO	NiRs	• Release NO, promoting vasculogenesis and matrix deposition, modulating wound inflammation	[90]
Anti-scarring	ADSCs/MnO_2	Antioxidant	• MnO_2 nanoparticles reduce IL-1, IL-6, and α-SMA levels • Synergistically promote wound closure and reduce scar hyperplasia with ADSCs	[91]
	Curcumin/Fe-SiO_2	Antioxidant	• SiO_3^{2-}, Fe^{3+}, and Fe-Curcumin chelates exhibit synergistic activity	[92]
	GA-Sorafenib @MN	Antioxidant	• Sorafenib inhibit macrophage chemotaxis and fibroblast activation	[93]

Abbreviations: OXD, oxidase; POD, peroxidase; SOD, superoxide dismutase; CAT, catalase; HPO, Haloperoxidase; NiRs, nitrite reductase; DNase, deoxyribonuclease; ROS, reactive oxygen species; IL, interleukin; VEGF, vascular endothelial growth factor; α-SMA, α-smooth muscle actin; ADSCs, adipose-derived mesenchymal stem cells; eDNA, extracellular DNA; AHLs, acyl-homoserine lactones.

Generation of ROS or RNS

As previously described, pro-oxidant nanozymes can catalyze the production of ROS, including H_2O_2, ·OH, $·O_2^-$, or $^1O_2$; and NiRs-like nanozymes can catalyze RNS production, such as NO. ROS or RNS exert antimicrobial effects by disrupting pathogen cell membranes by promoting lipid peroxidation, damaging DNA, impairing protein function, and compromising cell wall integrity.[68,97,99,100] Peng et al discovered that MoS_2 nanosheets exhibit NiRs-like nanozyme properties, catalyzing the conversion of NO_2^- to NO.[77] NO demonstrates antibacterial activity while simultaneously inducing effector cells to release neutrophil extracellular traps. Yu et al developed chitosan nanofiber microspheres loaded with Ag nanoparticles and Fe_3O_4 nanoparticles (Ag-Fe_3O_4-NMs), enabling sustained Ag^+ release and catalyzing H_2O_2 decomposition at low concentration to generate ·OH.[45] The synergistic action between Ag^+ and ·OH exhibits potent antibacterial activity. Borhani et al applied a hydrogel loaded with chitosan supported iron oxide nanoparticles and Ag nanoparticles to burn wounds.[101] The hydrogel loaded with 12.5 ppm Ag nanoparticles and 100 ppm iron oxide nanoparticles exhibits superior antibacterial and non-cytotoxic properties, and accelerates wound healing after 14 days.

Furthermore, certain nanozymes exhibit photogenerated ROS kinetics under illumination, where light exposure significantly enhances ROS production, leading to synergistic antibacterial activity. For instance, TiO_2 nanoparticles and ZnO nanoparticles generate three types of ROS (·OH, $·O_2^-$, and $^1O_2$) under UV irradiation.[102] Wang et al reported a hollow-structured Cu_2MoS_4-based bacteria-targeting nanozyme (PV@HCMS), exhibiting outstanding photothermal conversion efficiency and POD-like catalytic properties.[78] It generates highly cytotoxic ·OH via NIR-enhanced Fenton-like reactions, demonstrating potent bacterial eradication capabilities for treating infected burn wounds.

Disruption of Bacterial Biofilms

Bacterial biofilms consist of microbial communities and their Extracellular Polymeric Substances (EPS), including polysaccharides, proteins, lipids, and extracellular DNA (eDNA).[103] These biofilms can cause chronic infections in burn wounds, delaying wound healing. Nanozymes may exert antibacterial effects against biofilms through the following mechanisms.

Firstly, various nanozymes can generate ROS or RNS to kill bacteria within biofilms. Li et al reported a copper-based bimetallic nanozyme ($CuCo_2S_4$) exhibiting POD-like activity that can convert H_2O_2 into ·OH.[79] $CuCo_2S_4$ nanozymes demonstrated superior bactericidal efficacy against diverse bacteria, effectively disrupting preformed MRSA biofilms in vitro and promoting healing of MRSA-infected burn wounds in vivo. Wu et al successfully synthesized manganese single-atom enzyme materials with distinct coordination environments (Mn-N_x/SAE).[80] Studies have shown that Mn-N_4 /SAE exhibits superior mimetic activities of POD and glutathione oxidase. In the acidic physiological environment associated with infection, 808-nanometer laser irradiation significantly enhanced enzyme activity and markedly promoted wound healing by eliminating biofilms. Notably, their team also developed an intelligent DNA nanomedicine capable of breaking down biofilms and targeting drug-resistant bacteria.[81] This nanomedicine initiates biofilm degradation through the in situ generation of potent oxidative radicals, achieving deep penetration and precise bacterial targeting. By utilizing aptamers for specific bacterial recognition, nanomedicines can directly concentrate therapeutic agents at the site of infection. The synergistic effect of intense oxidative stress and sustained Ag^+ release ensures continuous and precise targeting of pathogens, effectively eliminating drug-resistant strains.

Secondly, hydrolase-like nanozymes can specifically cleave chemical bonds within EPS, such as phosphate bonds, amide bonds, and glycosidic bonds, thereby disrupting the structure of bacterial biofilms. eDNA plays a crucial role in stabilizing biofilm networks, connecting bacteria to each other and linking bacteria to substrates. Nanozymes with DNase-like activity possess unique advantages in biofilm removal and inhibition of bacterial resistance.[104] Liu et al designed a series of cerium-based MOFs (MOF/Ce) exhibiting DNase- and POD-mimetic activities.[82] The MOF/Ce nanozyme can not only hydrolyze eDNA to disrupt established biofilms but also eliminate biofilm-associated bacteria in the presence of H_2O_2. Lin et al developed a ternary AuAgCu hydrogel with immobilized DNase (AuAgCu@DNase).[83] This hydrogel effectively hydrolyzes eDNA within bacterial biofilms, enabling laser-induced ROS and photothermal heating to penetrate deep into the biofilm for thorough sterilization. In a model of MRSA-infected wounds, AuAgCu@DNase hydrogels demonstrated excellent efficacy in killing drug-resistant bacteria along with superb biocompatibility.

Additionally, quorum sensing is a regulatory system in which bacteria produce chemical signaling molecules for communication and modulate collective behavior; it is closely linked to antibiotic resistance. HPO-like nanozymes can catalyze the oxidation of halide ions (Br^-, Cl^-, or I^-) to generate the corresponding hypohalous acids (HBrO, HClO, or HIO). These acids subsequently oxidize and halogenate bacterial organic signaling molecules, such as acyl-homoserine lactones (AHLs), thereby disrupting quorum sensing and inhibiting bacterial communication. Zhou et al developed a cerium-based MOF (Ce-MOF) exhibiting HPO-like activity, demonstrating significant antibacterial properties and the ability to inhibit formation of bacterial biofilm.[66]

Anti-Oxidative Stress Effect

Following extensive burns, the body's redox balance is disrupted, leading to ROS accumulation through multiple pathways—a phenomenon termed oxidative stress. Post-burn ROS production exhibits distinct phases: during the acute phase, ROS levels surge significantly, primarily due to neutrophil respiratory bursts; in the subacute phase, ROS remain elevated, associated with persistent inflammation and mitochondrial dysfunction; in the chronic phase, ROS levels gradually decline but remain above physiological thresholds, continuing to disrupt the wound healing process.[105]

CAT- and SOD-like nanozymes exhibit antioxidant effects in burn wound treatment due to their ROS scavenging capabilities. Studies have confirmed that CeO_2 nanoparticles exhibit SOD- and CAT-like activity while also scavenging ·OH and ·NO.[106] Zhou et al designed a mesoporous silica-cerium oxide (MS-CeO_2) nanozyme which demonstrates excellent radical scavenging capacity.[84] When conjugated with miR129, it reduces intracellular ROS, effectively promotes cell migration, angiogenesis, and inhibits apoptosis, synergistically accelerating the healing of radiation-induced skin injury in mice.

Design strategies for nanozymes with multifunctional efficacy and environmental responsiveness represent a pivotal trend moving forward. Bold et al synthesized Ag nanoparticles from *Rhodiola rosea*, which not only inhibit both Gram-positive and Gram-negative bacteria, but also demonstrate significant DPPH and H_2O_2 scavenging activities, promoting closure of burn wounds in mice.[85] The wound-healing mechanism of Ag nanoparticles relies primarily on the release of Ag^+ and plant-derived active ingredients. Sun et al prepared a composite microneedle patch (MSR@MN) comprising γ-polyglutamic acid as the base and Ruthenium clusters modified magnesium silicate nanosheets as the enzyme-like component. Ruthenium clusters exhibit excellent ROS scavenging capacity and, as confirmed by sequencing analysis, help activate the peroxisome proliferator-activated receptor signaling pathway. Meanwhile, the magnesium silicate is degraded under physiological conditions, releasing magnesium ions and silicate ions, thereby enhancing cell proliferation, migration, and angiogenesis. Animal models have confirmed that the microneedle patches promote repair of radiation-induced skin defects by remodeling the pathological environment.[11]

Anti-Inflammatory Effect

Inflammation serves as a defensive immune response in the body, playing a crucial role in clearing damaged cells and combating foreign pathogens. As previously discussed, inflammatory dysfunction in burn wounds, particularly the persistent presence of M1 macrophages in chronic wounds, impedes the healing process.[21] ROS are key signaling molecules in the inflammatory process. Extensive research indicates that antioxidant nanozymes exert anti-inflammatory effects by scavenging ROS and promoting macrophage polarization toward the M2 phenotype, thereby accelerating burn wound healing.[87,107–109]

Wu et al reported an environment-responsive metal-polyphenol coordination nanozyme named F@Gala, synthesized by chelating Fe^{3+} with the bioactive flavonoid galangin.[86] Under NIR light irradiation, F@Gala efficiently catalyzes the conversion of endogenous H_2O_2 into bactericidal ·OH in an acidic microenvironment during the early stages of infection. As the infection subsides and the wound environment returns to normal, F@Gala exhibits CAT-and SOD-like antioxidant activity, mitigating oxidative damage and suppressing inflammation. Meanwhile, the released galangin regulates macrophage polarization, shifting from the pro-inflammatory M1 phenotype to the reparative M2 phenotype, thereby promoting angiogenesis, collagen deposition, and tissue regeneration.

Huang et al developed a Prussian blue nanozyme hydrogel based on sulfated alginate (PB@Algs-H).[87] The Prussian blue nanozyme exhibits POD-, CAT-, and SOD-like activities to efficiently scavenge excess ROS and suppress inflammation in

wounds. Simultaneously, it synergizes with sulfated alginate to trigger M1-to-M2 macrophage polarization, promoting the healing in a mouse model of deep second-degree burn wounds.

Zhang et al integrated MnO_2 nanozymes into mesoporous polydopamine nanoparticles loaded with photosensitizer indocyanine green (MI-MPDA).[88] MnO_2 nanozymes on the surface of MI-MPDA causes bio-responsive O_2 generation in the infection microenvironment (low pH and high H_2O_2), effectively alleviating biofilm hypoxia. Sustained O_2 supply can further enhance NIR-triggered $^1O_2$ production of indocyanine green, effectively eliminating MRSA, *Pseudomonas aeruginosa* and their biofilms. As MnO_2 nanozymes mediate ROS scavenging, MI-MPDA downregulate inflammatory signaling pathway factors (such as TNF-α, IL-6, and IL-1β), thereby ameliorating inflammatory conditions. Simultaneously, the catalytic reaction product O_2 prevents macrophages from transforming into the M1 phenotype due to the overexpression of hypoxia-inducible factor-1α (HIF-1α), promoting their shift toward the M2 phenotype. Under NIR irradiation, MI-MPDA not only effectively eliminate formed biofilms but also alleviate oxidative stress and associated inflammation, promoting healing of *Pseudomonas aeruginosa*-infected burn wounds.

Pro-Angiogenic Effect

Since neovascularization can supply nutrients and oxygen to tissues, promoting angiogenesis is a critical strategy for facilitating burn wound healing. Extensive research indicates that nanozymes containing SiO_2,[48,110] CuO,[111,112] TiO_2,[113] ZnO,[114] and CeO_2[89] possess angiogenic capabilities, potentially related to the released ions.[115] Duan et al designed a delivery system utilizing porous silica (PSi) for electrostatic adsorption of VEGF.[110] Their study revealed that PSi releases Si^{4+} to upregulate HIF-1α, VEGF and Kinase Insert Domain Receptor (KDR) expression in human umbilical vein endothelial cells (HUVECs), thereby activating endothelial cell migration and tubulogenesis. PSi and VEGF synergistically promote vascular growth. Interestingly, in subsequent work, Duan et al developed platinum nanoparticles based on PSi (Pt@PSi NPs) for promoting healing in infected burn wounds.[48] Mechanistic studies revealed that Pt@PSi NPs not only exhibit excellent NIR photothermal activity and POD-like catalytic activity with synergistic antibacterial effects, but also release Si^{4+} under the stimulation of NIR and platinum nanozyme, significantly improving endothelial cell migration, luminal formation and promoting angiogenesis, demonstrating synergistic wound-healing effects.

Additionally, nanozymes may promote angiogenesis by catalyzing the production of ROS or RNS. CeO_2-based nanozymes exert anti-inflammatory effects by regulating ROS levels and promote angiogenesis by activating the HIF-1α/VEGF pathway, demonstrating that antioxidant and pro-angiogenic effects are not mutually exclusive but rather synergistic. Zubairi et al found that CeO_2-loaded chitosan-collagen hydrogels exhibits excellent angiogenic capabilities, with CeO_2 activating HIF-1α and upregulating VEGF expression by modulating ROS levels, thereby enhancing angiogenesis.[89] CeO_2-loaded hydrogels effectively accelerate the healing of chronic ulcers and burn wounds. Tang et al developed spermine trichloride quantum dots (CQDs-NO) that release NO when co-cultured with cells or glutathione peroxidase.[90] CQDs-NO can enhance angiogenesis and cell migration in HUVECs. By promoting vasculogenesis and matrix deposition, while modulating wound inflammation, CQDs-NO accelerate the healing process of deep burn wounds.

Anti-Scarring Effect

Hypertrophic scar formation is driven by abnormal fibroblast activation, imbalance in collagen deposition, and dysregulated matrix remodeling.[116] During normal wound healing, the ratio of type I to type III collagen is dynamically regulated and gradually returns to normal alignment during the remodeling phase. In contrast, under chronic inflammatory conditions, TGF-β1 continuously activates the SMAD signaling pathway, inducing fibroblasts to overproduce type I collagen and fibronectin while simultaneously inhibiting the expression of MMPs, thereby leading to disordered collagen deposition and alignment.[117] Concurrently, myofibroblasts exhibit abnormal proliferation and sustained expression of α-SMA, leading to increased tissue tension and contracture, which further compromises the mechanical stability and appearance of the skin.[118] In research on nanozymes promoting burn wound healing, the focus has shifted from the singular approach of "accelerating wound closure" to a more advanced strategy of "promoting wound healing while preventing scar formation".

Studies have demonstrated that Fe-, Mn-, Cu-, Mo-, Zr-, and Ce-based nanozymes can be utilized in anti-scar strategies by mimicking antioxidant enzyme activity, regulating macrophage immunity, modulating fibroblast function,

and controlling collagen expression.[116] Shahmohammadi et al investigated the therapeutic effect of adipose-derived mesenchymal stem cells (ADSCs) combined with MnO_2 nanoparticles on second-degree burn wounds in rats.[91] Results indicated that MnO_2 nanoparticles reduce IL-1, IL-6, and α-SMA levels, synergistically promoting wound closure and reducing scar hyperplasia with ADSCs. Zhang et al designed a Curcumin/Fe-SiO_2 nanocomposite for burn wounds.[92] The released bioactive components (SiO_3^{2-}, Fe^{3+}, and Fe-Curcumin chelates) exhibited synergistic activity in both inhibiting scar hyperplasia and promoting follicular regeneration.

Tao et al reported a coordination nanoplatform integrated with microneedles (GA-Sorafenib@MN) designed to facilitate scarless regeneration of burn wounds.[93] Based on single-cell transcriptomic analysis and high-throughput virtual screening, sorafenib was identified as the optimal candidate drug. To enhance solubility and anti-inflammatory properties, it was complexed with gallium (III) to form GA–sorafenib nanoparticles, which were then embedded into photo-crosslinked microneedles. Mechanistically, GA–Sorafenib@MN inhibits CXCL2/CXCR2-driven macrophage chemotaxis and TGF-β/Smad3-mediated fibroblast activation, while simultaneously suppressing the NLRP3 inflammasome and TLR4/NF-κB signaling pathways. This reshapes the immune-fibrosis axis at the wound site, reduces the deposition of collagen type I and type III, and restores the integrity of the ECM.

Other Wound-Healing Effects

Multiple nanozymes have been demonstrated to accelerate burn wound healing and reduce hypertrophic scarring by promoting the proliferation and migration of fibroblasts and keratinocytes, enhancing collagen deposition, and facilitating ECM remodeling. Zhang et al developed platinum-based nanoparticle assemblies (PNAs) that mimic CAT and POD enzymes and generate GSH under ultrasonic irradiation.[119] Experiments confirmed that both PNAs themselves and ultrasonically irradiated PNAs can promote fibroblast proliferation, endothelial cell differentiation, and keratinocyte migration. Shidramshettar et al prepared Ag nanoparticles using *Eclipta prostrata* leaf extract, and their synthesized Ag nanoparticles exhibit significant antioxidant and antibacterial activity.[120] Owing to their coating with *Eclipta prostrata* biomolecules, the Ag nanoparticles promote burn wound healing by inducing fibroblast differentiation into myofibroblasts. Seisenbaeva et al treated rat's burn wounds with a solution containing TiO_2 nanoparticles.[121] TiO_2 nanoparticles can adsorb proteins such as fibrinogen and fibronectin, promoting coagulation and forming a protective layer on the wound surface. This protective layer not only prevents infection and inflammation, but also provides a scaffold for cell adhesion and migration, thereby accelerating burn wound repair and reducing scar formation.

Conclusion and Perspectives

This review summarizes the pathophysiological characteristics of burn wounds and elucidates the potential mechanisms by which nanozymes promote burn wound healing from the perspective of their catalytic activity. Nanozymes exhibit multifaceted effects beyond antibacterial activity, including protection against oxidative stress, reduction of wound inflammation, promotion of angiogenesis, and prevention of hypertrophic scar. ROS or RNS act as a double-edged sword in burn wound healing: while they exert beneficial antibacterial and pro-angiogenic effects, they also readily induce oxidative stress and immune dysregulation. Pro-oxidant nanozymes catalyze ROS production, exhibiting overall antibacterial properties; antioxidant nanozymes, conversely, scavenge ROS and demonstrate antioxidant and anti-inflammatory characteristics. Certain nanozymes promote angiogenesis by catalyzing O_2 or NO production or releasing pro-angiogenic factors. Antioxidant nanozymes represent a viable anti-scarring strategy by regulating macrophage immunity, modulating fibroblast function, and controlling collagen expression.

Given the limited research on the application of nanozymes in burn wounds, this paper does not conduct a systematic meta-analysis or compare the advantages and disadvantages of various nanomaterials. Instead, we summarize several mechanisms by which nanozymes promote wound healing in burn injuries and provide illustrative examples. Overall, previous research on the application of most nanozymes in burn wounds has primarily focused on antibacterial, anti-oxidative stress, and anti-inflammatory effects. There is relatively limited research on their applications in promoting angiogenesis and anti-scarring effects. Additionally, it remains uncertain whether nanozymes actively reprogram the fibroblast phenotype or merely accelerate the transition to the remodeling phase.[116] Currently, although the mechanisms

by which nanozymes promote burn wound healing are not yet fully elucidated, their already demonstrated therapeutic potential provides a theoretical foundation for the design of advanced burn wound dressings.

Despite their promising prospects, the application of nanozymes in burn wound treatment still faces significant translational barriers. First, most nanozymes exhibit insufficient catalytic activity and poor substrate selectivity.[122] Second, the long-term retention of non-essential metals poses a risk of chronic toxicity, necessitating a shift toward ultra-small structures or biodegradable metals that can be cleared by the kidneys.[123] Third, targeted delivery and microenvironment-responsive activation technologies remain underdeveloped.[124] Some responsive nanozymes are designed for the acidic microenvironment of wounds, which may deviate from the original intent of clinical translation, as burn infected wounds in clinical settings are often slightly alkaline. In contrast, anti-infective and pro-angiogenic designs responsive to NIR light have greater translational potential, as the widespread use of infrared therapy lamps in burn units provides a source of NIR stimulation.

Future research can focus on the following key areas. (1) A deeper understanding of how nanozymes promote angiogenesis and prevent pathological scarring is needed, along with strategies to effectively translate these findings into clinical practice. (2) Next-generation nanozymes–such as those with single-atom structures, biomimetic designs, and microenvironment-responsive properties–show great promise and warrant further in-depth investigation. (3) Igorous long-term biosafety assessments of biodegradable nanozymes must be conducted to ensure their safe application in humans.

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