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Nanozymes in neuropathic pain: strategies bridging oxidative stress, mitochondrial repair, and neuroimmune modulation for targeted therapy

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Abstract

Neuropathic pain is one of the most debilitating neurological conditions, significantly challenging to manage due to the complex interplay of oxidative stress, neuroinflammation, and mitochondrial dysfunction in its pathogenesis. Nanozyme (nanomaterials with enzyme-like activity) technology offers a promising strategy to tackle these multifaceted mechanisms. These nanozymes can scavenge reactive oxygen species (ROS), modulate inflammatory pathways, and reverse mitochondrial dysfunction, providing notable neuroprotection and pain relief for affected individuals. Additionally, nanozymes exhibit targeted delivery to the injury sites by using mechanisms such as lysosome-mediated endocytosis (e.g., SOD&Fe3O4@ZIF-8 nanozymes) and mannose receptor-mediated cellular uptake (e.g., mSPIONs nanozymes). Given the limitations of current treatment options, we underscore the advantages of nanozymes, including their multifunctional capabilities and potential to enhance therapeutic outcomes in pain management. This review focuses on the underlying mechanisms of neuropathic pain, particularly emphasizing the role of oxidative stress and its impact on disease progression. We examine the applications of nanozymes for treating neuropathic pain, highlighting their potential to scavenge ROS, relieve mitochondrial dysfunction, modulate neuroinflammatory pathways, and repair blood-spinal cord barrier integrity. Furthermore, this paper provides an overview of the current landscape of nanozyme research in neuropathic pain and future directions for their clinical translation in pain management, emphasizing their potential role in improving therapeutic outcomes.

Keywords Neuropathic pain, Reactive oxygen species, Mitochondrial dysfunction, Neuroinflammation, Nanozymes, Targeted drug delivery, Therapeutic interventions

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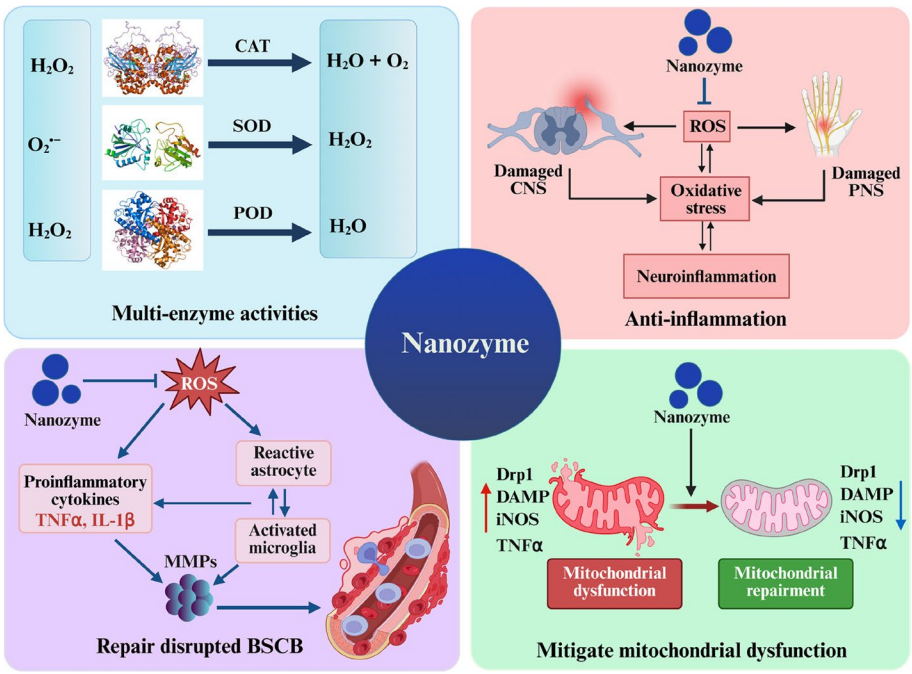
Graphical Abstract



Introduction

Neuropathic pain is a chronic, severely debilitating condition that is distinguished by abnormal pain signaling due to injury or dysfunction in the peripheral or central nervous system. It is characterized by hyperalgesia, allodynia, and spontaneous pain, which substantially diminishes quality of life [1, 2]. It frequently arises from various conditions such as chemotherapy-induced peripheral neuropathies, nerve injuries, inflammatory diseases, genetic neuropathies, and channelopathies [3–7]. According to recent statistics, the prevalence of neuropathic pain has steadily increased by 7–10%, highlighting its substantial impact on public health [8, 9]. Central sensitization, peripheral sensitization, and neuroinflammation are some of the hypotheses proposed to explain the onset and maintenance of neuropathic pain [10–12]. Central sensitization theory is one of these hypotheses that has become widely accepted. It states that when pain signals constantly stimulate the central nervous system, it undergoes maladaptive changes like increased neuronal activity, activation of microglia and astrocytes, and the production of cytokines that promote inflammation [13]. A significant driver of these pathological alterations is the overproduction of reactive oxygen species (ROS), chemically reactive molecules that can harm cellular structures. Excessive ROS leads to oxidative stress, a condition in which antioxidant defenses are overwhelmed, disrupting redox homeostasis. This imbalance contributes to mitochondrial dysfunction, exacerbates neuroinflammation, and ultimately promotes the chronicity and severity of neuropathic pain [14, 15].

The excessive production of ROS serves a dual function in cellular processes. ROS are necessary for appropriate cellular signaling and homeostasis within a certain range, but their excessive generation, combined with reactive nitrogen species (RNS), causes oxidative stress, which is a major contributing component to the pathophysiology of neuropathic pain [16, 17]. In neuropathic pain disorders, overproduction of ROS disturbs mitochondrial activity, damages cellular components like lipids, proteins, and DNA, and triggers inflammatory pathways, thereby aggravating neuronal damage and pain sensitivity. Overproduction of ROS also activates microglia and astrocytes, releasing pro-inflammatory cytokines and chemokines, which exacerbate neuroinflammation and contribute to the persistence of pain [18]. This persistent neuroinflammation exacerbates pain perpetuation [1]. Though the body has natural defense mechanisms including antioxidant enzymes such as superoxide dismutase (SOD), catalase (CAT), peroxidase (POD), and glutathione peroxidase (GPx), however under pathogenic conditions these systems occasionally become

overwhelmed or ineffective, leading to oxidative stress that cause an im-balance in redox homeostasis (the balance between oxidants and antioxidants) [19]. Currently used treatments for neuropathic pain mostly address symptom management instead of addressing the underlying oxidative stress and mitochondrial malfunction. Thus, to effectively treat neuropathic pain, it is essential to create tailored treatment techniques.

In recent years, nanomaterial-based-artificial enzymes (nanozymes) have emerged as an expanding field in response to the pathological oxidative stress implicated in neuropathic pain [20]. Since Yan et al. discovered the POD-like activity of Fe_3O_4 nanoparticles in 2007 [21, 22], nanozymes have been increasingly recognized as a subgroup of nanomaterials with intrinsic enzyme-mimetic properties, achieving a promising alternative to natural enzymes in therapeutic applications such as redox homeostasis [23–25]. Nanozymes provide a comprehensive strategy to neutralizing excessive ROS by replicating and increasing the catalytic functions of natural antioxidant enzymes such as SOD, CAT, POD, and GPx [22, 26, 27]. In contrast to endogenous enzymes, which can be unstable under pathological conditions, have low bioavailability, and rapid turnover rates [28], nanozymes have improved stability, adjustable catalytic activity, low production costs, and can withstand a wide range of pH and temperature [29–32]. These advantages render nanozymes effective in addressing oxidative stress-induced neuroinflammation associated with neuropathic pain. Recent developments in nanotechnology have enabled precise manufacturing with specific targeting motifs, permitting efficient transport across the blood-spinal cord barrier (BSCB) [33–35]. Notably, mannose, a key sugar molecule, serves as a targeting agent for BSCB transport, enabled by its mannose receptor (MR), which is extensively expressed in immune cells and endothelial cells of the nervous system. Thus, mannose-coated nanozymes can selectively bind to MR and efficiently penetrate the BSCB via a receptor-mediated transcellular transport mechanism [36]. This targeted delivery enhances their therapeutic potential by enabling direct interaction with neuronal tissues, mitigating inflammation, and protecting against oxidative damage. By effectively modulating oxidative stress and neuroinflammatory pathways, nanozymes hold significant promise in addressing the root mechanisms of neuropathic pain rather than merely managing its symptoms.

After evaluating the latest trends in nanozyme research, it is obvious that the field has undergone a tremendous increase in studies between 2014 and 2023, as evidenced by the rise in published articles from 12 in 2014 to 1159 in 2023 [37]. Despite this tremendous expansion, the use of nanozymes in the management of neuropathic pain is still relatively new. As of January 2025, only nine studies have been reported on using nanozymes such as TPP-Au-Ru, ceria-zirconia, mesoporous polydopamine (MPDA), manganese oxide, ruthenium-based metal–organic frameworks (Mito-Ru MOF, ER-Ru MOF), iron oxide, and cerium oxide nanoparticles for treating experimental neuropathic pain models. Conversely, there has been comparatively more research on the application of nanozymes in other neurological disorders, such as ischemic stroke. However, the investigation of nanozymes in the application of neuropathic pain is still in its early stages, with the majority of studies focusing on the synthesis, characterization, and overall antioxidant capabilities of these nanomaterials. It is still unclear how exactly nanozymes work within the context of neuropathic pain regarding cellular and molecular mechanisms. This gap underlines the need for more targeted research to better understand the relationships between nanozymes and specific pain pathways, neuroinflammatory processes, and immune responses associated with neuropathic pain.

Pathogenesis of neuropathic pain

The complex pathophysiology of neuropathic pain includes the excessive production of ROS, oxidative stress, altered signal transmission, neuroinflammation, mitochondrial dysfunction, ectopic activity, altered peripheral and central nociceptive fibers, and neuronal apoptosis in neurons and glial cells [16, 38, 39]. Like natural enzymes, synthetic nanozymes hold great potential as therapeutic agents for addressing these pathophysiological mechanisms and mitigating neuropathic pain. Thus, the current section aims to clarify the mechanisms by which nanozymes can regulate the pathophysiological processes that contribute to neuropathic pain.

The role of ROS-induced oxidative stress in the development of neuropathic pain

Oxidative stress is a key component in the pathogenesis of neuropathic pain, resulting from an imbalance between the production of ROS and the body's antioxidant defense system [40]. ROS, such as superoxide anion (O_2^-), hydrogen peroxide (H_2O_2), and hydroxyl radicals (OH•), are normal byproducts of cellular metabolism. Under normal settings, ROS serve critical roles in cellular signaling, immunological response, and homeostasis [41]. However, excessive ROS production overwhelms the antioxidant defense system, resulting in oxidative stress, which greatly contributes to the development and maintenance of neuropathic pain [42]. The neuropathic pain condition leads to an increase in ROS generation by injured neurons, activated microglia, and invading immune cells [43]. Certain intracellular signaling pathways, such as the nuclear factor kappa B (NF-κB) and the

mitogen-activated protein kinase (MAPK) pathways, are activated in response to increased ROS levels. Initially, ROS triggers the activation of PLC-γ and Src, directly or indirectly, which results in the phosphorylation of Ras and Raf, and then initiates ERK activation. Moreover, via triggering p22phox, activated ERK indirectly modifies ROS levels, which leads to increased ROS production. Secondly, ROS stimulates ASK1 via several mechanisms, which then activate JNK and p38 [44] Fig. 1a [45–47]. These pathways result in the production of pro-inflammatory cytokines and neurotrophic factors, which contribute to pain sensitivity [48, 49]. Elevated ROS levels have also been linked to neuronal hyperexcitability and impaired synaptic transmission in neuropathic pain models, such as the spared nerve injury (SNI) model, which exacerbates pain perception [50]. The most immediate effect of ROS formation during neuropathic pain is substantial damage to proteins, lipids, and DNA, ultimately causing mitochondrial cell death [51]. The oxidative environment can also impair the function of nociception-related ion channels and receptors, exacerbating the pain perception and resulting in a continuous cycle of inflammation and pain [52–54].

Mitochondrial dysfunction as a key mechanism in the pathogenesis of neuropathic pain

Mitochondrial dysfunction substantially contributes to the onset and maintenance of neuropathic pain, primarily through its contribution to oxidative stress, energy depletion, and neuronal hyperexcitability. Mitochondria serve as the cell's powerhouses, creating adenosine triphosphate (ATP) via oxidative phosphorylation. Its function is significantly impaired in neuropathic pain situations, including nerve damage and chronic inflammation [55]. Impairment of the electron transport chain (ETC) results in electron leakage, which interacts with oxygen to generate superoxide radicals (O_2^-), triggering a cascade of ROS generation. Moreover, impaired mitochondria produce cytochrome c and other pro-apoptotic proteins, initiating neuronal apoptosis and exacerbating neuronal loss in pain pathways [56]. The resultant energy deficiency disrupts the action of ion pumps, including the Na^+/K^+-ATPase, resulting in neuronal hyperexcitability and abnormal pain signaling [57]. In addition to energy depletion, it initiates a vicious cycle of pathological events that intensify pain. For example, increased pain sensitivity has been associated with mitochondrial fragmentation, which is mediated by dynamin-related protein 1 (Drp1) Fig. 1b [58]. The excessive fission alters mitochondrial dynamics and increases the production of ROS [58, 59]. This mitochondrial dysfunction also triggers the release of mitochondrial DNA, ROS, cytochrome c, and other damage-associated molecular patterns (DAMPs) into the extracellular space, where they act as alarmins, activating microglia and astrocytes via particular receptors like TLR4, TLR9, P2X7R, and RAGE, among others [60]. TLR9 and RAGE receptors activate MyD88-dependent NF-κB, leading to transcription of pro-inflammatory cytokines (TNF-α, IL-1β, IL-6) [61], while P2X7R activates potassium efflux and NLRP3 inflammasome assembly [62]. Concurrently, MAPK pathways (p38 and JNK) are also activated, increasing inflammatory responses via phosphorylation of transcription factors such as CREB and AP-1 [63]. The NLRP3 inflammasome assembles and cleaves pro-caspase-1 into active caspase-1, which then converts pro-IL-1β into its physiologically active form [64]. This leads to a self-sustaining loop of neuroinflammation where cytokine release (especially IL-1β and TNF-α) promotes more neuronal injury and mitochondrial dysfunction, resulting in persistent DAMP release Fig. 1b.

Critically, these chronic inflammatory signals cause substantial phenotypic alterations in glial cells. Microglia are morphologically transformed from ramified to amoeboid phase and acquire a pro-inflammatory M1 phenotype with increased expression of CD86, iNOS, and MHC-II, while downregulating anti-inflammatory M2 markers such as Arg-1 [65, 66]. Astrocytes are also activated, upregulating GFAP and complement protein C3 while losing glutamate transporters GLT-1/GLAST, which worsens excitotoxicity [67, 68]. Prolonged inflammation leads to epigenetic and post-translational changes that reduce the Nrf2 antioxidant defense mechanism [69], maintaining NF-κB and MAPK signaling and promoting central sensitization [70]. This acute to chronic pain transition includes TRP channel sensitization, modified voltage-gated sodium/calcium channels, and abnormal synaptic plasticity mediated through AMPA receptor trafficking and BDNF-TrkB signaling [71]. These processes together create a self-sustaining cycle

(See figure on next page.)

Fig. 1 Mechanism of Neuropathic Pain. **a** The pain signal is initiated by noxious stimuli at the peripheral nerve terminals of the skin. ROS trigger excitatory signals in DRG neuron cells, activating the NF-κB and MAPK pathways. This stimulation leads to the production of chemokines and cytokines, which then activate microglial cells, resulting in neuropathic pain. **b** Neuron injury leads to excessive mitochondrial fission, which is driven by the upregulation of Drp1, decreased ATP production, and reduced activity of the electron transport chain (ETC). The elevated ROS levels activate the MAPK, NF-κB signaling pathways, and NLRP3 inflammasome, resulting in the upregulation of pro-inflammatory cytokines (such as TNF-α, IL-1β, and IL-18) and enzymes (including iNOS and COX-2). Nanozymes neutralize ROS, suppressing these pathways, diminishing inflammation, and attenuating neuropathic pain

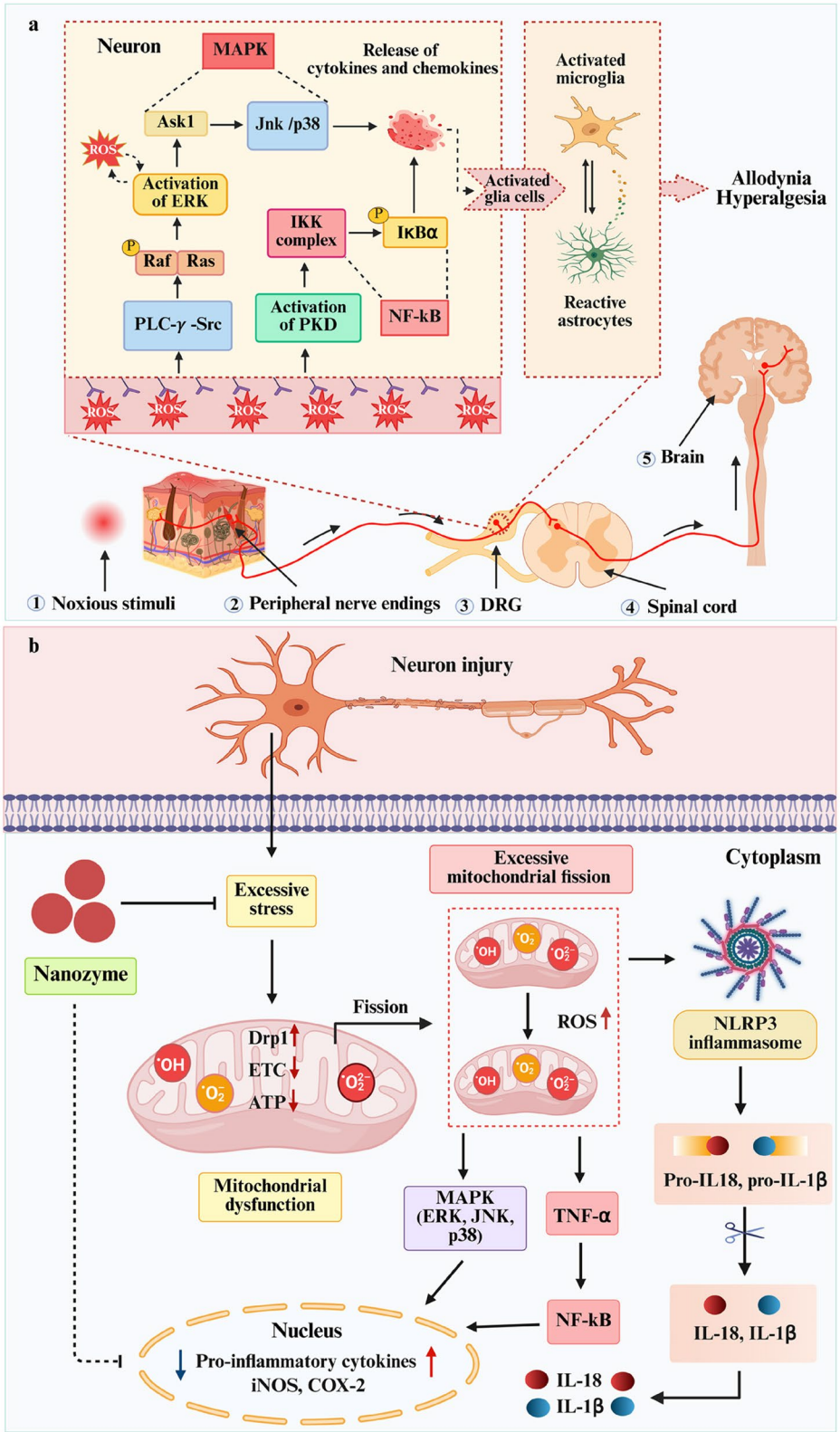


Fig. 1 (See legend on previous page.)

that perpetuates chronic pain states. Furthermore, the relationship between the gut-brain axis and mitochondrial dysfunction has gained attention because changes in the gut microbiota may affect mitochondrial health and contribute to systemic inflammation, which in turn exacerbates neuropathic pain [72, 73]. Addressing mitochondrial dysfunction via new therapies that promote mitochondrial biogenesis, boost electron transport chain function, or eliminate ROS presents a promising strategy for disrupting this loop and delivering effective relief for neuropathic pain.

Role of neuroinflammation in the pathophysiology of neuropathic pain

Neuropathic pain is mainly caused by neuroinflammation, which is triggered by nerve injury and mediated by microglia, astrocytes, and neurons [74]. Overproduction of ROS triggers leukocyte infiltration, activates microglia, and promotes the release of inflammatory cytokines. Microglia, the innate immune cells in the central nervous system (CNS), can show pro- and anti-inflammatory characteristics. The pro-inflammatory microglia release cytokines such as IL-1β, IL-6, and TNF-α, and enhance neuronal injury that leads to the onset of neuropathic pain [75]. Conversely, cytokines like TGF-β and IL-10 are released by anti-inflammatory microglia and facilitate tissue repair and inflammation attenuation [76, 77]. However, excessive ROS production polarizes microglia into a pro-inflammatory phenotype and inhibits their anti-inflammatory action [78]. This discrepancy in the activation of microglia leads to persistent chronic neuroinflammation and neuropathic pain [79, 80].

Astrocytes also contribute to neuropathic pain by regulating neuroinflammation. Activated microglia stimulate pro-inflammatory astrocytes to secrete TNF-α, IL-1α, and C1q. These astrocytes further produce neurotoxic chemicals (e.g., complement C3 d), which can cause neuronal death [81–85]. Thus, the interaction between astrocytes and microglia in the dorsal root ganglia and spinal cord is a major factor in neuroinflammation and neuropathic pain [86, 87]. Recent studies emphasized the significant role of epigenetic changes in microglia and astrocytes after nerve damage, which might change their transcriptional patterns and aid in neuropathic pain development [88–90]. Another significant finding is the gut-brain axis, where modifications in gut microbiota affect neuroinflammation and pain perception [91]. Modulation of microglial and astrocytic activation represents a therapeutic method for treating neuropathic pain since it attenuates neuroinflammation and promotes pain signaling resolution.

Impact of altered peripheral and central nociceptive fibers on sensory processing in neuropathic pain

Modifications in peripheral nociceptive fibers have a significant impact on the development of neuropathic pain, particularly through the mechanism of peripheral sensitization and abnormal nerve transmission. Nerve injury causes a substantial increase in pain-related gene expression in DRG neurons, resulting in a reconfiguration of nociceptive pathways [92–95]. This reconfiguration results in increased excitability of C and Aδ pain-signaling fibers. It has been suggested that sensitization of vasoactive C-nociceptors is a major cause of neuropathic pain. These fibers are hypersensitive to both noxious and non-noxious stimuli, which can result in hyperalgesia and allodynia [96–98]. Peripheral nociceptive fibers also exhibit molecular changes in the expression and functionality of ion channels, such as voltage-gated sodium channels (Nav) and calcium channels (Cav). These modifications accelerate neuronal hyperexcitability and involuntary activity, which characterize neuropathic pain [99–101]. Moreover, activation of transient receptor potential (TRP) channels, particularly TRPV1 and TRPA1, has also been linked to peripheral sensitization, which leads to mechanical and thermal hypersensitivity in neuropathic pain [102, 103].

Similarly, central sensitization occurs when continuous activation of peripheral nociceptive fibers raises the sensitivity of central nociceptor neurons within the spinal cord [104]. Continuous nociceptive input from the periphery increased production of excitatory neurotransmitters, including glutamate and substance P, which activate N-methyl-D-aspartate (NMDA) receptors and many signaling pathways. This leads to long-term potentiation (LTP) of synaptic transmission, augmenting the sensitivity of spinal neurons to incoming nociceptive signals [105, 106]. During this phase, Aβ fibers undergo a functional shift that enables them to contribute to pain signaling and intensify pain perception [107]. The interaction of neuronal and non-neuronal cells, such as glial cells, further elevates central sensitization. The glial cells secrete pro-inflammatory cytokines and neurotrophic factors and reduce inhibitory controls mediated by GABAergic and opioidergic systems [108–110]. These central changes result in the expansion of receptive fieldts, allowing neurons to respond to stimuli from a wider range of regions, and decreasing the spatial and temporal discrimination of pain. These maladaptive changes exacerbate the chronicity and intractability of neuropathic pain, rendering it a difficult condition to manage [111].

Blood-spinal cord barrier injury induces neuropathic pain

The blood-spinal cord barrier (BSCB), similar to the blood–brain barrier (BBB), is necessary to maintain

spinal cord homeostasis. Its major function is to protect the spinal cord from dangerous substances in the bloodstream and facilitate the transport of essential nutrients [112–114]. Neuropathic pain can result from BSCB disruption, which allows immune cells and inflammatory mediators from the bloodstream to infiltrate the spinal cord tissues. This influx leads to a local inflammatory response by activating microglia and astrocytes, which produce pro-inflammatory cytokines and mediators such as TNF-α and IL-1β [115, 116]. These inflammatory substances excite nearby neurons, hence increasing pain transmission. Moreover, BSCB disruption results in the extravasation of albumin and other plasma proteins into the spinal cord parenchyma. Albumin stimulates astrocytes through the transforming growth factor-beta (TGF-β) signaling pathway, thus exacerbating neuroinflammation and disturbing glutamate homeostasis. The resultant surplus of glutamate excessively stimulates NMDA receptors on spinal neurons, resulting in calcium influx, oxidative damage, and neuronal hyperexcitability [65, 117]. This mechanism contributes to central sensitization, a condition characterized by increased reactivity of spinal neurons to nociceptive stimuli.

The primary cause of BSCB disruption is increased permeability and breakdown of tight junction proteins such as claudins, occludins, and zonula occludens (ZO) [116]. These alterations are induced by inflammatory, oxidative, and mechanical processes that compromise the structural integrity of endothelial cells. Pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, are released after injury or disease, reducing the expression of tight junction proteins, thus impairing the integrity of the barrier's sealing function [118]. Excessive production of ROS, frequently arising from nerve injury or secondary ischemia–reperfusion damage, induces oxidative stress that harms endothelial cells and activates matrix metalloproteinases (MMPs), leading to the degradation of tight junction components Fig. 4b [119–121]. Physical trauma or mechanical stress from nerve injury can directly compromise tight junctions, while infections or toxins related to the injury may additionally affect endothelial cells, exacerbating barrier permeability [122, 123]. These mechanisms collectively augment BSCB permeability, facilitating the infiltration of immune cells, inflammatory mediators, and toxins into the spinal cord, thus contributing to neuroinflammation, central sensitization, and the onset of persistent neuropathic pain. Exploring these mechanisms is essential to develop targeted treatment strategies that restore blood-spinal cord barrier integrity and alleviate neuropathic pain symptoms.

Structural determinants of nanozyme activity in neuropathic pain therapy

The catalytic properties of nanozymes, akin to enzymes, are mostly dictated by their structure. Elucidating the correlation between the catalytic activity and structure of nanozymes is essential for comprehending their catalytic mechanisms, developing a new generation of nanozymes with superior catalytic activity, and achieving the rational design and synthesis of nanozymes. Many studies have indicated that the dimensions, morphology, surface chemistry, and oxidation states of nanozymes significantly influence their enzyme-like catalytic activity [124–126]. These features allow them to imitate important antioxidant enzymes such as CAT, SOD, GPx, and POD [22, 26, 27]. They enable nanozymes to scavenge ROS and regulate oxidative stress, making them particularly effective in targeting neuroinflammation, a critical contributor to neuropathic pain. The structural characteristics of well-known nanozymes and their significance for neuropathic pain treatment are discussed below.

Mesoporous polydopamine nanoparticles (MPDA-NPs)

Mesoporous polydopamine nanoparticles (MPDA-NPs) have a huge surface area and a highly porous structure that allows for effective drug loading and prolonged release of therapeutic drugs like morphine Fig. 3(f). To mitigate morphine-induced antinociceptive tolerance (MAT) and oxidative stress, its polydopamine (PDA) core offers intrinsic antioxidant properties, ROS scavenging, and redox balance restoration. The mesoporous design enables high drug payloads and surface functionalization, which improves targeted delivery and bioavailability. The structural architecture of MPDA-NPs renders them particularly efficient in alleviating neuropathic pain by preserving analgesic efficacy, minimizing hepatotoxicity, and inhibiting microglial activation in the spinal cord, Fig. 2 [127].

Ceria-zirconia nanoparticles ($Ce_{0.7}Zr_{0.3}O_2$ or 7 CZ NPs)

Ceria-zirconia nanoparticles (Ce0.7Zr0.3O2 or 7 CZ NPs), manufactured by controlled thermal breakdown, demonstrate selective uptake by microglia due to their customized surface features and composition, such as a specific ratio of cerium (Ce) to zirconium (Zr) and greater Ce^{3+} concentration Fig. 3(c). Functionalization with phospholipid-PEG and targeting ligands, such as CD11b antibodies, further improves their analgesic properties, dispersibility, biocompatibility, and selectivity for inflammatory cells, Fig. 2 [129].

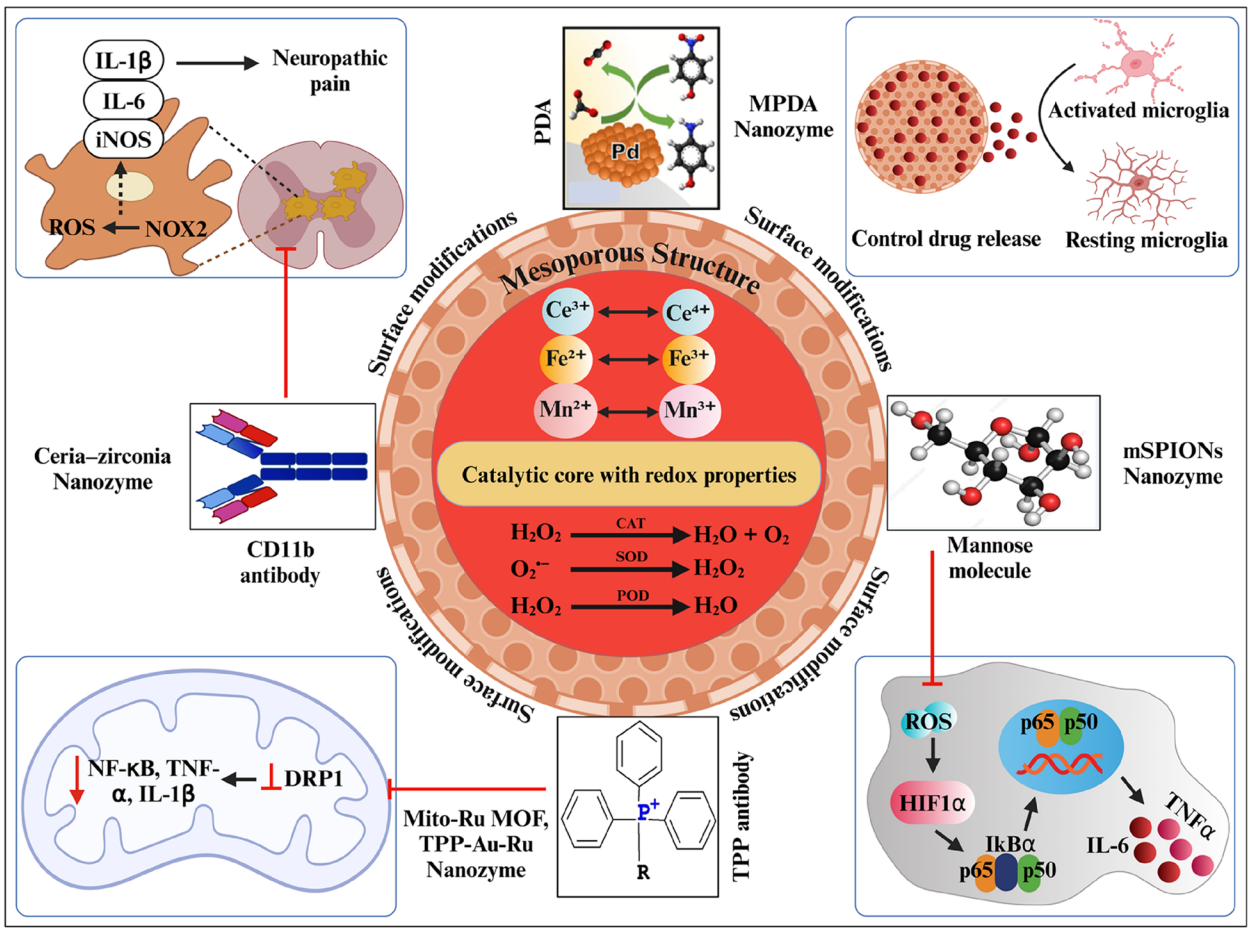


Fig. 2 This schematic illustrates the multifunctional roles of mesoporous nanozymes in neuropathic pain treatment. The catalytic core, composed of Ce^{3+}/Ce^{4+}, Fe^{2+}/Fe^{3+}, and Mn^{2+}/Mn^{3+}, facilitates ROS scavenging through catalase (CAT), superoxide dismutase (SOD), and peroxidase (POD)-like activities. Functional surface modifications, including PDA for drug delivery, mannose for selective microglial targeting, CD11b for macrophage engagement, and TPP for mitochondrial targeting, contribute to neuroinflammation reduction and pain relief

Cerium oxide nanoparticles

Cerium oxide nanoparticles, produced using a hydrothermal method, demonstrated adjustable dimensions, morphology, and surface Ce^{3+}/Ce^{4+} ratios, which directly affect their ROS scavenging and anti-inflammatory characteristics Fig. 3(j). These nanoparticles have demonstrated the capacity to reduce neuropathic pain through the modulation of macrophage polarization, underscoring the impact of their structural design on immune cell behavior and pain relief Fig. 2 [134].

SOD-Fe_3O_4@ZIF-8 (SFZ) nanozyme

The structural characteristics of nanozymes directly affect their catalytic efficiency and stability, allowing them to carry out various biological functions [135]. For example, antioxidant cascade nanozymes regulate the MAPK/p-65 signaling pathway to mitigate inflammatory pain, illustrating their multi-enzyme-like functions in targeting specific biochemical pathways associated with neuropathic pain. A notable example is the fabrication of SOD-Fe_3O_4@ZIF-8 (SFZ) nanoparticles, which integrate SOD and Fe_3O_4 within a pH-responsive ZIF-8 matrix Fig. 3(d). These SFZ nanoparticles display a rhombic polyhedron morphology (400–500 nm) and showed pH-dependent release of SOD and Fe_3O_4, facilitating cascaded catalytic activity for ROS removal. Moreover, SFZ nanoparticles exhibit effective uptake by microglia through lysosome-mediated endocytosis and display significant antioxidant and anti-inflammatory activities [130].

Manganese oxide nanoparticles (MnO_2 NPs)

The catalytic activity of MnO_2 NPs in neuropathic pain treatment is primarily determined by structural architecture. The multivalent redox chemistry of manganese ($Mn^{2+}/Mn^{3+}/Mn^{4+}$) allows these nanozymes to imitate various antioxidant enzymes (SOD, CAT, and POD), enabling complete ROS scavenging irrespective

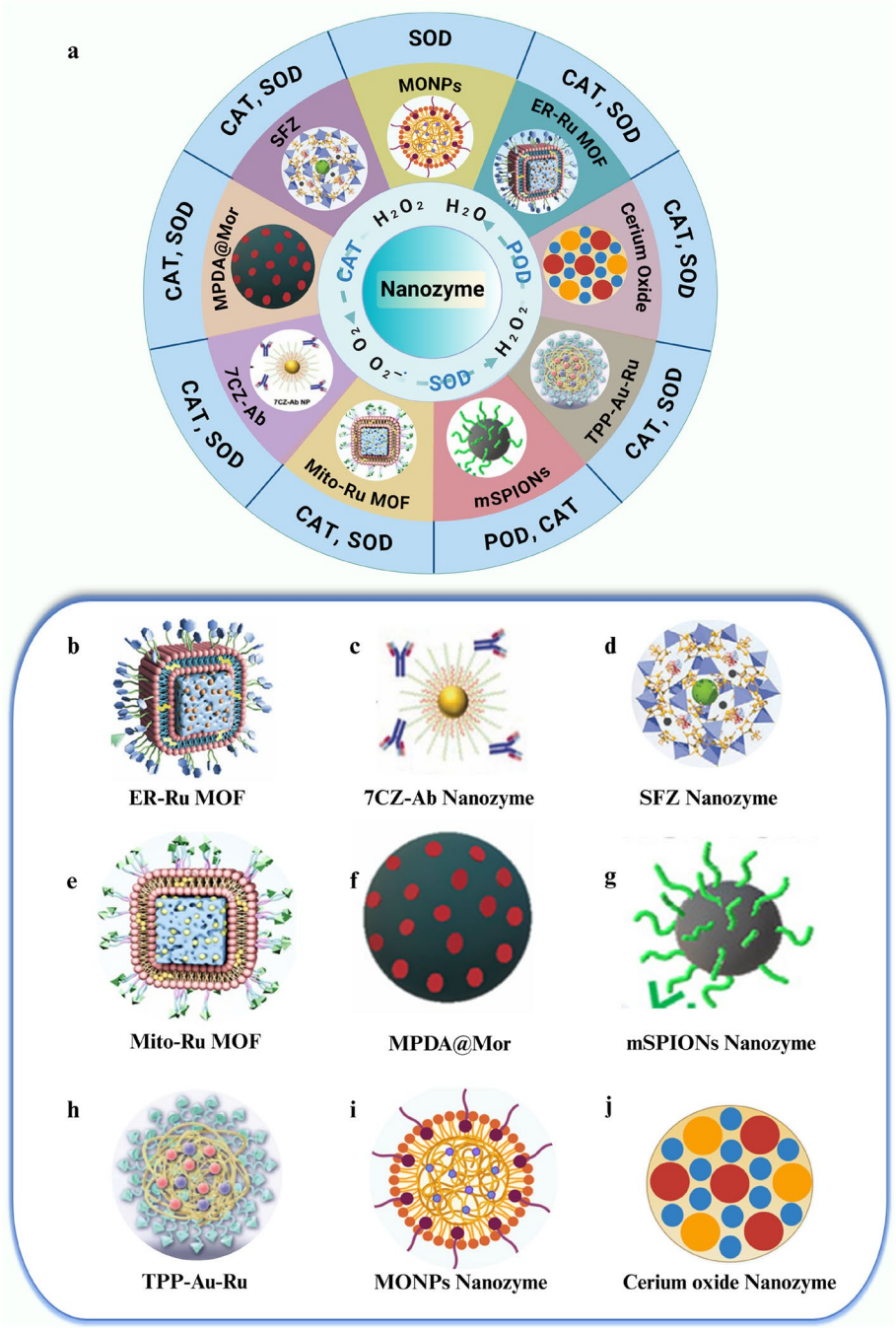


Fig. 3 Nanozymes: Structure and enzymatic activity. **a** Enzymatic activity of nanozymes in neuropathic pain (**b**-**j**). The information explains the structures of the nanozymes employed to treat NP. It is crucial to highlight that nanozymes have been specifically formulated and engineered for their respective various applications, therefore, the structural distinctions are vital to their efficiency. **b** Adapted with authorization from ref [128]. Copyright 2023 Advanced Healthcare Materials. **c** Adapted with authorization from ref [129]. Copyright 2019 Nanoscale. **d** Adapted with authorization from ref [130]. Copyright 2023 Advanced Science. **e** Adapted with authorization from ref [131]. Copyright 2023 Journal of Materials Chemistry B. **f** Adapted with authorization from ref [127]. Copyright 2021 antioxidants. **g** Adapted with authorization from ref [132]. Copyright 2023 iScience. **h** Adapted with authorization from ref [133]. Copyright 2025 Advanced Healthcare Materials

of endogenous mechanisms. Their crystalline structure and surface flaws work as active catalytic sites, while the nanoparticle size (usually 20–50 nm) promotes biodistribution and cellular internalization in neural tissues. Recent findings show that these structural properties allow MnO_2 NPs to successfully reduce COX-2-mediated neuroinflammation and pain responses in rodent models Fig. 3(i) [136]. The lack of essential surface modifications for basic activity emphasizes their intrinsic catalytic benefits; however, tailored delivery could be improved through future functionalization methods.

Mannose-coated SPIONs (mSPIONs) nanozyme

Mannose-coated superparamagnetic iron oxide nanoparticles (mSPIONs) are engineered with an iron oxide nanoparticle core (7–8 nm in diameter) and a mannose surface coating that targets macrophages selectively Fig. 3(g). The mannose coating improves the nanoparticle's ability to bind to macrophage receptors, allowing their uptake and localization in macrophages, where ROS levels are elevated during chemotherapy-induced peripheral neuropathic pain (CIPNP). Under physiological conditions, the iron oxide core acts like a catalase, decomposing H_2O_2 into water and oxygen, scavenging ROS, and lowering oxidative stress. This combined activity allows mSPIONs to alleviate CIPNP by reducing inflammation and neuropathic pain, providing a viable nanomaterial-based treatment strategy Fig. 2 [132].

Bimetallic cluster nanozymes (TPP-Au-Ru)

At the molecular level, nanozymes emulate natural enzymes via their precisely designed active sites and surface modifications, which enable specialized catalytic reactions. For instance, bimetallic cluster nanozymes such as TPP-Au-Ru utilize their active sites, consisting of zero-valent Au and Ru (0), to demonstrate significant SOD/CAT-like activity Fig. 3(h). Surface modifications, including conjugation with triphenylphosphonium (TPP), augment their mitochondria-targeting efficacy and dispersibility, facilitating precise localization and enhanced catalytic activity. These nanozymes not only emulate natural enzymes such as SOD and catalase but also exceed them in stability and versatility, rendering them highly efficient in biomedical applications Fig. 2 [133].

Mitochondria-targeting nanozymes (Mito-Ru MOF)

Mitochondria-targeting nanozymes, such as Mito-Ru MOF nanozyme, are manufactured via biomimetic mineralization. They consist of a cube-shaped zeolitic imidazolate framework (ZIF-8) that is loaded with bovine serum albumin (BSA) and ruthenium (Ru) nanozymes, which are immobilized and reduced in situ Fig. 3(e). Liposomes are encased within the Ru MOF to improve biocompatibility, and TPP ligands are included to functionalize the nanozyme for mitochondria-specific targeting. This structural composition allows Mito-Ru MOF to effectively degrade ROS, reduce inflammatory markers such as TNF-α and NF-κB, and inhibit NEAT1 expression, therefore mitigating TMD pain by addressing oxidative stress and inflammation at their origin Fig. 2 [131].

Endoplasmic reticulum-targeting nanozymes (ER-Ru MOF)

Nanozymes such as ER-Ru MOF emulate natural enzymes to mitigate oxidative and endoplasmic reticulum stress (ERS), contributing to central post-stroke pain (CPSP). These nanozymes, designed with SOD and CAT-like functions, eliminate ROS (e.g., H_2O_2, $\cdot O_2^-$, ·OH) and inhibit matrix metalloproteinase activation, thereby mitigating pain hypersensitivity Fig. 3(b). By directing p-DBSN-modified liposomes towards the endoplasmic reticulum, ER-Ru MOF enhances protein folding stability and mitigates endoplasmic reticulum stress, thus, its encapsulated ruthenium core preserves catalytic activity without aggregation or functional degradation [128]. This dual-action strategy of nanozymes reduces oxidative damage and reinstates cellular homeostasis, offering a potential treatment approach for CPSP and associated neuroinflammatory disorders, Fig. 2.

Collectively, the functional efficacy of nanozymes is significantly affected by their structural modifications, allowing them to surpass the limitations of traditional therapies and address the complex nature of neuropathic pain. Furthermore, these structural developments enable nanozymes to cross biological barriers like the blood-spinal cord barrier and reach intracellular spaces like the endoplasmic reticulum and mitochondria, where they can alter important pathways like the TNFα/NF-κB/NEAT1 axis [131, 137]. Thus, nanozymes offer unmatched precision, stability, and therapeutic potential by bridging the gap between nanomaterial engineering and biological application, therefore providing a transforming approach to treat neuropathic pain.

Multienzyme-like activities of nanozymes investigated in neuropathic pain

The subsequent analysis focuses on the enzyme mimetic activities and structural properties of several nanozymes tested in neuropathic pain, Fig. 3a-i. The enzyme-like

functions of these nanozymes are illustrated in Fig. 3(a). To provide clarity, these nanozymes are categorized based on their dominant enzyme-mimetic activities.

SOD-CAT dual mimics

Ceria zirconia nanozymes (7 CZ-Ab and 7 CZ), adopted with microglial-targeting antibodies, show synergistic SOD and CAT-like activities. These activities enable serial scavenging of superoxide radicals (O_2^-) and hydrogen peroxide (H_2O_2), which reduces neuroinflammation in spinal cord injury models [129, 138–140]. Likewise, SOD-Fe_3O_4@ZIF-8 nanozymes combine Fe_3O_4's catalase-like activity with the encapsulated SOD's superoxide-scavenging function, thus reducing mitochondrial oxidative stress in chemotherapy-induced peripheral neuropathy [130]. Ruthenium nanozymes such as Mito-Ru MOF, ER-Ru MOF, and TPP-Au-Ru also possess SOD- and CAT-mimetic activities that target subcellular organelles such as mitochondria and the endoplasmic reticulum to eliminate ROS [131, 133, 137]. Mesoporous polydopamine nanoparticles (MPDA-NPs) are also SOD- and catalase-mimics, which help in the reduction of accumulation of ROS within neuronal tissues [127].

Cascade POD-CAT mimics

Mannose-coated superparamagnetic iron oxide nanoparticles (mSPIONs) exhibit POD and CAT-mimetic activities, facilitating ROS removal via cascade reactions. The POD-like activity transforms H_2O_2 into hydroxyl radicals (•OH), and the following CAT-like activity decomposes excess H_2O_2 into water and oxygen, improving therapeutic efficacy in neuropathic pain models [132].

SOD-dominant mimics

Manganese oxide nanozymes (MONZs) possess SOD-dominant activity, preferentially suppressing superoxide radicals (O_2^-); a principal instigator of NLRP3 inflammasome activation in chronic constriction injury (CCI) models [136]. Unlike the double-enzyme cascades of C-Z nanozymes (SOD-CAT) or mSPIONs (POD-CAT), these SOD-dominant mimics exhibit a precedence toward rapid O_2^- removal, breaking oxidative stress-facilitated neuroinflammatory signaling at its origin.

Nanozymes investigated in neuropathic pain

The therapeutic effectiveness of nanozymes for treating neuropathic pain

Nanozymes offer protective and beneficial therapeutic effects in neuropathic pain disorders via diverse mechanisms. They include the inhibition of inflammatory responses, reduction of ROS, improvement of neuronal health, and modification of pain signaling pathways. The main mechanism of action of nanozymes is to directly scavenge ROS, which reduces the oxidative stress linked with neuropathic pain. To further enhance their analgesic effects, nanozymes have been demonstrated to balance endogenous antioxidants and inhibit pro-inflammatory cytokines. This comprehensive strategy emphasizes the potential of nanozymes as a strong therapeutic for neuropathic pain.

Role of nanozymes in eliminating ROS to alleviate oxidative damage in neuropathic pain

Antioxidant nanozymes effectively eradicate ROS in neuropathic pain. Nanozymes having SOD-like activity transform superoxide anion radicals ($O_2^{\bullet-}$) into H_2O_2 and oxygen (O_2) [141]. In contrast, nanozymes that exhibit CAT-like activity, break down H_2O_2 into H_2O and O_2 [142]. Nanozymes can also inhibit the production of hydroxyl radicals (•OH), thus scavenging various types of ROS [143]. For instance, ceria-zirconia nanozymes had performed an enhanced activity in eliminating superoxide anions (O_2^-) and hydroxyl radicals (•OH), which are the primary offenders in the pathogenesis of various inflammatory disorders [129]. Nevertheless, several nanozymes, such as mSPIONs, MPDA, ER-Ru MOF, Mito-Ru MOF, TPP-Au-Ru, SOD-Fe_3O_4@ZIF-8, and MnO_2 nanozymes, demonstrated multiple enzyme-like functions, which enhanced their effectiveness in reducing ROS levels in various neuropathic pain models Fig. 3a, Table 1 [127, 130–133, 136, 137]. Studies have revealed that Fe_3O_4 nanozymes can reduce ROS levels via modifying the MAPK signaling cascade and raise the activity of SOD enzymes in the CFA mice model, which are markers of free radical stress [130]. An in vitro study has also demonstrated that these nanozymes can reduce the expression of pro-inflammatory markers such as IL-6 and COX-2 [132].

Alleviation of mitochondrial dysfunction in neuropathic pain by nanozymes

Recent research shows that nanozyme-mediated mitochondrial targeting is a potential therapeutic approach for neuropathic pain since it addresses both oxidative stress and neuroinflammation at the molecular level. The study of Bai et al. [131] with Mito-Ru MOF nanozymes demonstrated how these structures aggregate in mitochondria and exert their therapeutic functions through numerous coordinated mechanisms. Their SOD-mimetic activity transforms superoxide radicals (O_2^-) into H_2O_2, while CAT-like activity further reduces H_2O_2 to water and oxygen, directly lowering oxidative stress. In addition to ROS scavenging, these nanozymes disrupt the TNFα/NF-κB/NEAT1 pathway by blocking IκBα degradation, Fig. 1b. This prevents NF-κB from translocating to the nucleus and activating pro-inflammatory cytokine

Table 1 Experimental methods for treating neuropathic pain with nanozymes

Enzyme-like activities	Nanozyme types	Animal models	Sample volume	Dosages	Nontoxic concentration range	Administration routes	Detection methods of therapeutic mechanisms	Ref.
CAT-SOD	MPDA@Mor nanozyme	PSNT, Wistar Rat, Male, 7 weeks old	$n = 3–6$	15 mg/kg	10 to 150 μg/mL	i.p injection	1. ROS evaluation in THP-1 cells 2. OX-42 protein levels (WB) 3. TNF-α and NF-κB levels (ELISA) 4. PWT test by Dynamic Plantar Aesthesiometer 5. Pharmacokinetic Studies	[127]
CAT-SOD	Ceria zirconia nanozyme	SNT, C57BL/6 Mice, Male, 7–10 weeks old	$n = 2–12$	10 μg/5μL	0.01–0.04 mM	i.t injection	1. Microglial activation and oxidative stress (IHC), 2. Uptake of nanozymes by microglia (Flow Cytometry) 3. iNOS, IL-6, IL-1β (qRT-PCR) 4. ROS levels and oxidative damage (Immunofluorescence) 5. PWT by Von Frey Test 6. MTS Assay	[129]
CAT-SOD	SFZ nanozyme	CFA, ICR Mice, Male, Adult	$n = 3–8$	2 μg/10μL, 4 μg/10μL, and 8 μg/10μL	2 to 64 μg/mL	i.t injection	1. p-ERK, p-p38, p-JNK, and p-65 (WB) 2. TNF-α, IL-6, IL-1β, IBA-1, and GFAP (qRT-PCR) 3. ROS hypoxia levels in microglia (FC) 4. GFAP and IBA-1 (IHC) 5. SFZ Localization (TEM) 6. PWT by Von Frey Test	[130]
SOD	MnO_2 NPs	PSNT Wistar Rat, Male, 7 weeks old	$n = 3–6$	50 μg/10μL	10 to 100 μg/mL	i.t injection	1. COX-2 protein (WB) 2. COX-2 expression (IHC) 3. Structural characteristics of MnO_2 NPs (TEM) 4. Evaluation of ROS scavenging (FC) 5. PWT by Dynamic Plantar Aesthesiometer and Hargreaves test	[136]
CAT-SOD	ER-Ru MOF nanozyme	CPSP, C57BL/6 mice, Male, 7–8 weeks old	$n = 3–10$	3, 5, or 8 mg kg − 1	5 to 200 μg/mL	i.v. injection	1. ROS markers, TNF-α, and IL-6 (IHC) 2. MMP-2, MMP-9, and EMMMPRIN (WB and qRT-PCR) 3. Distribution of Ru nanozymes (EM and In Vivo Imaging) 4. Von Frey filaments and acetone tests	[128]

Table 1 (continued)

Enzyme-like activities	Nanozyme types	Animal models	Sample volume	Dosages	Nontoxic concentration range	Administration routes	Detection methods of therapeutic mechanisms	Ref.
CAT-SOD	CONPs	SCI, Wistar rats, Female, Adult	$n = 5–12$	0.5 mg/mL and 1 mg/mL	100 µg/mL and 200 µg/mL	i.t injection	1. IL-1β, TNF-α, iNOS, CD86, Arg-1, IL-10 (qRT-PCR) 2. Macrophage polarization (IF) 3. PWT by Von Frey Filaments and PWL by Hargreaves Test 4. Characterization of CONPs (TEM, XRD, XPS, and DLS)	[134]
CAT-SOD	Mito-Ru MOF nanozyme	CFA, Mice, Male, 6–8 weeks old	$n = 3–39$	8 mg kg − 1	60 µg/mL	i.v. injection	1. NEAT1 mRNA levels (qRT-PCR) 2. p65 and phosphorylated p-p65 proteins (WB) 3. HWT test by von Frey filaments 4. 8-OHGD, NF-kB and p-p65 (IF) 5. Protective effects of Mito-Ru MOF (FC, Live/Dead Staining and JC-1 Staining)	[131]
POD-CAT	mSPIONs	CIPNP, C57BL/6 mice, Male, 8–10 weeks old	$n = 3–14$	10 mg/kg	0, 25, 50, and 100 µg/mL	i.p injection	1. Expression of IL-6 and TNF-α (ELISA) 2. HIF1a, p-p65, and p65 protein levels (WB) 3. MWT by electronic von Frey aesthesiometer 4. Fluorescent Probes (PO1 and DCFH-DA) to detect intracellular ROS and H_2O_2 5. Characterization of mSPIONs (TEM, XRD, FTIR, and DLS)	[132]
CAT-SOD	TPP-Au-Ru nanozyme	CCI mouse model	$n = 3–6$	10 mg/kg	0 to 100 µg/mL	i.v. injection	1. ROS in BV2 microglia (Flow Cytometry & Fluorescence Microscopy) 2. Mitochondrial membrane potential (JC-1 Assay) 3. p65, p-p65, MAPK, p-MAPK (WB) 4. IL1β, IL6, and IL8 (RT-qPCR) 5. Mechanical allodynia assessment (Von Frey Filament Test) 6. Nanozyme biodistribution & BBB penetration (In Vivo Imaging)	[133]

gene expression. By preserving mitochondrial transmembrane potential, they block cytochrome c release and caspase-3 activation, thus protecting neurons from apoptosis. These synchronized actions account for the improved mitochondrial activity and neuronal survival rates reported in their model of temporomandibular joint pain. Although the particle size remained stable and exhibited pH-responsive catalytic behavior, significant translational challenges persist. These challenges include a lack of data on in vivo biodistribution, clearance, and

targeting efficiency. Although acid-sensitive degradation suggests a potential clearance route, this remains unverified. To support clinical translation, further studies are necessary to investigate pharmacokinetics, systemic toxicity, and the potential for progression toward human trials.

The structural design of nanozymes is crucial to determine their therapeutic efficacy. For example, triphenylphosphine (TPP)-conjugated nanozymes such as TPP-Au-Ru take advantage of the negative mitochondrial transmembrane potential for targeted delivery, resulting in greater mitochondrial uptake than non-targeted counterparts. After mitochondrial internalization, these bimetallic nanozymes use Ru^{3+}/Ru^{4+} redox cycling to scavenge O_2^- and inhibit mitochondrial ROS (mtROS), thus preventing NLRP3 inflammasome activation. Concurrently, their CAT-like activity promotes H_2O_2 decomposition, which often triggers the ASK1/p38 MAPK pathway activation, leading to the NF-κB pathway activation. Most pioneering, these nanozymes indirectly enhance the cell's intrinsic antioxidant defenses by altering critical cysteine residues on KEAP1, allowing Nrf2 to translocate to the nucleus and induce protective enzymes like heme oxygenase-1 and mitochondrial SOD. The study recognizes the promising preclinical potential of the TPP-Au-Ru nanozyme, with minimal cytotoxicity in BV2 microglial cells and no significant toxicity in mice at the tested doses. However, critical translational challenges must be addressed to understand its therapeutic mechanism. While the ability of nanozyme to localize within mitochondria is compelling, as evidenced by its colocalization with the mitochondrial matrix, there is a notable lack of quantitative data regarding its targeting efficiency [133]. Furthermore, the study overlooks essential clearance mechanisms, such as biodistribution, metabolic breakdown, and excretion pathways, which are vital for evaluating long-term safety and appropriate dosing regimens. Comprehensive studies focusing on chronic exposure, targeted optimization, half-life, and pharmacokinetics are imperative to bridge the significant gap between these promising preclinical findings and their successful clinical application.

In addition to these findings, Liu et al. [132] investigated mSPION nanozymes in CIPNP models. Their work revealed additional mechanisms by which nanozymes protect mitochondrial function. These iron-based nanozymes improve mitochondrial ultrastructure by suppressing lipid peroxidation biomarkers like malondialdehyde and disrupting the interaction between MAPK and NF-κB signaling pathways. Their peroxidase-mimetic activity depletes local pools of hydrogen peroxide, blocks IKKβ phosphorylation, and prevents transcription of inflammatory mediators such as IL-1β. Furthermore, by chelating free iron ions involved in the Fenton reaction, these nanozymes limit the formation of highly harmful hydroxyl radicals, facilitating mitochondrial ROS-induced NLRP3 inflammasome assembly, Fig. 1b. mSPIONs show promising preclinical safety, boosted by the FDA-approved status of SPIONs and minimal cytotoxicity in J774 A.1 cell at relevant doses. Their stability in the physiological environment further supports their biocompatibility, although long-term in vivo toxicity has yet to be tested. The mannose coating improved macrophage targeting, which was evidenced by a reduction in pro-inflammatory cytokines in the sciatic nerve. However, potential off-site effects on central microglia necessitate further refinement of targeting specificity. Importantly, the mechanisms of clearance and biodistribution were not addressed, highlighting the need for future studies to evaluate excretion pathways and potential tissue accumulation, which are essential for clinical translation. These conclusions collectively show that mitochondria-targeted nanozymes produce therapeutic effects by: (1) Primary antioxidant defense (direct ROS scavenging via SOD/CAT/POD mimics); (2) Secondary anti-inflammatory functions (NF-κB/MAPK/NLRP3 inhibition); (3) Tertiary mitochondrial dysfunction restoration (maintaining ΔΨm, inhibiting fission, and reducing apoptosis).

Nanozymes as inhibitors of inflammatory responses in neuropathic pain management

Nanozymes have the potential to significantly reduce neuropathic pain by regulating inflammatory responses. These nanozymes scavenge ROS, decrease the levels of pro-inflammatory cytokines, and improve neuronal health. Furthermore, nanozymes enhance neuroprotection by converting microglia from pro-inflammatory to anti-inflammatory states [144]. Various nanozymes, which prevent glial cell activation and balance endogenous antioxidants, have been synthesized and investigated for their efficacy in treating neuropathic pain. For instance, Ban et al. [145] established cubic cerium oxide nanoparticles, transforming macrophages from an inflammatory to an anti-inflammatory phenotype. This shift was confirmed after reduced expression of M1 markers, including TNF-α, IL-1β, CD86, and iNOS, and enhanced expression of M2 markers, such as IL-10 and Arg-1. Likewise, TPP-functionalized Au-Ru nanozymes demonstrated significant anti-inflammatory effects through the MAPK/NF-κB signaling pathway. By scavenging ROS and inhibiting pro-inflammatory cytokines, these nanozymes significantly reduce neuroinflammation, offering a viable approach for managing neuropathic pain [133].

Nanozymes can be tailored to target microglia, thus inducing their phenotype and function. For example,

Choi et al., 2019 [129] designed a dual NPs system of ceria–zirconia, conjugated with and without CD11b microglial marker. The conjugation of CD11b antibody on the surface of ceria-zirconia nanoparticles increases their targeting capacity to microglia and inhibits microglia activation, thus significantly reducing ROS levels and inflammation [146]. Moreover, the inhibitory effects extended to the lower expression of pain-mediating genes such as iNOS, IL-6, and IL-1β, the pro-inflammatory mediators in neuropathic pain. Although the study shows strong preclinical efficacy, translational challenges remain to be addressed. Regarding biocompatibility, the authors performed MTS assays, finding no significant cytotoxicity of CZ and CZ-Ab nanoparticles up to a concentration of 0.04 mM in primary glial cells, indicating short-term safety in vitro. In terms of targeting efficiency, the study highlights enhanced and selective uptake of CD11b-conjugated CZ nanoparticles by microglia in both in vitro and in vivo models, showcasing precise cellular targeting. However, the clearance mechanisms of the nanoparticles from the central nervous system were not investigated, leaving it as an unaddressed question for future translational development.

The SOD&Fe_3O_4@ZIF-8 nanozymes which was developed by integrating SOD and Fe_3O_4 nanoparticles into ZIF-8, has also demonstrated enhanced uptake in activated microglia. In vivo treatment significantly reduced the activation of astrocytes and microglia, downregulating pro-inflammatory cytokines expression, and inhibited the MAPK signaling pathway, contributing to their potent analgesic effect in the CFA-induced pain model [46]. A study by Kuthati's group has revealed that MPDA@Mor nanozymes treatment inhibits microglial cell activation and significantly lowers TNF-α levels in the PSNT rat model. This formulation also successfully inhibited NF-κB activation, which is primarily involved in the inflammatory reactions associated with NP [127]. The study shows promising findings regarding biocompatibility and the targeting of inflammation sites. However, more research is necessary to understand the mechanisms of systemic clearance, dose-dependent toxicity, and the scalability of SFZ NP production to ensure a successful transition from preclinical findings to clinical applications. For example, the long-term fate of degraded ZIF-8 components, such as zinc ions, and Fe3O4 NPs in vivo has not yet been explored.

Nanozymes target central and peripheral nerves to relieve neuropathic pain

Nanozymes specifically target both central and peripheral nociceptors and show an effective therapy for neuropathic pain. For example, mSPIONs nanozymes selectively reduce peripheral neuropathic pain caused by chemotherapy. They inhibit pro-inflammatory cytokines and reduce ROS levels in macrophages near the affected peripheral nerves. This specific activity mitigates inflammation and targets the inflammatory mechanisms that lead to pain hypersensitivity [132]. Some studies revealed that elevated levels of cyclooxygenase-2 (COX-2) can alter the excitability of the peripheral nociceptive terminals, which increases the sensitization of both peripheral and central nerves [147]. However, MnO_2 NPs have shown potential in reducing spinal cord COX-2 levels, attenuating neuropathic pain induced by PSNT. MnO_2 NPs also assist in rebalancing nociceptive signaling pathways by regulating COX-2 expression. The study confirms that CNS-1 cells are biocompatible and effective at scavenging ROS, with intrathecal delivery reducing mechanical allodynia and suppressing COX-2 expression. However, several important gaps should be addressed to enhance clinical relevance, including a lack of data on systemic biodistribution, clearance, and the aggregation behavior in physiological fluids [136].

Another study by Ling et al. [46] found that the SFZ nanozyme potentially targets both peripheral and central nociceptors. It inhibited spinal glial cell activity by reducing oxidative stress and regulating the pro-inflammatory microenvironment. As previously discussed, Bai et al. [131] developed an ER-Ru-MOF nanozyme loaded into liposomes and delivered to the endoplasmic reticulum. These nanozymes efficiently target central sensitization, provide neuroprotection, and attenuate central post-stroke pain by scavenging mitochondrial ROS and RNS. ER-Ru MOF nanozymes demonstrate significant preclinical promise, confirmed by biocompatibility assays and neuron-specific accumulation. However, critical gaps such as in vivo targeting efficiency, clearance pathways, and long-term biodistribution need to be addressed for clinical translation. TPP-Au-Ru nanozymes also exhibit considerable therapeutic potential for neuropathic pain by targeting the central and peripheral neural systems. Their potential to accumulate in the brain and spinal regions following intravenous administration underscores their ability to traverse the blood–brain barrier (BBB). This distinctive characteristic enables nanozymes to mitigate oxidative damage and inflammation in the dorsal root ganglia (DRG) and the central nervous system (CNS), presenting a promising approach for pain management by modulating both central and peripheral pathways [133].

Restoration of blood spinal cord barrier integrity by nanozymes

Nanozymes, especially those based on iron oxide, demonstrated considerable promise in mitigating the

underlying mechanisms of neuropathic pain by directing blood-spinal cord barrier breakdown and related neuroinflammation [148]. The blood-spinal cord barrier (BSCB) is frequently impaired in neuropathic pain due to heightened permeability and the degradation of tight junction proteins, including claudins, occludins, and zonula occludens (ZO). This disruption is caused by inflammatory cytokines (e.g., TNF-α, IL-1β, IL-6), oxidative stress, and matrix metalloproteinases (MMPs), which deteriorate tight junction components and deteriorate barrier permeability [137, 149]. Nanozymes facilitate BSCB repair by eliminating ROS, reinstating redox homeostasis, and mitigating oxidative stress. For example, mSPIONs nanozyme effectively targets damaged peripheral nerves and relieves chemotherapy-induced neuropathic pain. These nanozymes efficiently reduce ROS and pro-inflammatory cytokines levels such as TNF-α and IL-6 in macrophages near damaged nerves Fig. 4b [132]. Furthermore, nanozymes inhibit the activation of microglia and astrocytes, which contribute to neuroinflammation by releasing MMPs and inflammatory mediators [149]. Treatment with MnO_2 NPs markedly diminished the activation of astrocytes and oligodendrocytes in the dorsal horn of rats after peripheral nerve damage, illustrating the capacity of nanozyme-like materials to inhibit glial cell-mediated neuroinflammation [136]. Thus, nanozymes improve the integrity of BSCB as well as repair nerves by regulating these inflammatory pathways. These findings emphasize the potential of nanozymes as multifaceted therapeutics for neuropathic pain by offering a mechanistic approach to repair BSCB disruption, reduce neuroinflammation, and alleviate chronic pain.

Experimental methods: animal models and administration routes of nanozymes

Researchers have commonly employed several animal models to evaluate the efficacy of nanozymes as a potentially effective therapeutic approach for the management of neuropathic pain (Table 1). Remarkably, nanozyme treatment led to a momentous reduction in mechanical allodynia in different animal models of neuropathic pain. For example, in rats with partial sciatic nerve transection (PSNT), MnO_2 NPs treatment markedly decreased the levels of oxidative stress and pain sensitivity compared to the control group [136]. Furthermore, in PSNT rats, MPDA@Mor therapy distinctly reduced pro-inflammatory cytokines, enhanced endogenous antioxidant levels, and decreased morphine antinociceptive tolerance [127]. In another study, ceria zirconia (CZ) nanozymes considerably raised paw withdrawal thresholds and improved analgesic impact in the SNT-induced neuropathic pain mouse model, indicating that CZ NPs can offer long-lasting pain relief [129]. In addition, Ling et al. [46, 130] found that the SOD&Fe3O4@ZIF-8, SFZ nanozymes therapy significantly decreased astrocyte and microglia activation, downregulated pro-inflammatory cytokine levels, and suppressed the MAPK signaling pathway, leading to their strong analgesic effects in the CFA-induced pain model. Additionally, the mSPIONs nanozyme, a mannose-targeted iron oxide nanozyme, was examined in chemotherapy-induced peripheral neuropathic pain, demonstrating its potential to reduce chemotherapy-related pain [132]. Similarly, TPP-Au-Ru nanozymes exhibited substantial analgesic efficacy in a chronic constriction injury (CCI) animal model by successfully modulating ROS, diminishing inflammatory pathways (NF-κB and MAPK), and alleviating mechanical allodynia [133].

Cell assays were also used to evaluate the efficacy of nanozyme. Specifically, human monocytic THP-1 cells were commonly used to investigate the efficiency of MPDA nanozymes in decreasing ROS levels [127]. Furthermore, CNS-1 cells were used to examine the cytotoxicity of various nanozymes, which revealed no detectable cytotoxic effects within certain concentration ranges Table 2. Additionally, in models of neuropathic pain, ceria-zirconia nanoparticles have defensive effects on microglial cells, decreasing pro-inflammatory cytokines [129].

To understand the therapeutic mechanism of nanozymes in neuropathic pain, it is crucial to evaluate their effects utilizing various research methods. *In vitro* and *in vivo* studies are commonly conducted, but differences in nanozyme doses and routes lead to variations between *in vitro* and *in vivo* applications. Different nanozymes exhibit unique effective doses and modes of delivery, as summarized in Table 1. Animal experiments use intraperitoneal (i.p.), intravenous (i.v.), and intrathecal (i.t.) administration methods. The i.p injection allows nanozymes to penetrate the systemic circulation, resulting in extensive distribution and possible neuroprotective effects across the body [137]. The i.v. injection enables nanozymes to rapidly enter the bloodstream, facilitating immediate access to the peripheral and central nervous systems for efficient pain modulation [150]. However, the i.t injection enables nanozymes to directly access the DRG and spinal cord, essential sites for neuropathic pain processing [151].

In reviewed studies, only MPDA@Mor nanozymes [127] were delivered intraperitoneally. The nanozymes, such as CZ NPs [129], SFZ NPs [130], MnO_2 NPs [136], and CONPs [134], were administered intrathecally, however, the remaining nanozymes, such as ER-Ru MOF [128], Mito-Ru MOF [131], TPP-Au-Ru [133], and mSPIONs [132], were given intravenously. Intraperitoneal and intravenous delivery are safer and simpler than

intrathecal injection, which requires a direct approach to the central nervous system and poses higher risks. These systemic delivery approaches improve the viability of clinical applications for nanozyme treatments by reducing procedural complications.

In vitro experiments have also demonstrated that nanozymes have potent antioxidant capabilities, effectively scavenging ROS in several cell types. To explore these effects, the researchers employed a variety of concentration gradients, falling between 0–200 μg/mL. Different concentration gradients are required for different nanozymes. In in vitro studies, six different cell types, such as CNS-1 cells, BV2 glial cells, BMDM cells, SH-SY5Y cells, J774 A.1 cells, and macrophage RAW 264.7 cell lines, were employed to assess cell viability and ROS elimination as presented in Table 2.

Our review also outlines the experimental procedures employed in the studies we investigated on nanozymes and neuropathic pain. Researchers commonly used von Frey filament and hot plate behavioral tests to assess pain relief and efficacy [129, 133, 136]. Many researchers employed enzyme-linked immunosorbent assay (ELISA) and Western blot (WB) to measure changes in target gene protein expression levels to comprehend the mechanisms of action of nanozymes [127, 132, 133]. The qPCR analysis was also employed to evaluate alterations in the expression levels of genes that are linked with inflammation and pain pathways [133, 134]. Additionally, to measure neuronal injury and inflammatory alterations, investigators frequently used hematoxylin and eosin (H&E) and 4′,6′-diamidino-2-phenylindole (DAPI) staining [127, 133, 134]. Immunohistochemistry analysis was utilized to evaluate microglial and astrocyte activation, and the distribution of nanozymes inside the spinal cord. These methods shed light on the neuroprotective effects of different nanozymes and their potential use in clinical pain management applications (Table 1) [129].

Comparatively, MPDA@MOR and ceria zirconia nanozymes are first-generation designs, nonspecifically quenching ROS and reducing pro-inflammatory cytokines (e.g., TNF-α, IL-6) to mitigate morphine tolerance and mechanical allodynia. In contrast, second-generation constructs like ER-Ru MOF and TPP-Au-Ru employ sophisticated targeting (endoplasmic reticulum, mitochondrial enrichment) to inhibit spatially restricted effectors such as MMP-2, MMP-9, and NF-κB/MAPK inhibition while preserving redox homeostasis, demonstrating efficacy in recalcitrant disorders such as central post-stroke pain and chronic construction injury. Notably, CONPS and Mito-Ru MOF therapeutically extend beyond symptom mitigation by reprogramming macrophage polarization and mitochondrial function to address the neuro-immune axis dysfunction that drives chronic pain Table 3. These developments underscore a crucial design principle: maximal therapeutic efficacy requires pairing enzymatic potency and biodistribution control. This paradigm can overcome the problems with cell-type specificity and BSCB/BBB that are frequently associated with traditional therapies.

Route of nanozymes delivered to the site of injury

Nanozymes have established considerable potential in neuropathic pain treatment by efficiently targeting crucial areas of the nervous system, including the brain, spinal cord, and peripheral nerves [132, 152, 153]. Their tiny size and increased solubility provide significant advantages in overcoming biological barriers such as the BBB and BSCB [133]. In neuropathic pain disorders, the integrity of these barriers may be impaired due to inflammation and nerve damage, thereby facilitating nanozyme to penetrate affected tissues [154, 155]. However, the degree of barrier interruption varies, which can impact the efficiency of nanozyme distribution. Most recent approaches for improving nanozyme delivery in neuropathic pain treatment include mannose receptor-mediated endocytosis [132], lysosome-mediated endocytosis [130], targeting specific cellular structures like mitochondria or the endoplasmic reticulum [128, 131], and modulation of immune cells like macrophages and microglia [127].

Lysosome-mediated endocytosis of SOD&Fe3O4@ZIF-8, SFZ nanozyme

SOD&Fe_3O_4@ZIF-8-SFZ nanozyme penetrates microglial cells efficiently via lysosome-mediated endocytosis. In neuropathic pain conditions, activated microglia within the spinal cord increase lysosomal activity due to an inflammatory microenvironment [156]. The rise in lysosomal activity enhances lysosomal-mediated cellular uptake of nanozymes. For instance, in a study led by Ling's group, SOD and Fe_3O_4 nanoparticles were

(See figure on next page.)

Fig. 4 Nanozymes can be delivered by various distinct routes. The SFZ nanozymes enter the macrophage cell by lysosome-mediated endocytosis and scavenge ROS. Mannose-coated superparamagnetic iron oxide nanoparticles (mSPIONs) can traverse the cell membrane via receptor-mediated endocytosis with the help of adhesion molecules such as mannose molecules (CD206). ER-Ru MOF, Mito-Ru MOF, and TPP-Au-Ru enter the cell by endocytosis, where Mito-Ru MOF and TPP-Au-Ru specifically bind with mitochondria, and ER-Ru MOF binds with the endoplasmic reticulum (Abbreviations: MRM: Mito-Ru-MOF, ERM: ER-Ru-MOF). **b** The BSCB is disrupted by excessive ROS, which then activates microglia, astrocytes, and pro-inflammatory cytokines. These factors then cause MMPs to break down tight junction proteins, which results in pain. Nanozymes reduce ROS levels, recover BSCB integrity, and alleviate pain

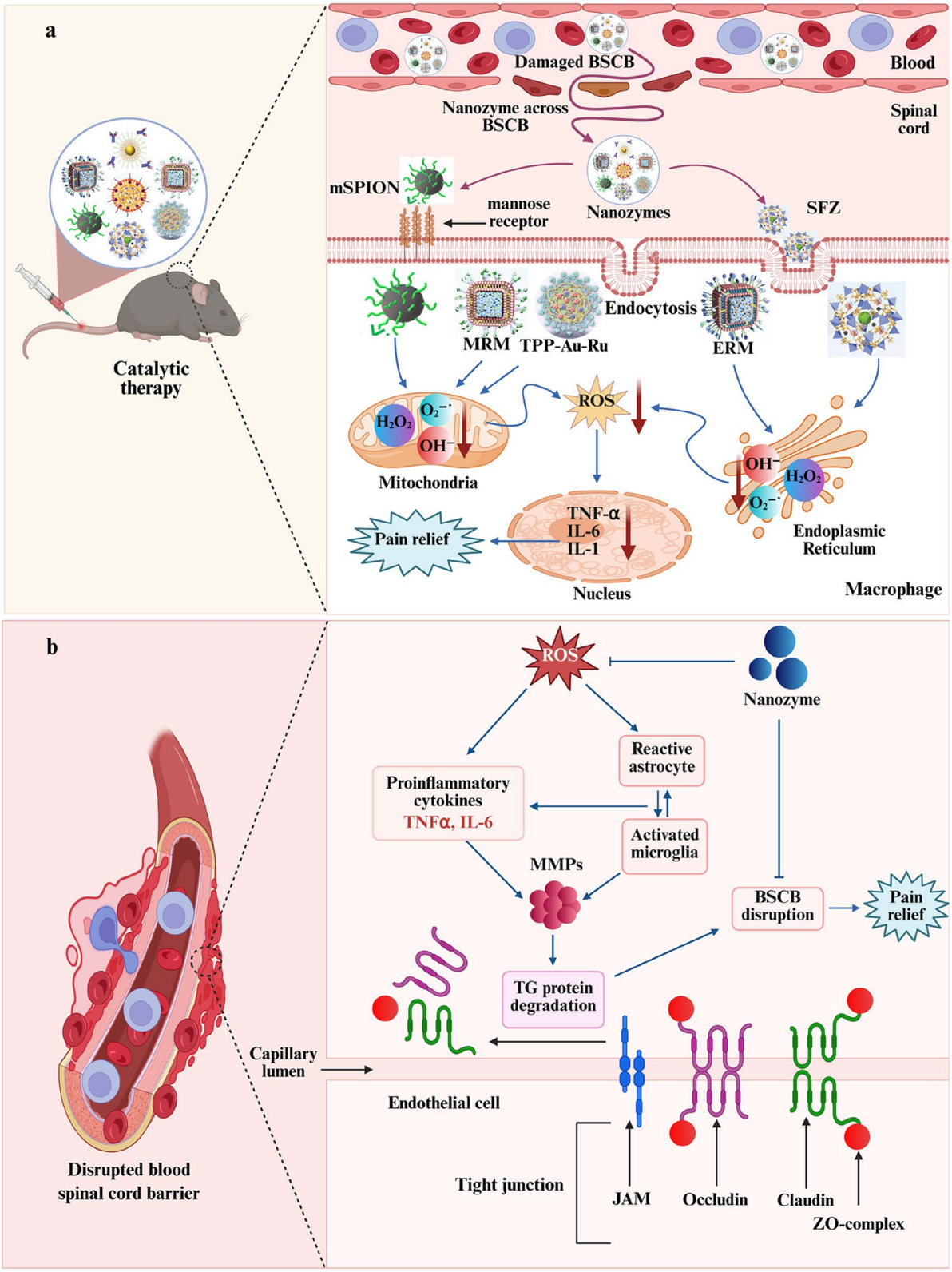


Fig. 4 (See legend on previous page.)

Table 2 Experimental methods in cell models for exploring the protective effects of nanozymes in neuropathic pain

Nanozyme Type	Cell lines	Processing mode	Treatment concentrations	Ref.
MPDA@MOR Nanozyme	CNS-1 tumor cell lineTHP-1 cells	Tetrazolium salt to Formosan Exposed to DCFDA (10 μM)	10 to 150 μg/mL	[127]
C-Z Nanozyme	mixed glia cells	Tetrazolium salt to Formosan	0.04 mM	[129]
SFZ Nanozyme	BV2 cell	Exposed to H2DCFDA probe	2 to 64 μg/mL	[130]
MnO_2 NPs	BMDM cells CNS-1 cells	Tetrazolium salt to Formosan, LDH release quantification	10 to 100 μg/mL	[136]
ER-Ru MOF Nanozyme	SH-SY5Y cells	Exposed to ABTS and DPPH free radicals	5 to 200 μg/mL	[128]
CONPS	Macrophage RAW 264.7 cell lines	Not found	100 μg/mL and 200 μg/mL	[134]
Mito-Ru MOF Nanozyme	Not found	Exposed to DCFH-DA probe	60 μg/mL	[131]
mSPIONS	J774 A.1 cells	Exposed to PO1 and DCFH-DA probes	0, 25, 50, and 100 μg/mL	[132]
TPP-Au-Ru nanozyme	BV2 cell	Exposed to DCFH-DA probe, 4-HNE staining & MDA ELISA for lipid peroxidation	20 μg/mL	[133]

enclosed within a ZIF-8 framework forming a multi-enzyme-mimic nanozyme [130]. The ZIF-8 encapsulation facilitates the uptake of the nanozyme into activated microglial cells via lysosome-mediated endocytosis. After internalization, the SFZ nanozyme are break down in the moderately acidic environment of the spinal cord, discharging the incorporated SOD and Fe_3O_4 nanoparticle. These constituents then perform a series of catalytic reactions, where ROS, especially superoxide anions ($O_2^{-\bullet}$), are catalyzed into H_2O_2 and O_2. Moreover, they inhibit the release of inflammatory cytokines such as TNF-α, IL-6, and IL-1β, block the MAPK/p-65 signaling pathway, thus alleviating inflammatory pain and preventing additional glial cell activation Fig. 4a.

Mannose receptor-mediated endocytosis of mSPIONs nanozymes

mSPIONs nanozymes can efficiently enter macrophages via mannose receptor-mediated endocytosis. Its mannose functionalized surface enables rapid recognition and internalization by macrophages, analogous to the natural binding with mannose receptors. During neuropathic pain, mannose receptors (CD206) are significantly upregulated on the surfaces of M2 macrophages that are alternatively activated [157, 158]. The mannose molecules on the surface of nanozyme have a high selectivity and affinity for mannose receptors on M2 macrophages. This binding provokes the uptake of the nanozymes by macrophages. After internalization, mSPIONs nanozymes function similarly to catalase under neutral environments, breaking H_2O_2 into H_2O and O_2. Thus, these nanozymes mitigate oxidative stress in macrophages and improve their therapeutic efficiency in the treatment of neuropathic pain Fig. 4a [132].

Targeting specific cellular structures like mitochondria and the endoplasmic reticulum

Bai's group developed an innovative ER-Ru MOF nanozyme [137]. The liposome coating incorporating p-dodecylbenzene sulfonamide (p-DBSN) allows these nanozymes to target the endoplasmic reticulum (ER). In the CPSP model, the ER is an important site for oxidative stress, which promotes neuroinflammation [159]. Once localized to the ER, the ER-Ru MOF nanozyme inhibits ROS production in the same way as catalase reduces oxidative stress in other cells. By inhibiting ROS production, the ER-Ru MOF nanozyme further suppresses the expression of MMPs and pro-inflammatory cytokines such as IL-6 and TNF-α. This combined effect reduces oxidative stress in the ER, inhibits neuroinflammation, thus significantly relieves pain, and improves overall consequences in CPSP models Fig. 4a.

Similarly, in another study, Bai et al. [131] developed Mito-Ru MOF nanozyme. They are specifically engineered to accumulate in mitochondria. The incorporated triphenylphosphine (TPP) and liposomes have boosted their mitochondrial uptake. Once internalized, the nanozymes are broken down to release their constituents and perform their activities. They scavenge ROS and mitigate oxidative stress, which is frequently aggravated in an inflammatory pain environment. Moreover, these nanozymes downregulate the expression of TNF-α, NF-κB, and NEAT1 pathway, thus effectively reducing inflammation and relieving pain associated with TMJ disorders. Recently, Cheng et al. (133) synthesized TPP-Au-Ru nanozymes to target mitochondria and alleviate neuropathic pain. In this context, TPP served as a mitochondria-targeting ligand, facilitating the accurate localization of bimetallic cluster nanozymes to the mitochondria, thus, the Au-Ru bimetallic configuration conferred substantial ROS-scavenging and

anti-inflammatory capabilities to the nanozymes [133]. These tailored approaches highlight nanozymes' ability to specifically target definite cellular structures, increasing their therapeutic efficacy in treating pain and inflammatory disorders by precisely modulating oxidative stress and inflammatory pathways, Fig. 4a.

Modulation of immune cells like macrophages and microglia

The modulation of macrophage polarization in the spinal cord is also an effective strategy to manage neuropathic pain. Cerium oxide nanoparticles have strong antioxidant properties that transform macrophages from M1 pro-inflammatory to M2 anti-inflammatory phenotype [160]. This modification of macrophage polarization decreases neuroinflammation and improves tissue repair in the spinal cord injury (SCI) mouse model. The study demonstrates biocompatibility in RAW 264.7 macrophages and effective spinal targeting through intrathecal delivery. The favorable Ce^{3+}/Ce^{4+} redox-active ratio indicates therapeutic potential; however, concerns persist regarding particle aggregation, insufficient systemic biodistribution, and uncharacterized clearance. While the observed polarization towards M2 macrophages is promising, it requires validation in higher species to ensure translational relevance [134]. Similarly, Choi et al., 2019 [129] prepared a dual NPs system of ceria–zirconia nanoparticles conjugated with and without CD11b microglial marker. The conjugation of CD11b antibody on the surface of ceria-zirconia nanoparticles increases the targeting capacity of the nanozyme to microglia and enhances their microglial uptake efficiently [146]. These nanozyme effectively scavenge ROS via its CAT and SOD mimetic activity in primary glial cells [161]. It revealed that CD11b conjugation improved the targeted delivery of nanozymes to primary glial cells, significantly reduced inflammation and ROS levels, thus inhibiting microglial activation in vitro and relieving neuropathic pain.

Advancing the clinical applications of nanozymes in neuropathic pain treatment

Although nanozymes have exhibited impressive therapeutic potential in preclinical models of neuropathic pain, their clinical application is still in its early stages. However, recent clinical trials utilizing multifunctional nanozymes in oncology suggest potential parallels. Notably, several nanozyme-based platforms already in clinical trials or application, which were originally synthesized for cancer therapy, have intrinsic enzyme-mimetic activity relevant to neuropathic pain pathology, such as scavenging ROS and modulating the inflammatory microenvironment. For example, the Nanotherm® Therapy System (NTTS), which includes superparamagnetic iron oxide nanoparticles (SPIONs), is CE-approved for recurrent glioblastoma therapy and is currently being investigated in new clinical trials, e.g., NCT06271421 [162]. These SPIONs, such as mannose-coated SPIONs, have been extensively explored in pain models for their CAT- and POD-like activities, and their ability to modulate oxidative stress may contribute to therapeutic effects beyond hyperthermia [132]. Clinical relevance of mSPIONs is also supported by FDA approval of SPIONs (e.g., Ferumoxytol) for anemia and imaging, which validates their safety profile [159].

Similarly, gold nanoparticles with oxidase-like catalytic activities have advanced to clinical trials (e.g., NU-0129, NCT03020017) [163]. Although synthesized for gene delivery and tumor targeting, their catalytic activity is similar to mechanisms used to treat neuropathic pain, such as decreasing oxidative damage, suppressing pro-inflammatory mediators, and preserving neuronal integrity. These studies, while not pain-specific, demonstrate the clinical viability, safety, and regulatory approval of nanozyme-active platforms. They provide a translational platform for repurposing or developing nanozymes specifically tailored to target ROS, neuroinflammation, and mitochondrial malfunction, all of which are the hallmarks of neuropathic pain. The next step would be to adapt these multifunctional platforms for neurological disorders and advance them in neuropathic pain through tailored clinical trials.

Conclusion and perspectives

Elevated ROS are directly accountable for the maintenance of neuropathic pain via multiple pathological mechanisms [164]. ROS directly sensitize pain-transducing ion channels (especially TRPV1 and voltage-gated sodium channels) by decreasing their threshold value for activation and increasing neuronal hyperexcitability. Concurrently, ROS trigger intracellular signaling pathways such as NF-κB and NLRP3 inflammasomes in glial and neuronal cells that start a neuroinflammatory cascade with ongoing production of pro-inflammatory cytokines (TNF-α, IL-6, IL-1β) and amplifying pain transmission [165]. Mitochondrial dysfunction caused by oxidative stress further exacerbates the process by disrupting cellular energy metabolism and calcium homeostasis in nociceptive neurons [164]. Specifically, ROS also suppresses endogenous antioxidant systems by inhibiting the Nrf2 pathway, resulting in a self-perpetuating loop of oxidative damage that prevents natural pain resolution [166]. This continuous redox imbalance causes structural alterations in the nervous system, such as synapse remodeling and axonal degradation, and the transition from acute to chronic pain states.

Existing therapies, like gabapentin, confront drawbacks such as nonlinear absorption (27–60% bioavailability)

Table 3 A comparative summary of nanozymes tested for neuropathic pain therapy

Nanozyme Type	Enzymatic activity	Target pathways	Relevance to neuropathic pain	Ref.
MPDA@MOR Nanozyme	CAT-SOD	ROS scavenging, NF-κB/TNF-α suppression, microglial inhibition, endogenous antioxidant restoration	Attenuates morphine tolerance, reduces oxidative stress, restores liver antioxidants, suppresses spinal microglial activation	[127]
Ceria zirconia Nanozyme	CAT-SOD	Nox2-derived ROS reduction, pro-inflammatory cytokine (IL-1β/IL-6/TNF-α) inhibition	Targets microglia to alleviate mechanical allodynia, inhibits spinal neuroinflammation	[129]
SFZ Nanozyme	CAT-SOD	Inhibits MAPK/p-65 signaling pathway, reduces p-ERK, p-JNK, p-p38, and p-65 phosphorylation, lowers TNF-α, IL-6, IL-1β	Relieves CFA-induced inflammatory pain, pH-responsive release in acidic inflammatory microenvironments	[130]
MnO_2 NPs	SOD	Suppresses COX-2 expression, reduces oxidative stress in macrophages	Ameliorates PSNT-induced mechanical allodynia, has no impact on thermal hyperalgesia, biocompatible with minimal cytotoxicity	[136]
ER-Ru MOF Nanozyme	CAT-SOD	ROS/MMP-2/9/EMMPRIN inhibition, TNF-α/IL-6/neuroinflammation suppression, ER stress modulation	Treats CPSP by reducing oxidative stress and neuroinflammation, alleviates mechanical/cold allodynia, enhances nanozyme delivery to neurons	[128]
CONPS	CAT-SOD	Macrophage polarization (M1 → M2), TNF-α/iNOS/IL, 1β downregulation, IL-10/Arg-1 upregulation	Attenuates SCI-induced NP by promoting M2 macrophages ($CD206^+$/$Arg\text{-}1^+$), reduces mechanical/thermal hypersensitivity, dose-dependent pain relief, and motor recovery	[134]
Mito-Ru MOF Nanozyme	CAT-SOD	Targets mitochondrial ROS, inhibits TNF-α/NF-κB/NEAT1 pathway, reduces oxidative stress and inflammation in Sp5 C	Treats CFA-induced TMJ pain by reducing ROS, inflammation, and NEAT1 expression in the spinal trigeminal nucleus	[131]
mSPIONS	POD-CAT	Scavenges ROS in macrophages, inhibits HIF1α/NF-κB pathway, reduces IL-6 and TNF-α levels	Relieves VCR-induced peripheral neuropathy, targets macrophages in sciatic nerves, and reduces mechanical allodynia	[132]
TPP-Au-Ru nanozyme	CAT-SOD	Mitochondrial ROS scavenging (via TPP targeting), NF-κB/MAPK inhibition (↓ p-p65, ↓ p-MAPK), ↓ pro-inflammatory cytokines (IL-1β, IL-6, IL-8)	Reduces mechanical allodynia (Von Frey test), sustained analgesia, crosses BBB, targets DRG and spinal cord, restores ΔΨm and ATP production	[133]

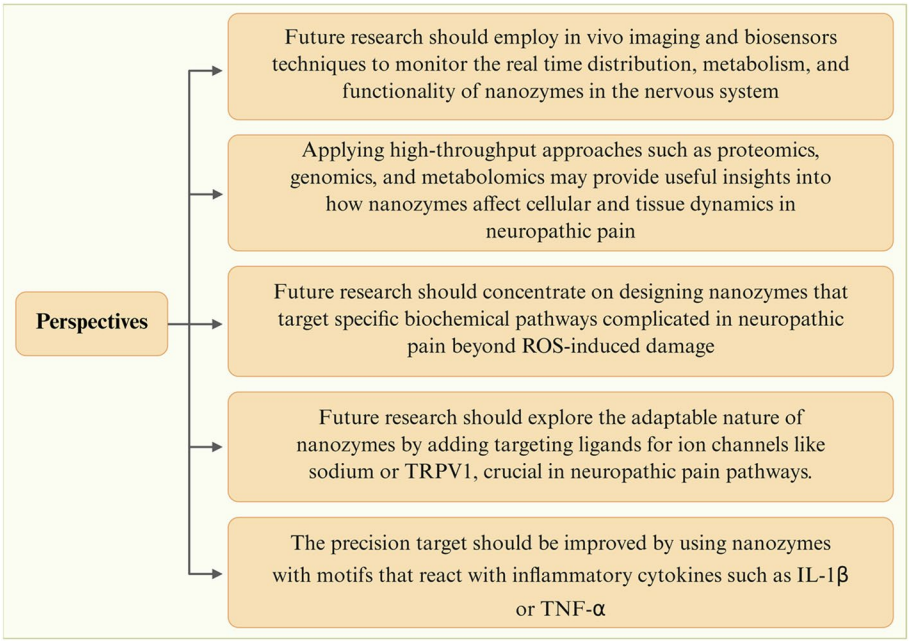


Fig. 5 Future research directions. Nanozymes for neuropathic pain management could relate to in vivo imaging, high-throughput techniques, targeted biochemical pathways, incorporation of ion channel ligands, and improving precision targeting through inflammatory cytokine motifs

[167] and dose-constrained neurocognitive adverse effects (dizziness, somnolence, ataxia) [168, 169], resulting in 12-month dropout rates of 45–50% [170]. Emerging findings also correlate its usage with a 1.7-fold higher fall risk in the elderly and synergistic opioid respiratory depression, demanding safer alternatives or precision dosage regimens [171–173]. Nanozymes, on the other hand, outperform traditional therapies in terms of bioavailability and stability by engineering nanostructures that achieve nearly 80–90% cellular uptake (compared to gabapentin's 27–60% absorption) and resist enzymatic destruction (half-lives >54 h vs. gabapentin's 5-7 h) [167, 174, 175]. Unlike small drug molecules, nanozymes remain catalytically active throughout pH/temperature ranges, allowing targeted release without dose dumping [176]. While nanozymes hold breakthrough potential for neuropathic pain therapy, their incidental pro-oxidant activity poses significant risks, including off-target cytotoxicity, chronic inflammation via NLRP3 activation, and exacerbated tissue damage in redox-sensitive organs (e.g., liver, neurons). Recent studies highlight such compromises, for example, Fe_3O_4 nanozymes caused neuronal oxidative stress and destroyed healthy cells at therapeutic levels [177]. To reconcile safety and efficacy, future studies are encouraged to focus on stimulus-responsive designs (e.g., H_2O_2 and pH-responsive activity) and real-time ROS monitoring systems such that pro-oxidant effects are spatially and temporally confined to pathologic sites.

Nanozymes have displayed momentous potential in medical applications, particularly in treating neuropathic pain. A significant illustration is the work of Liu et al. [176], who developed mannose-coated nanozymes (mSPIONs) to relieve chemotherapy-induced peripheral neuropathic pain. Their mannose coating facilitates targeted entry by macrophages, thus lowering pro-inflammatory cytokine release (e.g., TNF-α, IL-6) in the dorsal root ganglion. Further, its intrinsic catalase-like activity directly reduces cytotoxic H_2O_2 to H_2O and O_2 without forming toxic •OH by-products and mitigates oxidative stress in nerve tissues. This dual mechanism was demonstrated in a 2023 *iScience* article, where mSPIONs reduced mechanical allodynia in paclitaxel-treated mice by 60% without systemic toxicity and exceeding a 30% reduction of traditional therapies. Specific nanozymes possess multienzyme-like properties (e.g., combined SOD/catalase activity) that enable them to address diverse ROS species ($O_2^{\bullet -}$, H_2O_2) within pain pathways, improving therapeutic efficacy compared to single-enzyme mimics. The multienzyme function of nanozymes is crucial because neuropathic pain comprises interconnected oxidative and inflammatory pathways that single-activity systems cannot fully address. Moreover, nanozymes minimize immunogenicity and side effects by specifically targeting the injury site and reducing recognition by the immune system. For example, Pd@Au core–shell nanozymes avoided nonspecific immunogenicity, long-term accumulation risks, and systemic side effects, frequently associated with traditional therapies

[176]. Despite their promise for neuropathic pain therapy, nanozymes face three key challenges that hinder full mechanistic understanding. Firstly, their intricate bio-nano interactions with neural cells and immune mediators, particularly in disease-specific microenvironments, are poorly characterized. Secondly, their dynamic physiological conditions (e.g., pH variation) alter catalytic activity and render dose–response relationships unpredictable. Thirdly, a lack of standardized models to distinguish direct neuronal effects from indirect immunomodulation. Therefore, future research should employ in vivo imaging and biosensor techniques to monitor the real-time distribution, metabolism, and functional processes of nanozymes in the nervous system Fig. 5. High-tech methods such as catalytically induced MRI may reveal nanozyme penetration across the blood-nerve barrier with micrometer-scale resolution, whilst neuron-specific fluorescence bio-sensors provide quantitative evaluation of ROS scavenging kinetics within individual cells. These techniques could provide three critical perceptions: first, they would reveal the spatiotemporal dynamics of nanozyme build-up within pain-related neural circuits; secondly, they would permit relationship between the catalytic activity patterns and therapeutic outcomes; and thirdly, they would allow for the visualization of nanozyme interactions with precise subcellular organelles such as mitochondria and endoplasmic reticulum. These visualized nanozyme-organelle interactions explicitly outline their therapeutic mechanisms of action. For instance, the Mito-Ru MOF nanozyme selectively enters mitochondria, where its dual SOD/catalase activity truncates oxidative stress by >70% [131], similarly TPP-Au-Ru nanozyme stabilizes mitochondrial membranes to prevent leakage of cytochrome c and resultant neuronal apoptosis [133]. Concurrently, the ER-Ru MOF nanozyme targets the endoplasmic reticulum, removing misfolded protein aggregates by 60% and inhibiting the p-ERK-CHOP pathway [128]. Applying high-throughput approaches such as proteomics, genomics, and metabolomics may provide useful insights into how nanozymes alter cellular and tissue dynamics in neuropathic pain Fig. 5. These methods can transform our understanding of nanozyme mechanisms by offering systems-level perspectives of their bio-nano interactions. Proteomics can detect changes in protein expression caused by nanozymes (e.g., downregulation of inflammatory cytokines like TNF-α), genomics can disclose cell-type-specific transcriptional cascades in DRG neurons and glial cells, and metabolomics can monitor the recovery of disrupted metabolic pathways (e.g., ATP/NAD +levels) in neuropathic pain models. These approaches will empower the discovery of personalized medicine biomarkers, monitoring therapeutic side effects for safety optimization, and rational next-generation nanozyme design for improved specificity, ultimately overcoming barriers to nanozyme clinical translation for neuropathic pain.

In conclusion, nanozymes can be considered crucial therapeutic agents for neuropathic pain as indicated by their potential in scavenging ROS, reducing oxidative stress, and modifying inflammatory responses. Nanozymes diminish neuroinflammation by scavenging ROS, suppressing glial activation (microglia/astrocytes), and reducing pro-inflammatory cytokine production (TNF-α, IL-6). Their surface engineering allows for tailored immune cell interactions. For example, mannose-coated nanozymes modulate macrophage polarization from pro-inflammatory M1 to anti-inflammatory M2 phenotypes. This dual action affects the neuroinflammatory cascade at multiple levels, providing superior resolution of chronic inflammation than standard anti-inflammatory medications [176]. Such two-way action halts the neuroinflammatory cascade at different sites, achieving greater resolution of chronic inflammation than conventional anti-inflammatory drugs. However, the management of neuropathic pain involves unique challenges, especially when administering nanozymes to specific spinal cord and brain regions. The main challenges in the delivery of nanozymes across the BSCB and BBB are cellular size exclusion (> 30 nm excluded), efflux pump clearance (80% cleared by P-gp/MRP1), immunoprotected sequestration (60–90% lost to RES), catalytic variability (degradation by serum), and lack of pain-specific targeting (e.g., TRPV1/NLRP1 pathways) [178–180]. Recent developments in receptor-mediated endocytosis improve nanozyme delivery to pain-specific regions by enabling cell-specific targeting and localized therapeutic effects. As previously discussed in a Liu et al. study, mSPIONs specifically bind to mannose receptors, which are significantly expressed on macrophages that invade the sciatic nerve in vincristine-induced neuropathic pain. This binding triggers effective cellular uptake, allowing mSPIONs to reach precisely in pain-signaling regions while reducing off-target distribution [176]. However, more research is required to enhance these delivery systems and ensure that nanozymes can efficiently penetrate and concentrate in the damaged tissues of the spinal cord and brain.

Furthermore, future research should investigate the adaptable nature of nanozymes by incorporating targeting ligands or drugs particular to ion channels, such as sodium or TRPV1 channels, which are critical in neuropathic pain signaling pathways Fig. 5. Encapsulating or conjugating sodium channel blockers into nanocarriers allows for enhanced drug bioavailability, solubility, and target-specific delivery, resulting in better therapeutic effects. This nanoscale specificity could be a game

changer to significantly reduce off-target effects and improve the overall safety profile of sodium channel-targeted treatments [181]. Furthermore, by conjugating TRPV1-specific ligands (e.g., capsaicin analogs or inhibitory peptides) to nanozyme carriers, researchers could potentially achieve dual therapeutic actions: the intrinsic catalytic property to antagonize ROS-mediated channel sensitization and targeted activation threshold modulation of TRPV1 [182]. This method would improve the spatial specificity of treatment and yield long-term therapeutic effects via controlled release kinetics at pain origins. Additional research can examine how such functionalized nanozymes could synergize with existing TRPV1 modulators while preserving selectivity to bypass undesirable thermal sensitivity effects. Nanozyme surfaces can be engineered with inflammatory cytokine-binding motifs, such as TNF-α antibodies or IL-6 receptor fragments, to target inflamed tissues while neutralizing pro-inflammatory signals and scavenging ROS Fig. 5. This approach is similar to the ion channel-targeting strategies described above. A novel dual-function strategy can be enabled by nanozymes that incorporate neural growth factors for nerve regeneration and antioxidants to reduce oxidative stress. This integrated technique provides synergistic effects by encouraging nerve regeneration through growth factors (e.g., NGF, BDNF) and neutralizing oxidative damage with antioxidant nanozymes. It could improve therapeutic accuracy by protecting weak growth factors from degradation, allowing for precise delivery to damaged nerves, and delivering long-term release at pain sites.

The practical implementation of nanozymes for neuropathic pain therapy demands a detailed examination of their therapeutic strategies and potential risks. It should be known how nanozyme substrates and products interact with neural tissues to minimize potential toxicity and side effects. Till now, most of the studies have been conducted in rodent models, which may not adequately reflect the complexities of human neuropathic pain. Therefore, to more accurately mimic human settings and aid in medical translation, future research should concentrate on larger animal models, such as monkeys, dogs, or pigs. Larger animals better match human anatomy (e.g., nerve size, BSCB/BBB integrity), immunological responses, and pharmacokinetics, hence overcoming the limitations of rodent-scale biodistribution and dosage [183, 184]. Secondly, neuroinflammation, chronic pain pathways, and tissue-specific nanozyme accumulation trends in larger animal models reflect human disease progression and therapeutic challenges more accurately. Additionally, FDA/EMA guidelines often demand large-animal safety statistics (e.g., organ toxicity, immunogenicity) before initiating clinical trials, since rodents cannot predict human side effects accurately [185]. Furthermore, optimizing the timing and delivery methods for nanozyme intervention in neuropathic pain is essential to maximize efficacy and minimize side effects. The key factors include intervention timing regarding disease progression, administration route/method (e.g., IV vs localized), dosage frequency, release kinetics, cellular absorption dynamics, etc. Exploration of these perspectives is essential as the field moves closer to the predicted clinical incorporation of nanozymes, which is still a developing and promising area of research.

Abbreviations

NP	Neuropathic pain
CAT	Catalase
SOD	Superoxide dismutase
GPx	Glutathione peroxidase
POD	Peroxidase
BSCB	Blood Spinal Cord Barrier
MR	Mannose receptor
OS	Oxidative stress
ROS	Reactive oxygen species
Fe3O4	Iron (II, III) oxide
IL-1β	Interleukin-1 beta
TNF-α	Tumor necrosis factor alpha
MPDA NPs	Mesoporous polydopamine nanoparticles
Mito-Ru MOF	Mitochondria- ruthenium metal organic framework
ER-Ru MOF	Endoplasmic reticulum-ruthenium metal organic framework
CD11b	Cluster of differentiation molecule 11B
CZ	Ceria–zirconia
SOD-Fe_3O_4@ZIF-8	Superoxide dismutase and iron oxide nanoparticles encapsulated within zeolitic imidazolate framework-8
mSPIONs	Mannose-coated superparamagnetic iron oxide nanoparticles
MONZs	Manganese oxide nanozymes
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
MAPK	Mitogen-activated protein kinase
PLC-γ	Phospholipase C-gamma
Src	Sarcoma
Ras	Rat sarcoma
Raf	Rapidly accelerated fibrosarcoma
ERK	Extracellular signal-regulated kinase
p22phox	Cytochrome b-245 alpha chain
ASK1	Apoptosis signal-regulating kinase 1
JNK	Jun N-terminal kinase
SNI	Spared nerve injury
DRG	Dorsal root ganglion
NaV	Voltage-gated sodium channels
Cav	Voltage-gated calcium
TRP	Transient receptor potential
TRPV1	Transient receptor potential vanilloid-1
TRPA1	Transient receptor potential cation channel
CNS	Central nervous system
IL-6	Interleukin 6
TGF-β	Transforming growth factor-beta
C1q	Complement component 1q
C3 d	Complement component 3d
Drp1	Dynamin-related protein 1
DAMP	Damage-associated molecular pattern
BBB	Blood-brain barrier
TG	Tight junction
MMPs	Matrix metalloproteinases
PSNT	Partial sciatic nerve transection
CFA	Complete Freund's adjuvant
THP-1	Human leukemia monocytic cell line
CNS-1	Central nervous system 1
TNF-α	Tumor necrosis factor alpha

MnO_2	Manganese dioxide
COX-2	Cyclooxygenase-2
ZIF	Zeolitic imidazolate framework
CONPs	Cerium oxide nanoparticle
iNOS	Inducible nitric oxide synthase
Arg-1	Arginase
SFZ	SOD&Fe_3O_4@ZIF-8
NEAT	Nuclear-enriched abundant transcript 1
TPP	Triphenylphosphine
CIPNP	Chemotherapy-induced (peripheral) polyneuropathy
i.p	Intraperitoneal
i.v	Intravenous
i.t	Intrathecal
BV2	Microglial cell line derived from C57/BL6 mice
BMDMs	Bone-marrow-derived macrophage
SH-SY5Y	Human neuroblastoma cell line
J774 A.1	Cell line of immortalized mouse macrophages
ELISA	Enzyme-linked immunosorbent assay
WB	Western blot
qPCR	Quantitative polymerase chain reaction
H&E	Hematoxylin and eosin
DAPI	4′,6′-Diamidino-2-phenylindole
p-DBSN	P-dodecylbenzene sulfonamide
ER	Endoplasmic reticulum
CPSP	Central post-stroke pain
TMJ	Temporomandibular joint
SCI	Spinal cord injury

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Authors' contributions
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No datasets were generated or analysed during the current study.

Declarations

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