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Review article

The anti-oxidation related bioactive materials for intervertebral disc degeneration regeneration and repair

Yingjie Mai [a], Siying Wu [b], Penghui Zhang [a], Ningning Chen [a], Jun Wu [b,c,**], Fuxin Wei [a,*]

[a] Department of Orthopaedics, The Seventh Affiliated Hospital, Sun Yat-sen University, Shenzhen, Guangdong Province, 518107, China
[b] Bioscience and Biomedical Engineering Thrust, The Hong Kong University of Science & Technology (Guangzhou), Nansha, Guangzhou, Guangdong Province, 511400, China
[c] Division of Life Science, The Hong Kong University of Science & Technology, Hong Kong SAR, 999077, China

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ABSTRACT:

Intervertebral disc degeneration (IVDD) is a prevalent chronic spinal condition characterized by the deterioration of the intervertebral discs (IVD), leading to structural damage and associated pain. This degenerative process is closely linked to oxidative stress injury, which plays a pivotal role in its onset and progression. Oxidative stress in IVDD results from the excessive production of reactive oxygen species (ROS) and impaired ROS clearance mechanisms, disrupting the redox balance within the intervertebral disc. Consequently, oxidative stress contributes to the degradation of the extracellular matrix (ECM), promotes cell apoptosis, and exacerbates disc tissue damage. Current treatment options for IVDD face significant challenges in effectively alleviating the oxidative stress-induced damage and facilitating disc tissue repair. However, recent advancements in biomaterials have opened new avenues of hope for IVDD treatment by addressing oxidative stress. In this review, we first provide an overview of the pathophysiological process of IVDD and explore the mechanisms and pathways associated with oxidative stress injury. Then, we delve into the current research on antioxidant biomaterials employed in the treatment of IVDD, and outline the advantages and limitations of hydrogel, nanomaterials, polyphenol and inorganic materials. Finally, we propose the future research direction of antioxidant biomaterials in IVDD treatment. The main idea of this review is shown in Scheme 1.

1. Introduction

Intervertebral disc degeneration (IVDD), a common and serious condition among vertebrae-related diseases, is characterized by progressive structural damage caused by abnormal cell-mediated processes [1]. A series of pathophysiological changes, such as cell histological changes and intervertebral disc anatomical structure destruction, occur during degeneration. This process involves a decrease in proteoglycan content, a loss of disc height, and increased biomechanical instability [2]. This degeneration leads to chronic pain, movement disorders, and even neurological symptoms [3]. Patients frequently experience low back pain and lower extremity radiculopathies [4], causing significant discomfort and harm. Additionally, their social life can be significantly affected, as patients are often forced to limit social interactions and rely on long-term medication use, primarily painkillers [5]. The progressive degeneration of IVD limits physical mobility, significantly affecting patients' quality of life and potentially contributing to the global burden of musculoskeletal disorders [6]. This degenerative change can be caused by a variety of factors [7], including age, injury, genetics, and lifestyle. The rising global aging population emphasizes the increasing incidence of IVDD, which further highlights the urgent need for new treatment. Individuals over the age of 60 showing some degree of IVDD, the prevalence of IVDD increases with age and is expected to continue rising as life expectancy increases globally [8].

Conventional treatments for IVDD mainly include bed rest, pharmaceutical interventions, physical therapy, exercise regimens and

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* Corresponding author.
** Corresponding author. Bioscience and Biomedical Engineering Thrust, The Hong Kong University of Science & Technology (Guangzhou), Nansha, Guangzhou, Guangdong Province, 511400, China.
E-mail addresses: maiyj6@mail2.sysu.edu.cn (Y. Mai), swu585@connect.hkust-gz.edu.cn (S. Wu), zhangpenghui@sysush.com (P. Zhang), chennn8@mail.sysu.edu.cn (N. Chen), junwuhkust@ust.hk (J. Wu), weifuxin@mail.sysu.edu.cn (F. Wei).

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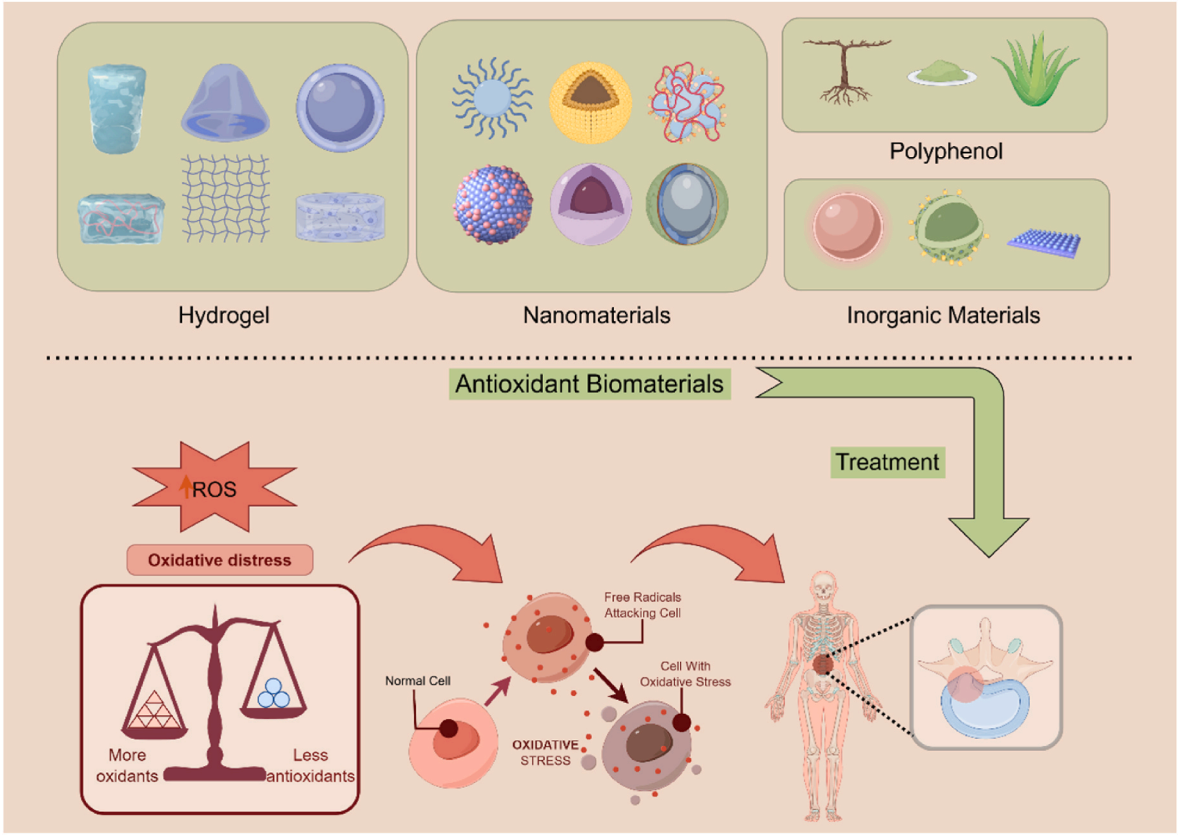
surgery [9]. While these treatment options can partially relieve patient's symptoms from IVDD, they all possess limitations. For instance, non-surgical treatments, such as physical therapy and pain management, often focus on symptom relief without addressing the underlying pathology of IVDD. The effectiveness of non-surgical treatments can vary significantly among individuals [10]. Even when they demonstrate some effectiveness, it usually results in clinical relief rather than addressing the root cause or reversing the degenerative process of the discs. Non-surgical approaches demand long-term management and considerable investment in terms of time and cost. Additionally, surgical interventions come with inherent risks such as bleeding, infection, and nerve damage. Although surgeries like spinal fusion and discectomy may provide short-term relief, studies have shown that some patients experience recurrent symptoms or require revision surgeries over time [11]. Moreover, the stability and long-term efficacy of surgical treatments remain uncertain, often accompanied by challenging postoperative rehabilitation and potential complications. Current conventional treatments for IVDD lack the capacity to fully repair or regenerate damaged disc tissue, and they do not effectively halt or reverse the progression of IVDD. Therefore, there is a pressing need for innovative treatment approaches, including regenerative therapies, that aim to restore disc structure and function.

Oxidative stress is recognized as a primary pathogenic factor of IVD [12]. As ROS is one of the products of IVDD, the delicate balance between ROS and antioxidants is essential to maintain the normal function and survival of intervertebral disc cells [13]. In the process of IVDD, the generation of ROS and the lack of antioxidant capacity will break the REDOX balance and accelerate the IVDD. The advancements and progress in antioxidant biomaterials have offered promising prospects for IVDD treatment. Antioxidant biomaterials play a pivotal role in combating oxidative stress, mitigating inflammation, enhancing blood circulation, and safeguarding the integrity of the intervertebral disc matrix and cartilage through their powerful antioxidant mechanisms. Therefore, the application of antioxidant biomaterials into the IVD is of great significance in alleviating oxidative stress and preventing IVDD and is expected to improve the microenvironment of intervertebral disc cells, which in turn reduces their degree of damage and even promote tissue regeneration and repair. The researchers explored the feasibility and effectiveness of applying antioxidant biomaterials to the treatment of disease through a variety of approaches and technologies [14], including bioengineering, nanotechnology, and drug delivery systems [15,16]. Some preliminary experimental and animal model studies have shown the potential of antioxidant biomaterials to reduce the progression of IVDD, improve disc cell metabolism, and increase tissue stability [17,18]. In this review, we first overview the structure and function of the IVD as well as the pathophysiological process of IVDD, and then discuss the mechanisms and signaling pathways related to IVDD and oxidative stress. Lastly, we summarize four types of antioxidant biomaterials used in the treatment of IVDD in recent years. It mainly includes antioxidant hydrogels, nanomaterials, polyphenolic organic materials, inorganic materials, and so on. These materials contribute to regeneration by stimulating the proliferation of nucleus pulposus cells, promoting extracellular matrix production, and restoring the structural integrity of the intervertebral disc. They also aid in repair by mitigating oxidative stress, inhibiting further tissue degeneration, and reinforcing the mechanical stability of the disc to alleviate symptoms such as pain and reduced mobility. We reviewed the main antioxidant substances, animal models, and cell types involved in the study of antioxidant biomaterials, the possible mechanisms or signaling pathways involved, the related biological effects, and the advantages and limitations of such materials, and finally proposed the possible research direction and further development space of antioxidant biomaterials in the field of



Scheme 1. Scheme of antioxidant biomaterials for IVDD. IVDD is strongly related to oxidative stress damage and inflammatory response. When the redox balance is disrupted, excess oxygen free radicals can damage disc cells, which in turn exacerbates IVDD. Antioxidant biomaterials currently used for IVDD include hydrogel, nanomaterials, polyphenol, inorganic materials, which can effectively mitigate oxidative stress damage and treat IVDD. Created by Figdraw.

IVDD (Fig. 1).

2. Intervertebral disc degeneration

2.1. Anatomy of intervertebral disc

The intervertebral disc, located between vertebrae, consists of a dense cellular matrix arranged in specific layers [19]. The nucleus pulposus (NP) at the disc's core contains proteoglycans, collagen, and 70 % water [20]. NP cells, embedded in a proteoglycan-collagen matrix, are sparse and decrease with age [21]. The NP is surrounded by the annulus fibrosus, composed of concentric lamellar structures [22]. The annulus fibrosus stabilizes the NP, maintaining hydrostatic pressure to resist daily mechanical stress. Collagen fibers in the annulus fibrosus connect with spinal ligaments, enhancing flexibility and stability [23].

The NP and annulus fibrosus form the soft tissue of the disc, capped by a thin cartilage endplate that connects to the vertebral endplate via calcified cartilage. Postnatal changes in the cartilage endplate reduce vascularity as ECM replaces blood vessels, similar to changes in the annulus fibrosus [24]. The intervertebral disc, the body's largest avascular tissue, relies on capillaries near the disc for nutrient and oxygen delivery via the cartilage endplate [25]. Nutrients diffuse from the outer annulus and endplate into the NP, highlighting the importance of the cartilage endplate in disc health. The NP, annulus fibrosus, and cartilage endplate are crucial for shock absorption, spinal support, and spinal cord protection (Fig. 2).

2.2. Pathophysiology of intervertebral disc degeneration

IVDD is influenced by various factors, such as age [26], genetic predisposition and environmental factors [1], mechanical stress [27], senescence [28], inflammatory response [12], oxidative stress damage, and so on. Currently, the precise pathogenesis of IVDD remains incompletely understood and is an active area of ongoing research. Throughout the process of IVDD, various anatomical, cytological and histological changes occur. In terms of anatomical structure, IVDD includes dewatering degeneration and fissure of the nucleus pulposus. Simultaneously, bulging and rupture of the annulus fibrosus further result in protrusion of the nucleus pulposus tissue, nerve compression, and subsequent development of lumbago [29]. Moreover, ossification of the cartilage endplate obstructs nutrient transport and promotes accumulation of metabolic waste, thereby accelerating aging and apoptosis of disc-related cells. In histology and cytology, alterations in cell numbers, ECM composition, and water content were observed [30]. In terms of the number of cells, the changes primarily manifest as a decrease in cell count, an increase in apoptosis, and a reduced ability for cell regeneration, contributing to a diminished capacity for repair and regeneration ability within the intervertebral disc. Regarding the ECM, collagen fibers gradually undergo degradation, becoming sparser, disorganized, and losing their typical structure (Fig. 3), resulting in reduced elasticity and pressure resistance of the intervertebral disc [31]. Simultaneously, the reduction of proteoglycan content leads to a decline in the intervertebral disc's ability to retain moisture and a subsequent decrease in water content, which further leads to diminished elasticity and impaired function of the intervertebral disc. Once the water content is reduced, the intervertebral disc begins to desiccate and harden, and becomes more vulnerable, resulting in further impairment of its normal biomechanical characteristics [32]. This vulnerability is compounded by the absence of blood vessels within the intervertebral disc.

The intervertebral disc is the largest avascular structure in the body, so the NP at the center of the disc is in a hypoxic state [34–36]. However, studies have shown that even in this hypoxic state, disc cell metabolism

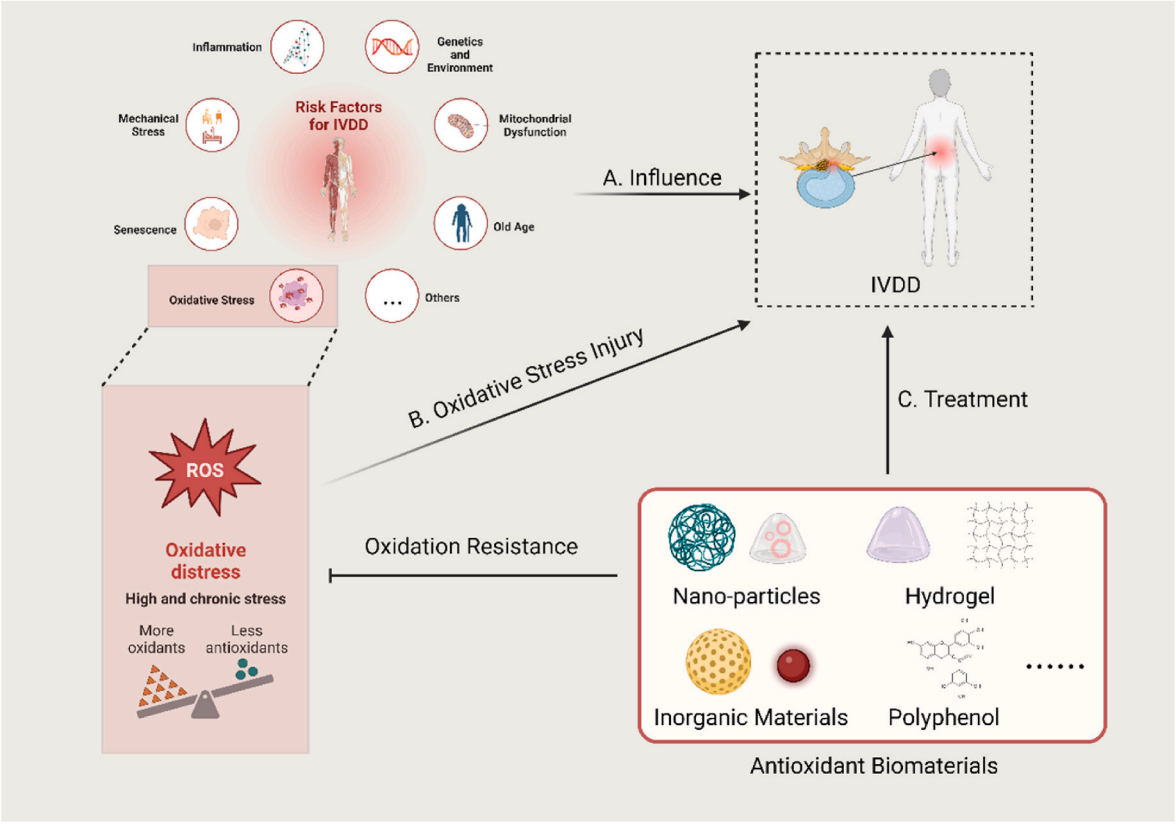


Fig. 1. IVDD and the treatment of antioxidant biomaterials. A. IVDD is related to age, heredity and environment, mechanical stress, senescence, oxidative stress damage and inflammatory response. B. Oxidative stress injury is particularly important for IVDD. C. Antioxidant biomaterials can treat IVDD by eliminating oxidative stress injury. Created with BioRender.com.

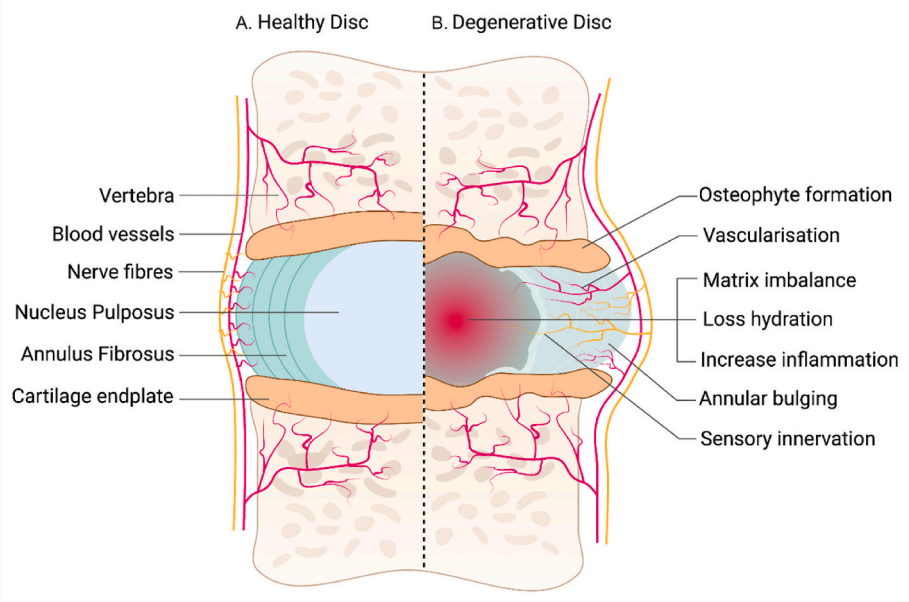


Fig. 2. The contrast between healthy intervertebral disc and degenerative intervertebral disc. A. The core of the disc is composed of the nucleus pulposus, encircled by annulus fibrosus, which is connected to the vertebrae through cartilage endplates situated both above and below it. Arteries supply the outermost region of the annulus fibrosus. B. IVDD can result in matrix imbalance, dehydration and inflammation. Structural changes in the intervertebral disc reduce the protective effects of the annulus fibrosus and cartilage endplates and the nutritional effects of peripheral blood vessels. Reproduced with permission [20]. Copyright 2022, I.L. Mohd Isa et al.

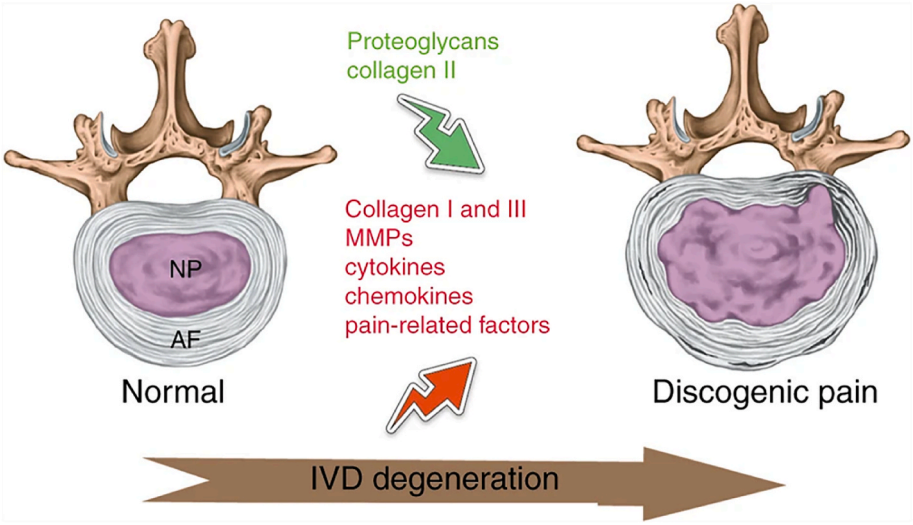


Fig. 3. Illustration of degenerative changes in painful intervertebral discs.
During IVDD, proteoglycans and collagen II are decreased, while collagen I and III are increased in the ECM. Emerging cytokines, chemokines, and pain-related factors synergistically contribute to discogenic pain development. Reproduced with permission [33]. Copyright 2021, F.-J. Lyu et al.

is not entirely anaerobic, and there remains a metabolic process in the body that utilizes oxygen [37,38]. Therefore, ROS will still be produced in the microenvironment of intervertebral disc, and its main sources include H_2O_2 produced in NP tissue [39], peroxisomes in AF cells [40], and so on. In addition, other studies have found that abnormal mitochondrial metabolism of intervertebral disc cells can produce a large number of ROS [41]. ROS is a general term for oxygen-containing free radicals and peroxides that are easily formed by oxygen metabolism in living organisms. It includes superoxide anion (O_2^-), hydroxyl radical (OH^-), hypochlorite ion (OCl^-), hydrogen peroxide (H_2O_2). They are natural by-products of oxygen produced during normal metabolism and play an important role in cell signaling and homeostasis. In the mitochondrial electron transport chain, a small number of electrons do not follow the normal transport order, but directly leak out of the electron transport chain and interact with oxygen to produce superoxide or hydrogen peroxide [42]. In the pathological state of intervertebral disc, mitochondrial dysfunction will exacerbate the occurrence of the above conditions, and thus increase the production of ROS [43]. Mitochondria are also the main attack targets of ROS, and a large number of ROS will aggravate mitochondrial dysfunction, thus triggering a positive feedback loop and aggravating oxidative stress damage [44]. In addition, the process of cellular senescence is also conducive to the production of ROS [26]. In the pathological state of intervertebral disc, the original avascular structure combined with the hardened cartilage endplate leads to slower metabolic exchange of substances, resulting in a large amount of ROS accumulation, while the reduced consumption of antioxidants

cannot be supplemented, resulting in an imbalance of REDOX homeostasis [12,45]. Crucially, Oxidative stress significantly hastens the deterioration of cell structure and functionality within IVDD. It intensifies cell apoptosis, speeding up the breakdown of the intervertebral disc's ECM, consequently worsening the disruption of its structural integrity and overall function. Moreover, oxidative stress acts as a catalyst for inflammation, exacerbating the degenerative cascade within the intervertebral disc.

In recent years, there has been growing recognition of the impact of oxidative stress on IVDD, and extensive research has focused on the pivotal role of oxidative stress injury in the development and progression of IVDD. Oxidative stress can accelerate the degeneration process of intervertebral disc through a variety of signaling pathways, and further aggravate the structural and functional decline of intervertebral disc by inducing inflammatory response and promoting cell apoptosis [13]. For example, the Nrf2 signaling pathway is closely related to alleviating IVDD in the presence of oxidative stress [46]. Excessive oxidative stress can result in the up-regulation of autophagy through the activation of the Keap1-Nrf2-p62 feedback loop [47]. In the process of IVDD, Nrf2 expression gradually decreases, resulting in a progressive decline in the protection of the disc by the autophagy pathway [47]. Consequently, excessive oxidative stress can aggravate IVDD. Furthermore, the absence of cell cycle regulator p16 may mitigate IVDD by promoting cell cycle and inhibiting cell senescence and oxidative stress [48]. Currently, the mechanisms underlying IVDD caused by oxidative stress primarily encompass inflammation, nutrient metabolism disorder, ECM metabolism, apoptosis, autophagy, cell senescence [12], as well as pyroptosis and ferroptosis [13]. ROS-induced apoptosis in NPCs is primarily mediated through mitochondrial damage, leading to the activation of intrinsic pathways that result in programmed cell death [49]. While autophagy can be a survival response to oxidative stress, excessive ROS can shift autophagy towards autophagic cell death in NPCs. By controlling ROS levels, antioxidant materials can help maintain the balance between protective autophagy and detrimental autophagic cell death [50]. Cell senescence, characterized by the irreversible arrest of cell division, is another major outcome of ROS-induced damage in NPCs. Senescent cells exhibit a pro-inflammatory secretory profile (senescence-associated secretory phenotype or SASP), contributing to a chronic inflammatory environment within the intervertebral disc [51]. Emerging research has identified ferroptosis and pyroptosis as forms of regulated cell death driven by ROS. Ferroptosis is characterized by iron-dependent lipid peroxidation, while pyroptosis is an inflammatory form of cell death associated with gasdermin-mediated pore formation in the cell membrane [52]. Antioxidant biomaterials, especially those incorporating nanomaterials, have the potential to inhibit these pathways [53]. Moreover, the signaling pathways associated with oxidative stress injury and IVDD mainly include NF-κB, Keap1-Nrf2-ARE, PI3K-Akt [12], the mitogen activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) (MAPK/ERK) signaling pathway, the Sirtuin (SIRT) protein, Mammalian target of rapamycin (mTOR), AMP-activated protein kinase (AMPK) and so on [13], which is shown in Fig. 4. The additional disruption of disc structure and function in the presence of oxidative stress and multiple adverse factors can lead to annulus tear, disc prolapse, endplate damage, schmorl nodes, disc stenosis, vertebral osteophytes, and discogenic pain [54].

The mechanism of IVDD caused by oxidative stress mainly includes inflammation, nutrient metabolism disorder, ECM metabolism, apoptosis, autophagy cell senescence, pyroptosis and ferroptosis. The

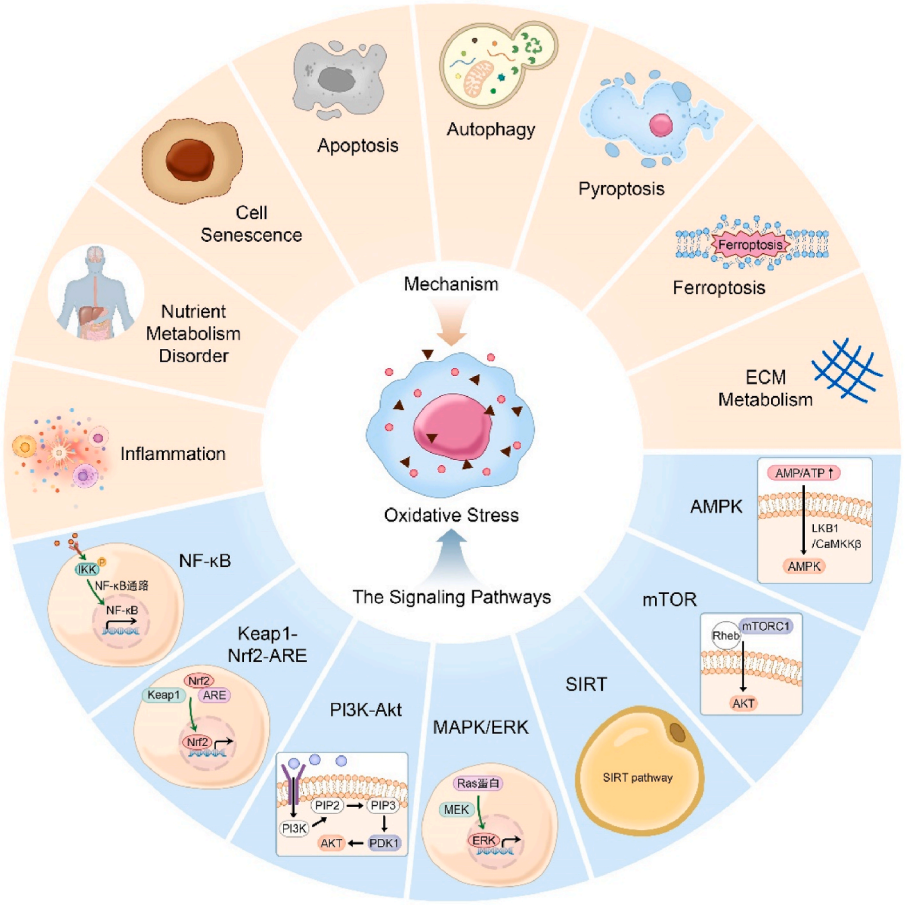


Fig. 4. Mechanisms and signaling pathways of IVDD under oxidative stress.

signaling pathways associated with oxidative stress injury and IVDD mainly include NF-κB, Keap1-Nrf2-ARE, PI3K-Akt, MAPK/ERK signaling pathway, the SIRT protein, mTOR, and AMPK.

2.3. Current treatment options for IVDD

2.3.1. Current treatment options

At present, the treatment of IVDD involves two main approaches: conservative treatment and surgical treatment. Conservative treatment includes a range of options such as bed rest, drug therapy, physical therapy, exercise therapy, epidural injection, lumbar traction, manual therapy, traditional Chinese medicine (TCM) therapy, and so on [9]. For patients with mild IVDD, conservative treatment is typically the initial preference, which includes the use of non-steroidal anti-inflammatory drugs [55]. Physical therapy includes heat therapy, electrotherapy [56], low intensity laser therapy, ultrasound therapy [57], and lifestyle modifications like strengthening exercise, improving posture, and weight management in overweight patients [58]. When patients experience prolonged symptoms and do not respond to conservative treatment, treatment modalities like decompression surgery with or without fusion surgery are generally recommended [20]. Some specific rehabilitation exercises can enhance spinal stability, reduce disc pressure, and alleviate symptoms, such as strengthening the body's core muscles and flexibility training [59]. Additionally, in TCM treatment, acupuncture can dredge the meridians and enhance blood circulation, effectively relieving discogenic pain and associated symptoms [60]. Patients with moderate IVDD may benefit from interventional therapies, such as intra-disc injection therapy, radiofrequency ablation, and other options [20]. If the IVDD is severe, neurological symptoms appear, or the failure of previous treatments, surgical treatment becomes a consideration. Surgical options may include open operation, minimally invasive procedures, lumbar fusion, lumbar artificial disc replacement, The primary objective of surgery is to reduce the pressure on the nerve and stabilize the spine [9,61].

2.3.2. Limitations of current treatment options and need for alternative approaches

Conventional treatment options for IVDD are associated with specific limitations, and conservative treatments like drug therapy and physical therapy usually only offer temporary relief of symptoms, but cannot provide a cure for IVDD. At the same time, long-term use of medication may also cause side effects [62], and physical therapy needs to be continued to maintain the effect. Rehabilitation training requires patients to have high compliance and active participation. Failure to cooperate or incorrect excise techniques can significantly impact the treatment effect. TCM treatment lacks well-established scientific verification and standardized operating procedures, and the efficacy can be easily influenced by individual differences. Although interventional therapy and surgical treatment have certain therapeutic benefits, there are still certain risks and potential complications. Additionally, the extended recovery period after surgical treatment can impact a patient's quality of life [63]. Given these constraints, there is an urgent need for innovative therapies that are more efficient and have fewer side effects in the treatment of IVDD.

Regarding the limitations of the current treatments of IVDD and the understanding of the oxidative stress mechanism involved in the pathophysiological process, there has been substantial research into antioxidant biomaterials as a novel therapeutic approach. Antioxidant biomaterials possess the capability to directly counteract oxidative stress damage by neutralizing or removing ROS and free radicals. This action serves to shield intervertebral disc cells and tissues from oxidative stress damage [64]. Furthermore, antioxidant biomaterials have good biocompatibility and biological activity [65], and can mitigate adverse reactions in surrounding tissues, stimulate cell regeneration and proliferation, and actively contribute to the repair and regeneration of intervertebral discs. In contrast to the traditional conservative treatment, antioxidant biomaterials offer longer-lasting effects and superior drug release control [66], which is a novel approach for the treatment of IVDD. In the following sections, we will review the current research findings on the application of antioxidant biomaterials in the treatment of IVDD.

3. Antioxidant biomaterials for IVDD

3.1. Biomaterials with antioxidant effects

In recent years, the rapid development in the field of biomaterials has brought promising prospects for the treatment of IVDD. Research efforts in this area have led to the development of various biomaterials-based approaches, including hydrogels, nanomaterials, and so on. Given that biomaterials are ultimately intended for human to use, they must have specific characteristics such as biocompatibility, chemical stability, processability and biological function. As mentioned earlier in the pathophysiological process of IVDD, ROS levels increase caused by oxidative stress is one of the important mechanisms contributing to intervertebral disc injury. The inherent processability and biological function of biomaterials enable them to serve as antioxidants or carriers for antioxidants. Oxidative stress-induced IVDD can be treated by enhancing antioxidant function or regulating the controlled release of antioxidants. Currently, antioxidant biomaterials used in the field of IVDD mainly include hydrogels, nanomaterials, polyphenolic organic materials, inorganic materials, and so on (Fig. 5). While these materials share the overarching goal of mitigating oxidative damage, each category presents distinct advantages and limitations in terms of biocompatibility, delivery efficiency, and long-term stability. Below, we explore the unique properties of these materials and analyze their comparative potential for IVDD treatment.

3.1.1. Hydrogels

Hydrogels are widely recognized for their excellent biocompatibility and ability to mimic the extracellular matrix of intervertebral discs [67]. Their high-water content and structural similarity to natural tissues allow them to encapsulate bioactive molecules, such as antioxidants, which can be released in a controlled manner. Hydrogels are particularly effective for local drug delivery, providing a sustained release of therapeutic agents, which makes them a promising choice for long-term ROS clearance [68]. However, hydrogels have limitations in mechanical strength, making them less suitable for cases requiring structural reinforcement of the disc. Some hydrogels, such as chitosan, inherently possess antioxidant qualities [69]. Chitosan is frequently employed in formulating drug delivery systems, leveraging its antioxidant properties to shield encapsulated drugs, thereby enhancing their stability and bioavailability [70]. Additionally, it finds application in wound dressings, mitigating oxidative stress, fostering wound healing, and preempting cellular inflammatory responses caused by oxidative harm [71]. Moreover, hydrogels, known for their biocompatibility, stability, and processability, offer researchers the opportunity to augment their antioxidant capabilities by integrating substances renowned for their exceptional antioxidant properties. Ferulic acid (FA) has been reported to have excellent antioxidant properties [72]. Cheng and co-workers [73,74] prepared a controlled-release system for FA within a chitosan-gelatin-glycerol phosphate (C/G/GP) hydrogel. FA in the C/G/GP hydrogel has the capacity to mitigate oxidative stress induced by H_2O_2 in NP cells and reduce their apoptosis by down-regulating MMP3 and up-regulating Aggrecan expression. FA-incorporated C/G/GP hydrogel proves to be an effective treatment for NP cells damage resulting from oxidative stress. What's more, some researchers have applied nanotechnology in hydrogels to treat IVDD. Ye and co-workers [17] demonstrate that the regenerative potential of allopurinol-loaded chitosan/alginate hydrogel for intervertebral discs may attributed to the allopurinol-incorporated chitosan dispersed in hydrogel nanoparticles, which protect cells from oxidative stress.

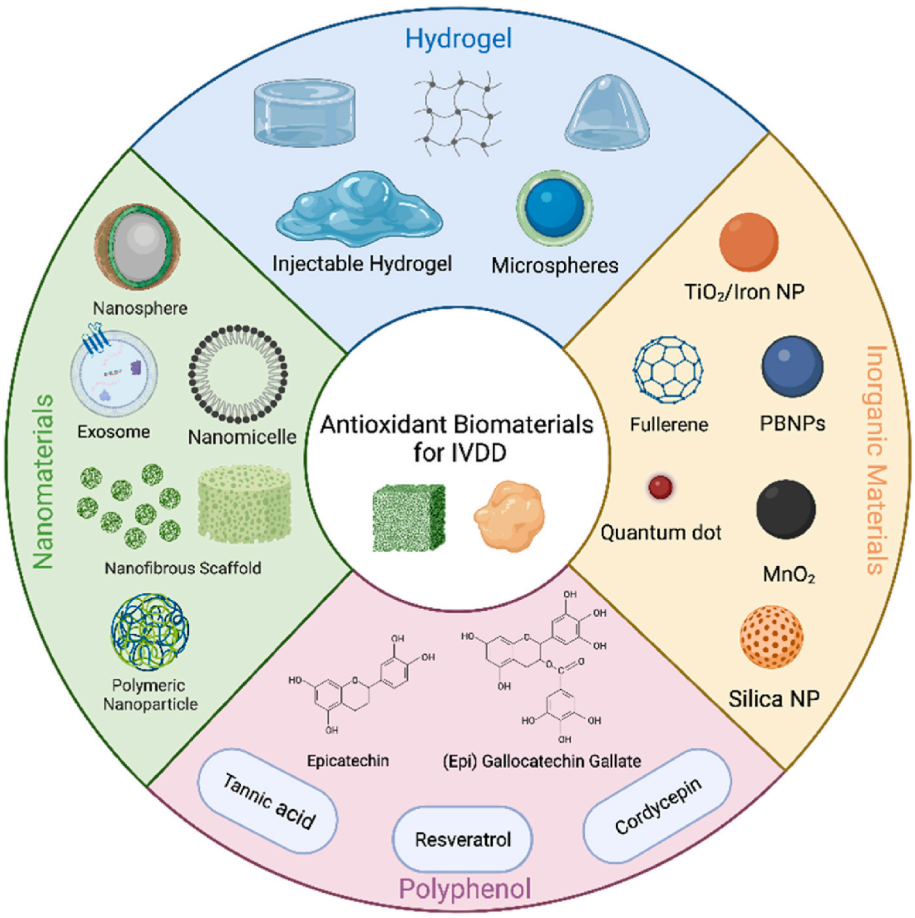


Fig. 5. Antioxidant biomaterials used in IVDD. Antioxidant biomaterials used in the field of IVDD mainly include hydrogels, nanomaterials, polyphenolic organic materials, inorganic materials, and so on. Created with BioRender.com.

Furthermore, allopurinol can quench free radicals generated by H_2O_2 and protect cells from peroxidation.

In addition to chitosan, recent studies have also explored the use of hyaluronic acid (HA). Luo and co-workers [75] combined dopamine modified HA and phenylboronic acid-modified chondroitin sulfate (CS-PBA) to form an injectable self-antioxidant hydrogel. The primary antioxidant effect of this hydrogel arose from the antioxidant properties of the dopamine groups. Combined with nanomedicine technology, Zhou and co-workers [76] found that Prussian blue nanoparticles (PBNPs) can relieve cellular oxidative stress and increase the activity of antioxidant enzymes in cells. Then Yang and co-workers [77] prepared a hydrogel consisting of PBNPs incorporated into Oxidized HA/Borax/Gelatin (PBNPs@OBG), which can reduce the oxidative stress damage induced by hydrogen peroxide to the NP (Fig. 6). According to these researches, though HA does not have antioxidant properties, it has moisturizing properties, filling properties, biocompatibility, and degradability, which can be combined well with antioxidant substances to enhance the antioxidant function of hydrogels. In the latest research, an injectable nanocomposite hydrogel was prepared by embedding epigallocatechin-3-gallate (EGCG) -coated hydroxyapatite nanorods in O-carboxymethyl chitosan crosslinked with aldehyde hyaluronic acid, and this hydrogel can regulate the phenotype of macrophages, control ECM synthesis and catabolism, reduce oxidative stress and alleviate IVDD [78].

In recent years, Gelatin methacrylate anhydride (GelMA) has garnered significant interest due to its cost-effectiveness, safety, and broad clinical applicability. Li and co-workers [79] synthesized a novel fucosan-functionalized GelMA microsphere (Fu@GelMA-MS), which improves IVDD by restoring REDOX balance and stromal homeostasis in NP. Recognizing the antioxidant properties of vanillin, Zhu and co-workers [80] employed vanillin to fabricate multi-functional GelMA microspheres, which can treat IVDD by delivering TGF-β3 and improving the release kinetics of TGF-β3. This multi-functional GelMA microsphere can preserve the height, water content, structure integrity and biomechanical properties of intervertebral disc by eliminating excessive ROS. The hydrogels mentioned above serve to remove ROS and reduce oxidative stress damage of intervertebral disc through their superior physicochemical properties and antioxidant properties of the compounds they carry. In addition, in recent research, Xin Tian and co-workers [81] developed a dynamic self-healing hydrogel loaded with Kartogenin (KGN), which alleviates the progression of IVDD by restoring REDOX balance. Subsequently, Feng Wang and co-workers [82] designed KGN@Poly (lactic-co-glycolic) acid-GelMA/Platelet-rich plasma (PRP) composite hydrogel and found that the KGN-loaded hydrogel protects MSCs from ROS microenvironment through NRF2/TXNIP/NLRP 3-axis. In addition to loading various antioxidants, researchers have used microgel-coated mesenchymal stem cells to treat disc degeneration, which can also reduce oxidative stress-induced pyroptosis [83]. In the latest study, some researchers combined hydrogels with nanomaterials and inorganic materials. Through microfluidic technology, lactate oxidase (LOX)-manganese dioxide (MnO_2)-nanozyme (LM) were immersed in glucose-rich acellular NP hydrogel microspheres to prepare an injectable hydrogel, which can catalyze hydrogen peroxide into oxygen and water. Moreover, it can reduce ROS caused by H_2O_2 and improve the hypoxic environment of the intervertebral disc [84]. The characteristics of the above hydrogel research are shown in Table 1. While hydrogels excel in biocompatibility and local delivery, they may fall short in terms of precision at the molecular scale.

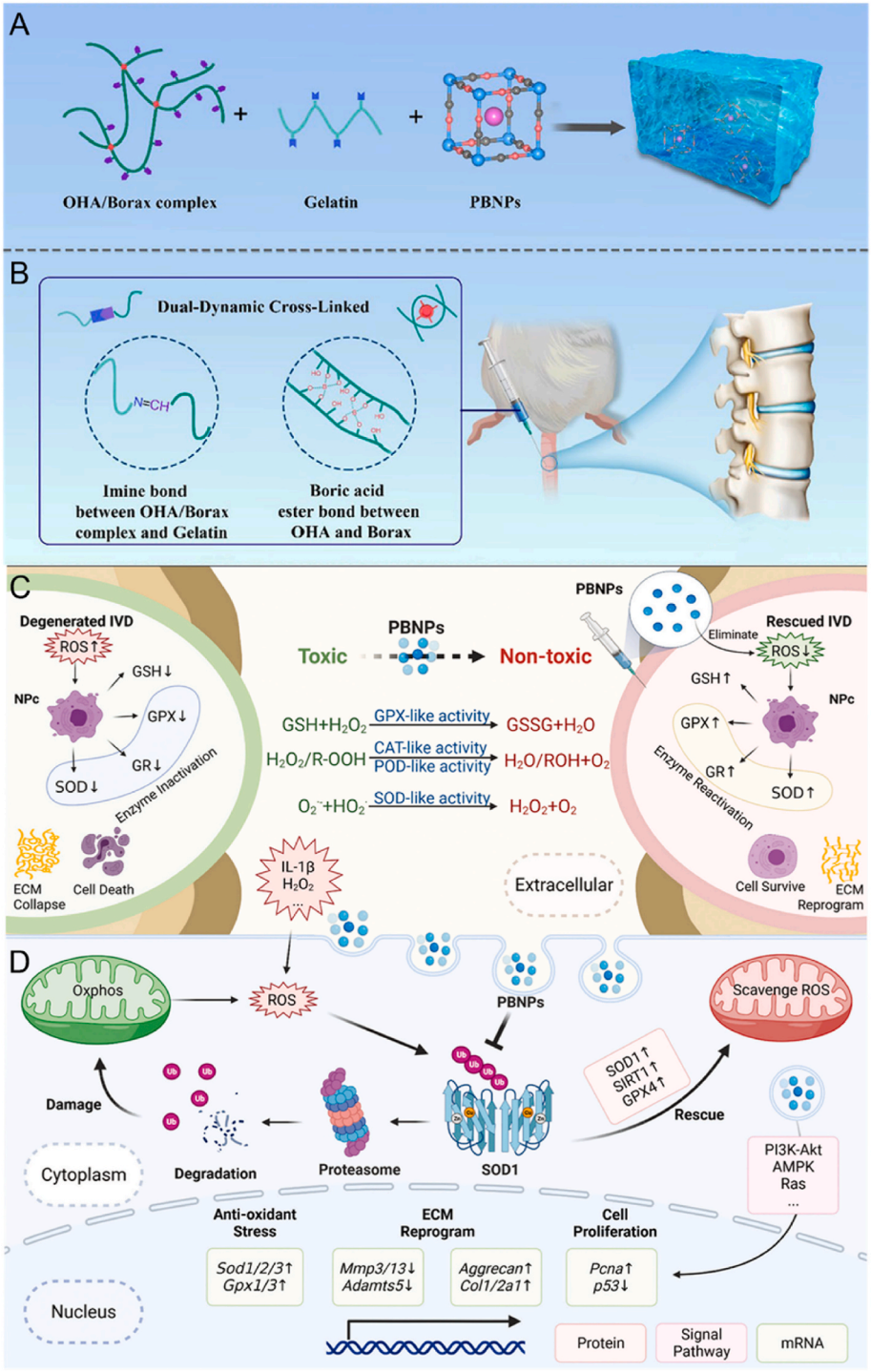


Fig. 6. PBNP-loaded hydrogel for the treatment of IVDD.
A. The hydrogel consisting of PBNPs incorporated into Oxidized HA/Borax/Gelatin (PBNPs@OBG) is prepared. B. Schematic diagram of the internal structure of hydrogel. Reproduced with permission [77]. Copyright 2022, L. Yang et al. C-D. Macroscopic and microscopic schematic diagram of PBNP affecting the redox microenvironment of intervertebral discs. Reproduced with permission [76]. Copyright 2022, T. Zhou et al.

This is where nanomaterials come into play, offering enhanced reactivity and targeted delivery due to their nano-sized structures.

3.1.2. *Nanomaterials*

Nanomaterials have garnered significant attention due to their high surface area and ability to penetrate biological barriers, allowing for precise targeting of oxidative stress within NP cells [85]. Their capacity for surface modification makes them ideal carriers for antioxidants or ROS-scavenging molecules. Nanomaterials like nanozymes have been shown to effectively clear ROS at a cellular level, thereby inhibiting NPC senescence and delaying disc degeneration. However, their long-term biocompatibility and potential toxicity remain areas of concern, which limit their immediate translation to clinical use [86]. The nanomaterials used in the treatment of IVDD mainly include nanoparticles, nano-micelles, nanofiber scaffolds, extracellular vesicles, and so on. Fullerol nanoparticles have demonstrated remarkable efficacy in

Table 1
Antioxidant hydrogels for IVDD.

Category	Antioxidant biomaterials	Experimental subject	Mechanism	Biological effect	In vivo model and administration method	Reference
Hydrogel	Alginate microgel	NP cells; Sprague–Dawley rats	NULL	ECM synthesis↑; ROS, pyroptosis↓	Needle-puncture-induced disc degeneration model. Intradiscally injection	Huang et al., 2024 [83]
Hydrogel	Injectable hydrogel microspheres	NP cells, MSC; Sprague–Dawley rats	TGFB2-OT1 and its downstream pathway	ROS↓; maintain the stability of intervertebral disc	Needle-puncture-induced disc degeneration model. Intradiscally injection	Peng et al., 2024 [84]
Hydrogel	Injectable nanocomposite hydrogel (HAP-EGCG@CS-HA)	Macrophagocyte, BMSC, NP cells; Sprague–Dawley rats	IL17 signaling pathway	ROS↓; maintain the stability of ECM	Needle-puncture-induced disc degeneration model. Intradiscally injection	Zhao et al., 2024 [78]
Hydrogel	Allopurinol-chitosan/ alginate hydrogel	Human dermal fibroblast cells; Sprague–Dawley rats	PI3K-AKT-NF-κB	Collagen type II and I, ECM synthesis, Cell viability and migration, healing of injured NP↑; inflammation↓	Needle-puncture-induced disc degeneration model. Intradiscally injection	Ye et al., 2023 [17]
Hydrogel	Fucoidan @GelMA-MS	NP cells; Sprague–Dawley rats	NULL	Collagen II, antioxidant enzymes↑; ROS↓	Needle-puncture-induced disc degeneration model. Intradiscally injection	Li et al., 2023 [79]
Hydrogel	GelMA-MS	NP cells; Adult male rats	PI3K-AKT	ROS↓; maintain the stability of intervertebral disc	Needle-puncture-induced disc degeneration model. Intradiscally injection	Zhu et al., 2023 [80]
Hydrogel	Dynamic self-healing hydrogel	NP cells; Sprague–Dawley rats	The activation of NRF2 and downstream antioxidant enzymes	ECM synthesis↑; restore the REDOX balance	Needle-puncture-induced disc degeneration model. Intradiscally injection	Tian et al., 2023 [81]
Hydrogel	KGN@PLGA-GelMA/PRP composite hydrogel	NP cells; Adipose Derived Stem Cells (ADSCs) rats;	NRF2/TXNIP/NLRP 3-axis	Antioxidant capacity of ADSCs; ECM synthesis↑;	Needle-puncture-induced disc degeneration model. Intradiscally injection	Wang et al., 2023 [82]
Hydrogel	Injectable auto-antioxidant hydrogel (DA-HA/CS-PBA)	NP cells of human; Sprague–Dawley rats	NF-κB pathway	ROS↓; maintain the stability of intervertebral disc ECM	Needle-puncture-induced disc degeneration model. Intradiscally injection	Luo et al., 2023 [75]
Hydrogel	Injectable PBNPs@OBG hydrogel	NP cells; Sprague–Dawley rats	Ras, p53, PI3K, Akt, AMPK	ROS↓; maintain the stability of intervertebral disc ECM	Needle-puncture-induced disc degeneration model. Intradiscally injection	Yang et al., 2022 [77]
Hydrogel	FA@G/C/GP hydrogel	NP cells of rabbits	NULL	ECM-degrading enzymes, Apoptosis of NP cells↓; ECM synthesis, Proliferation of NP cells↑	NULL	Cheng et al., 2011 [73], 2013 [74]

scavenging ROS [87], and it has been applied in many fields [88]. Liu and co-workers discovered that fullerol can inhibit inflammation by reducing ROS levels and reducing apoptosis [89]. In subsequent research, Yang and colleagues demonstrated that nanofullerols have the capacity to prevent IVDD by diminishing ROS levels [90]. Fullerol, specifically, exhibits substantial reductions in H_2O_2-triggered cytotoxicity and intracellular ROS levels [91], effectively reversing matrix degradation caused by H_2O_2 or IL-1β, and counteracting pain and inflammation [92]. Moreover, Dopamine has antioxidant properties [75], and Yang and co-workers [93] demonstrated that Polydopamine nanoparticles (PDA NPs) inhibit oxidative stress-induced ferroptosis in NP cells in vitro. PDA NPs clear ROS, chelate Fe^{2+} to reduce iron overload, and regulate iron storage protein expression. More importantly, PDA NPs co-locate with glutathione peroxidase 4 (GPX4) around the mitochondria and inhibit ubiquitin-mediated degradation, thereby playing a protective role by facilitating the conversion and clearance of phospholipid hydroperoxides (Fig. 7 A-B). In addition to preparing nanoparticles from substances such as fullerol and dopamine, which have antioxidant properties, researchers can also enhance or regulate the release of antioxidants by combining different nanoparticles or creating nanoplatforms. For example, Bari and co-workers [94] prepared the nanoparticle using a combination of sericin and crocetin, and the combination of sericin and crocin results in a formula with antioxidant, anti-elastase and anti-tyrosinase activity, aiming to prevent oxidative stress-induced disc damage. In addition to GelMA microspheres delivering TGF-β3 for the treatment of IVDD [80], the use of nanoplatforms also helps regulate the release of TGF-β3. In the research of Zhu and co-workers [95], they used hollow manganese dioxide (H-MnO_2) to build an intelligent biodegradable nanoplatform that can regulate the degenerative microenvironment and release TGF-β3, which is expected to achieve long-term therapeutic effects for needle-induced intervertebral disc (Fig. 7 C-D). Based on the remarkable antioxidant properties of Alginate [96,97], Qu and co-workers [98] prepared Pluronic nanoparticles and oligosaccharide nanomedicine of alginate sodium (ONAS), and revealed that nanoparticles loaded with alginate had better antioxidant effects in the treatment of degenerative lumbar disease. In the latest research, in view of the increase of natural Killer Group 2D (NKG2D) ligands on the surface of senile NP cells, researchers constructed a NP membrane (NNPm) overexpressing NKG2D. Then, mesoporous silica nanoparticles (SP) carrying peroxisome

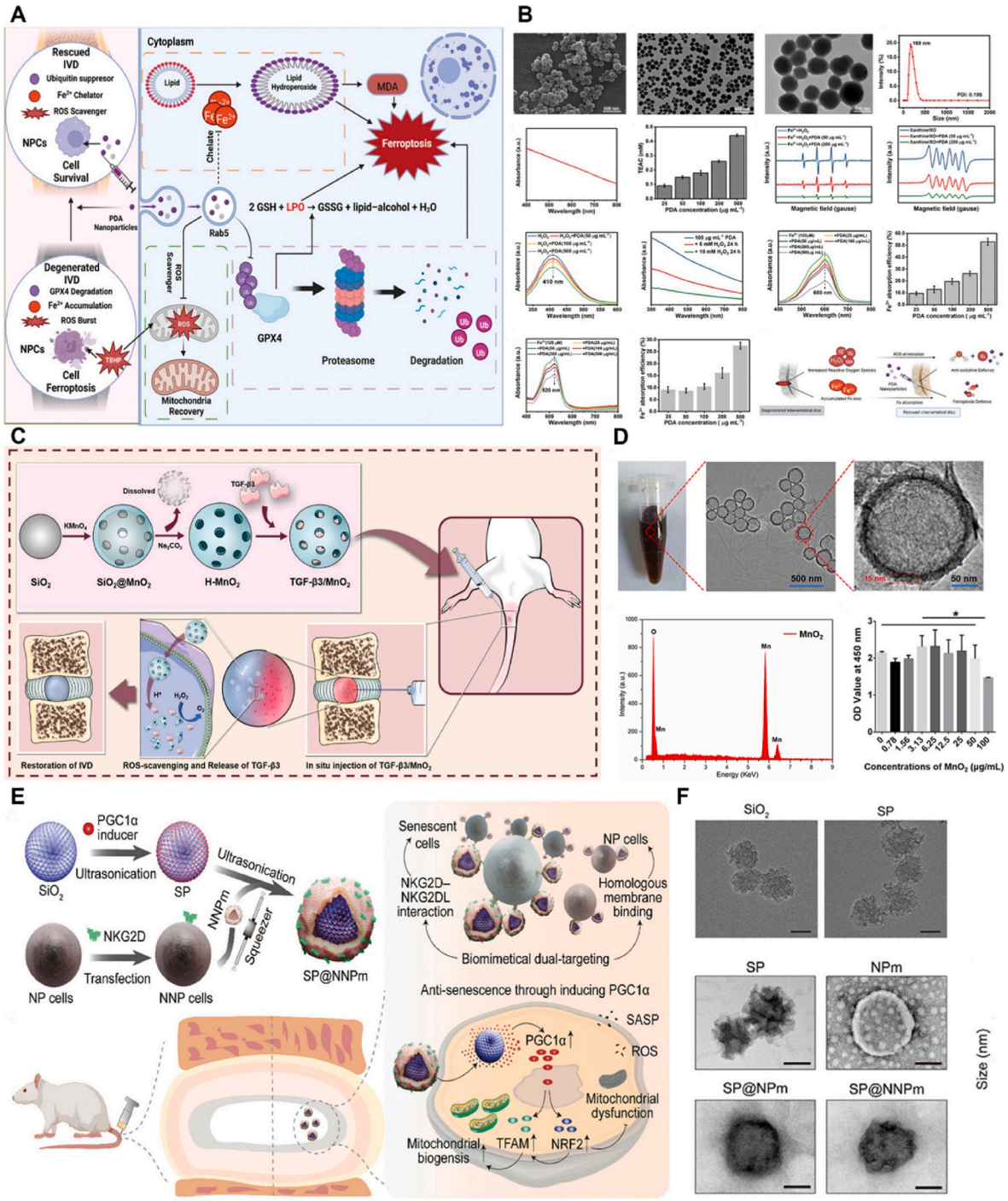


Fig. 7. Application of some antioxidant particles in the treatment of IVDD.
A-B. PDA NPs inhibit oxidative stress-induced ferroptosis in nucleus pulposus cells in vitro; and material characterization of PDA NPs. Reproduced with permission [93]. Copyright 2023, Y. Xiao et al. C-D. A smart biodegradable nanoplatform was constructed using H-MnO_2 to modulated the degenerative microenvironment and release TGF-β3; and Synthesis and characterization of MnO_2 NPs. Reproduced with permission [95]. Copyright 2022, L. Zhu et al. E-F. SP@NNPm effectively induces PGC1α-mediated mitochondrial biogenesis, alleviates oxidative stress, and thus alleviates IVDD. Reproduced with permission; scanning electron microscopy images of the nanoparticles SiO_2 and SP, and transmission electron microscopy images of the nanoparticles SP, NPm, SP@NPm, and SP@NNPm [99]. Copyright 2024, S. Liu et al.

proliferator-activated receptor-γ coactivator 1α (PGC1α) inducer were coated with the NNPm overexpressed with NKG2D and constructed SP@NNPm. It was found that the nanoparticle could selectively target senescent NP cells and reduce the expression of oxidative stress and senescent markers (Fig. 7 E-F) [99].

Nano-micelles are small spherical structures composed of polar and non-polar molecules, which are often used for drug delivery. Nano-micelles can deliver many bioactive molecules to maintain the anabolic homeostasis of the intervertebral disc ECM [100]. At present, researchers have used nano-micelles to deliver mRNA to treat IVDD [101]. In addition, some researchers have modified stem cells by nano-micelles combined with bioactive molecules to inhibit pyroptosis and promote the regeneration and recovery function of intervertebral disc tissue, which has a good tissue regeneration effect [102].

Meanwhile, nano-micelles can also treat IVDD by loading antioxidant substances. Yu and co-workers [103] designed a novel amphiphilic copolymer, capable of self-assemble into nanoscale micelles, acting as a single complex to support lipophilic KGN, with controlled release of KGN and apocynin, and can inhibit oxidative stress and protect cells (Fig. 8 A-B). In addition, in the field of nano-scaffold, Yu and co-workers [104] prepared a poly ether carbonate urethane urea (PECUU) nanofibrous loaded with fucoidan, which has antioxidant properties to improve the harsh microenvironment of IVDD. Furthermore, Yang and co-workers [105] designed an all-in-one nano-scaffold-based 3D porous hybrid protein (3D-PHP) for IVDD, and they incorporated enzyme-like 2D nanosheets into these nano-scaffolds further enabled robust scavenging of ROS (Fig. 8 C-D). Within the realm of nanomaterials, carbon dots find frequent applications in nanomedicine due to their enzyme-like activity and excellent free radical scavenging ability [106]. In the latest study, Wu and co-workers [107] prepared N-acetylcysteine-derived carbon point nano-enzyme (NAC-CDs) and demonstrated the powerful free radical scavenging and antioxidant capacity of NAC-CDs, and the elimination efficiency of toxic ROS is more than 90 %, which is an ideal antioxidant and anti-aging agent for the treatment of IVDD.

Extracellular vesicles, being natural nanomaterials, are frequently employed in the treatment of IVDD. Dai and co-workers [108] found that platelet-derived extracellular vesicles (PEVs) can reduce H_2O_2-induced oxidative stress damage, restore cell metabolism, and slow down the progression of IVDD. And in combination with the field of stem cell therapy, Liu and co-workers [109] designed Glutaredoxin3 (GLRX3+) mesenchymal stem cell-derived extracellular vehicles (EVs-GLRX3) to enhance the antioxidant capacity of NP cells. Furthermore, extracellular vesicles derived from human umbilical cord mesenchymal stem cells promote proliferation of NP cells, reduce H_2O_2-induced oxidative stress, and protect intervertebral discs by reducing ROS in NP cells [110]. As one of the extracellular vesicles, exosomes have been increasingly used in the treatment of IVDD in recent years. Xia and co-workers [111] found that bone marrow mesenchymal stem cell-derived exosomes improve IVDD through antioxidant and anti-inflammatory effects, and these exosomes can play antioxidant and anti-inflammatory effects by

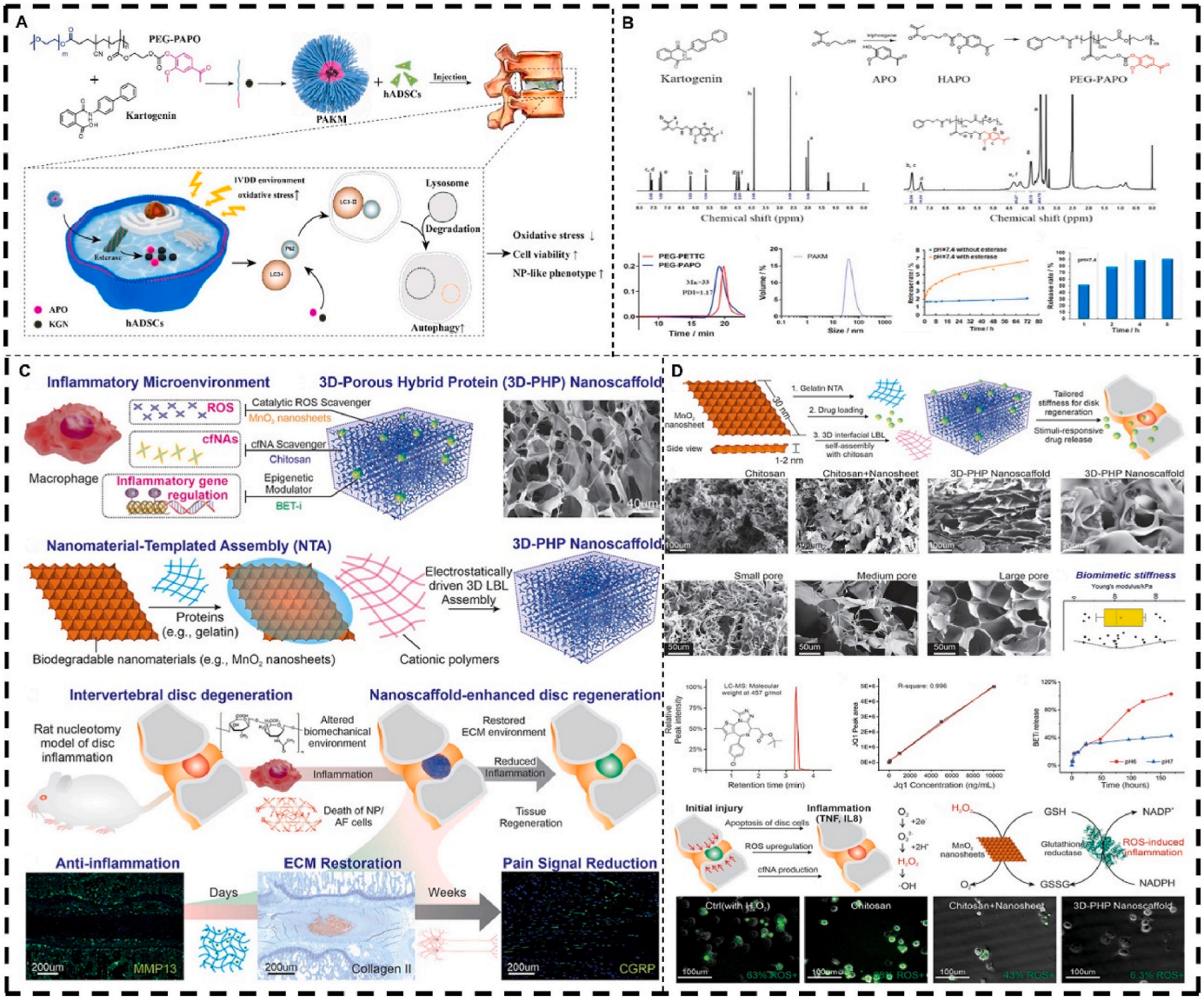


Fig. 8. The application of nano-micelles and nano-scaffolds in preventing oxidative stress damage of IVDD.
A-B. The team designed a novel amphiphilic copolymer PEG-PAPO, which can self-assemble into nano-micelles and load lipophilic kartogenin (KGN) as a single complex (PAKM). It has excellent controlled release ability and antioxidant ability, and can delay the IVDD. Reproduced with permission [103]. Copyright 2021, Ch. Yu et al. C-D. The preparation process and functions of 3D-PHP: it can effectively alleviate the IVDD caused by oxidative stress injury; Material characterization of 3D-PHP. Reproduced with permission [105]. Copyright 2023, L. Yang et al.

attenuating the H_2O_2-induced NLRP3 inflammasome activation. Similarly, Yu and co-workers [112] used the human embryonic stem cell-derived exosome (hESCs-Exo) and observed their capacity to mitigate H_2O_2-mediated NP cell damage by down-regulating the expression level of NLRP3 inflammation-related genes. Exosomes from bone mesenchymal stem cells (BMSCs-Exo) also alleviate compression model-mediated NP cell apoptosis by inhibiting oxidative stress [113]. Recently, some researchers studied the therapeutic effect of Wharton's Jelly MSC-derived EVs on human NP cells through three-dimensional alginic acid bead culture model in vitro, and found that this EVs can improve the growth and vitality of human NP cells, reduce the degradation of ECM and oxidative stress, and provide a new opportunity for IVDD [114]. In addition to being derived from stem cells, other studies have indicated that platelet-rich plasma (PRP)-derived exosomes (PRP-Exo) can reverse oxidative stress damage caused by H_2O_2 and play a protective role on NP cells [115].

Nanozymes are artificial enzymes with catalytic properties that mimic natural enzymes like superoxide dismutase and catalase, which are known to neutralize ROS [116]. Nanozymes could prevent ROS-induced senescence in NPCs by scavenging free radicals and restoring redox homeostasis. This is critical because senescence in NPCs contributes to the progressive degeneration of the intervertebral disc by disrupting cellular function and promoting inflammation. Recent work [117] has shown that nanozymes can inhibit the activation of the ROS-p53-p21 axis, a key pathway that drives cellular senescence in response to oxidative stress. By suppressing this axis, nanozymes not only reduce the extent of senescence in NPCs but also promote cell survival and maintain their functional capabilities. What's more, Shen and co-workers [18] constructed a functionalized hydrogel microsphere combined with manganese dioxide (MnO_2) -lactate oxidase composite nanozyme (MS@MCL). It was found that MS@MCL could eliminate oxidative stress when co-cultured with NP cells in vitro. In the latest study, a core-shell structured nanozyme was constructed with a Co-doped NiO nanoparticle (CNO) as the core and coated with a polydopamine shell, and it was found that PDA@CNO nanozyme has a variety of antioxidant-like activities. It can effectively remove kinds of oxygen free radicals, protect NP cells, and prevent further deterioration of IVDD [118]. This is particularly important in the context of IVDD, where maintaining healthy NPC populations is crucial for sustaining disc integrity and function. This highlights the therapeutic potential of nanozymes in targeting both oxidative stress and its downstream effects on cellular aging and degeneration. Given the chronic and progressive nature of IVDD, the ability of nanozymes to continuously scavenge ROS and inhibit NPC senescence makes them highly suitable for long-term therapeutic interventions. However, challenges such as the long-term safety, bioavailability, and targeted delivery of nanozymes need to be addressed before they can be widely used in clinical settings. The characteristics of the above nanomaterials research are shown in Table 2. In contrast to synthetic nanomaterials, polyphenolic organic materials offer a more natural approach to antioxidant therapy, deriving their efficacy from bioactive compounds found in plants. However, their inherent biological activity comes with different challenges, especially in terms of stability and bioavailability [119].

3.1.3. Polyphenols

Polyphenolic compounds, such as curcumin or resveratrol, are well-known for their natural antioxidant properties and have been studied extensively for their ability to reduce ROS levels. These materials can scavenge free radicals, reduce inflammation, and protect NPCs from oxidative stress [120]. Their primary advantage lies in their biocompatibility and low risk of toxicity compared to synthetic nanomaterials. However, polyphenols often face challenges related to poor solubility and bioavailability, making it difficult to deliver them effectively to the site of IVDD without modifications or carriers, such as hydrogels or nanomaterials. Polyphenols are micronutrients obtained from the diet, and their health benefits and protective effects as antioxidant compounds are well known [121]. And polyphenols have been extensively studied in different fields such as drug delivery and nano-biomaterials [122]. In recent years, based on the antioxidant properties of polyphenols, many researchers have explored the use of polyphenols in the treatment of IVDD and low back pain [123].

Resveratrol (RSV, 3,5,4′-trihydroxy-trans-stilbene) is a polyphenol compound derived from red wine or grapes, renowned for its natural antioxidant properties. It exhibits anti-inflammatory and anti-aging effects across various diseases. Demonstrating its ability to effectively inhibit metabolic factors contributing to oxidative stress, resveratrol acts as a ROS scavenger while also activating autophagy [124]. These actions help alleviate the progression of intervertebral disc degeneration [125,126]. For example, rabbits treated with resveratrol for IVDD exhibit regenerative characteristics, significantly mitigating the degenerative process [127]. Resveratrol helps to reduce oxidative stress caused by inflammatory environment, and can reduce the apoptosis of NP cells by reducing the ROS content in NP cells, prevent further degeneration of intervertebral disc, and enhance its regenerative capacity [128]. Moreover, in IVDD caused by mechanical overload, resveratrol partially alleviates NP cells senescence by reducing ROS production and suppressing NF-κB pathway activity [129], offering the potential for IVDD. Furthermore, studies have shown that resveratrol can reverse certain aspects of the molecular processes involved in IVDD in human NP cells [130]. Zhang and co-workers [131] found that resveratrol can reduce mitochondrial dysfunction and apoptosis under oxidative stress, and reduce the progression of IVDD, the mechanism of which may be related to resveratrol-induced autophagy. In addition, resveratrol has been shown to alleviates IVDD through the JAK/STAT3 pathway [132] or the AKT-FoxO1-SIRT1 axis [133]. Resveratrol may also alleviate low back pain caused by IVDD by reducing the oxidative response [134]. In summary, the antioxidant effects of resveratrol may be attributed to its regulation of mitochondrial dysfunction or the elimination of ROS [135]. In addition to NP cells, some researchers have found that resveratrol can reduce the apoptosis of annulus fibrosus cells through antioxidant effects [136].

There are several other polyphenols known for their antioxidant properties. For instance, Krupkova and co-workers [137] discovered that the polyphenol EGCG could alleviate low back pain associated with IVDD, and in further studies, they found that EGCG counteracts oxidative stress-induced damage to intervertebral disc cells in vitro by protecting mitochondrial membranes from depolarization [138]. Recently, Zhou and co-workers developed nanoscale network components consisting of copper ions and EGCG through metal coordination and oxidative polymerization (PG@Cu). The polymerization of natural polyphenols with metal ions gives the system a multifunctional property, with anti-oxidative stress, anti-apoptosis and anti-inflammatory capabilities, and can effectively remove ROS and prevent pyrodeath [139]. As a polyphenol, Tannic acid (TA) exhibits enhanced antioxidant properties when incorporated into polymer capsules after binding with catalase [140]. In a recent study, Wang and co-workers [141] designed injectable hydrogels encapsulated with TA nanoparticles that can clear intracellular ROS by down-regulating TNF-α expression. Proanthocyanidins [142] and anthocyanidins [143], both rich in antioxidant properties, hold promise for treating IVDD. However, the exact mechanisms by which they mitigate IVDD through antioxidant pathways are still uncertain. This uncertainty also applies to tyrosol [144]. In addition, cordycepin has a protective effect on NP cells and intervertebral disc, and can inhibit the production of some oxidative stress-related factors [145]. And Song and co-workers [146] found that tea polyphenols, natural antioxidants, play an antioxidative stress role by activating the Keap1/Nrf2/ARE pathway to delay IVDD. According to curcumin's ability to inhibit ROS, Silingardi and co-workers [147] synthesized materials functionalized with curcumin to develop bioactive materials with antioxidant properties of polyphenols. It's worth noting that these materials have been employed primarily in bone-related research rather than the treatment of IVDD. What's more, neochlorogenic acid is a class

Table 2
Antioxidant nanomaterials for IVDD.

Category	Antioxidant biomaterials	Experimental subject	Mechanism	Biological effect	In vivo model and administration method	Reference
Nanomaterials	SP@NNPm nanoparticles	NP cells; Sprague–Dawley rats	PGC1α–NRF2/TFAM pathway	ROS↓; reduce cell senescence	Needle-puncture-induced disc degeneration model. Intradiscally injection	Liu et al., 2024 [99]
Nanomaterials	Fullerol nanoparticles	NP cells of human; New Zealand White rabbits	NULL	ECM-degrading enzymes, ROS↓; maintain the stability of intervertebral disc ECM	Needle-puncture-induced disc degeneration model. Intradiscally injection	Yang et al., 2014 [90]
Nanomaterials	Polydopamine nanoparticles	NP cells; Sprague–Dawley rats	GPX4 ubiquitination suppression	Ferroptosis, ROS↓	Needle-puncture-induced disc degeneration model. Intradiscally injection	Yang et al., 2023 [93]
Nanomaterials	Nanoparticles Mix (sericin and crocetin)	NP cells of human	NULL	Proliferation of NP cell↑; Ferroptosis, ROS↓	NULL	Bari et al., 2023 [94]
Nanomaterials	TGF-β3/H-MnO_2 nanoparticles	NP cells; rats	The apoptotic gene BAX↓; proliferative genes MCL1 and BCL2↑	ROS↓; maintain the stability of intervertebral disc ECM	Needle-puncture-induced disc degeneration model. Intradiscally injection	Zhu et al., 2022 [95]
Nanomaterials	PEG-PAKM nano-micelle	ADSCs of human; NP cells; Sprague–Dawley rats	COX2, MMP-13↓; SOD↑	Promote human ADSCs differentiation into an NP-like phenotype; ROS↓	Needle-puncture-induced disc degeneration model. Intradiscally injection	Yu et al., 2021 [103]
Nanomaterials	Fucoidan-PECUU nanofibrous scaffold	NP cells; annulus fibrosus cells; Sprague–Dawley rats	IL-6 and Ptgs2 genes↓; Col1a1 and Acan genes↑	ROS↓; maintain the stability of intervertebral disc ECM	A box defect was constructed on AF tissue in the Co6-7 and Co7-8 discs of rats. Materials of nanofiber scaffold were implanted into the defect.	Yu et al., 2022 [104]
Nanomaterials	BETi-3D porous hybrid protein (3D-PHP) nano-scaffold	NP cells; rats;	NULL	ROS↓; maintain the stability of intervertebral disc ECM	Posterior midline incision was performed at Co6-7 level to expose the intervertebral disc and no.11 scalpel was used for incision of posterior AF. Nanoscaffolds were pushed into the empty space using a micropipette tip	Yang et al., 2023 [105]
Nanomaterials	N-acetylcysteine-derived carbon dots (NAC-CDs) nano-enzyme	NP cells; Sprague–Dawley rats	NULL	the level of inflammatory factors, ROS↓; reverse the progression of IVDD	Needle-puncture-induced disc degeneration model. Intradiscally injection	Wu et al., 2023 [107]
Nanomaterials	Wharton's Jelly MSC-derived extracellular vesicles	NP cells of human;	NULL	ROS, inflammation↓; maintain the stability of intervertebral disc ECM	NULL	Tilotta et al., 2024 [114]
Nanomaterials	Platelet-derived extracellular vesicles (PEVs)	NP cells; Sprague–Dawley rats	SIRT1–PGC1α–TFAM pathway	Restore impaired mitochondrial function, cell metabolism; ROS↓	Needle-puncture-induced disc degeneration model. Intradiscally injection	Dai et al., 2023 [108]
Nanomaterials	Glutaredoxin3 mesenchymal stem cell-derived extracellular vesicles (GLRX3- EVs)	NP cells; Sprague–Dawley rats	Break the vicious cycle of oxidative stress–mitochondrial damage–ROS outburst	ROS↓; maintain the stability of intervertebral disc ECM	Needle-puncture-induced disc degeneration model. Intradiscally injection	Liu et al., 2023 [109]
Nanomaterials	Human umbilical cord MSCs-derived extracellular vesicles (hUC-MSCs-EVs)	NP cells; Wistar rats;	NULL	NP cells viability and migration↑;	NULL	Ekram et al., 2023 [110]
Nanomaterials	Mice BMSCs-derived exosomes	NP cells; rabbits	NLRP3 inflammasome activation ↓	ROS, apoptosis of NP cells↓	Needle-puncture-induced disc degeneration model. Intradiscally injection	Xia et al., 2019 [111]
Nanomaterials	Mice BMSCs-derived exosomes	NP cells; rats;	NULL	Apoptosis of NP cells↓	NULL	Hu et al., 2021 [113]
Nanomaterials	Human embryonic stem cell-derived exosome	NP cells; Sprague–Dawley rats	NLRP3 inflammation-related genes↓	NP cells pyroptosis↓	Needle-puncture-induced disc degeneration model. Intradiscally injection	Yu et al., 2023 [112]
Nanomaterials	Platelet-rich plasma (PRP) -derived exosomes (PRP-Exo)	NP cells; C57BL/6 J mice	Keap1-Nrf2 pathway	NP cells pyroptosis↓	Needle-puncture-induced disc degeneration model. Intradiscally injection	Xu et al., 2021 [115]
Nanomaterials	Greigite nanozyme	NP cells; Sprague–Dawley rats	ROS-p53-p21 axis	ROS↓; rescued NPCs senescence phenotype; alleviated inflammatory response	Needle-puncture-induced disc degeneration model. Intradiscally injection	Yu et al., 2023 [117]

(*continued on next page*)

Table 2 (*continued*)

Category	Antioxidant biomaterials	Experimental subject	Mechanism	Biological effect	In vivo model and administration method	Reference
Nanomaterials	MCL@HAMA-MS (injectable nanozyme-hydrogel microsphere)	NP cells; Sprague–Dawley rats	"P53", "MAPK", "cell cycle" and "peroxisome" pathways	ROS↓; Regeneration of the ischemic tissue; maintain the stability of intervertebral disc ECM;	Needle-puncture-induced disc degeneration model. Intradiscally injection	Shen et al., 2022 [18]
Nanomaterials	PDA@CNO nanozyme	NP cells; Sprague–Dawley rats	NULL	ROS↓; maintain the stability of intervertebral disc ECM	Needle-puncture-induced disc degeneration model. Intradiscally injection	Wang et al., 2024 [118]

of phenolic compounds found in mulberry leaves, which has anti-inflammatory and anti-aging properties. Some scholars have found that neochlorogenic acid and bone marrow mesenchymal stem cells wrapped in hydrogel as a carrier to protect transplanted stem cells can effectively inhibit the oxidative stress process and reduce the apoptosis [148]. The characteristics of the above polyphenol research are shown in Table 3. While polyphenols provide a natural option with strong antioxidant effects, inorganic materials offer an alternative that combines stability with catalytic activity, making them ideal for long-term ROS clearance.

3.1.4. *Inorganic materials*

Inorganic antioxidant materials, such as cerium oxide and selenium nanoparticles, offer long-lasting antioxidant effects due to their chemical stability and ability to mimic natural enzymes like catalase or superoxide dismutase [149,150]. These materials provide a robust approach to neutralizing ROS in IVDD, as they can continuously react with ROS without being consumed in the process. This makes them suitable for sustained therapeutic interventions. However, the main limitation of inorganic materials is their biocompatibility and potential for accumulation in the body, which requires further study to ensure safety in long-term applications. Various inorganic materials with good antioxidant properties have gained attention in the research of IVDD treatment [66], such as fullerenes, MnO_2, silicon dioxide and so on. The application of antioxidant inorganic materials has brought a new idea for the treatment of IVDD. Fullerenes, also referred to Buckminster fullerenes or Buckyballs, have highly symmetrical cage structures of different sizes, and the C_{60} structure is the most abundant fullerene in the synthesized composition [151]. As a multifunctional delivery system, fullerene has a wide range of biomedical applications. Due to its special molecular structure, C_{60} has a dual behavior in the regulation of ROS, the ability to generate oxygen, as well as the ability to down-regulate ROS levels, and it is able to function in different ways under specific conditions [152]. Because of its exceptional structural feature, fullerenes are also known as "free radical sponges", and their antioxidant capacity is hundreds of times greater than traditional

Table 3
Polyphenols for IVDD.

Category	Antioxidant biomaterials	Experimental subject	Mechanism	Biological effect	In vivo model and administration method	Reference
Polyphenol	PG@Cu (EGCG)	NP cells; Sprague–Dawley rats	NLRP3 inflammasome-mediated Nod-like signaling pathway	ROS, apoptosis, inflammation, pyroptosis↓	Needle-puncture-induced disc degeneration model. Intradiscally injection	Zhou et al., 2024 [139]
Polyphenol	Neochlorogenic acid	BMSC, NP cells; Sprague–Dawley rats	NULL	ROS, apoptosis↓; maintain the stability of intervertebral disc	Needle-puncture-induced disc degeneration model. Intradiscally injection	Fang et al., 2024 [148]
Polyphenol	Tannic acid nanoparticles-injectable hydrogel gene delivery system	NP cells; Sprague–Dawley rats	MAPK/ERK pathway	ROS, inflammation↓; maintain the stability of intervertebral disc ECM	Needle-puncture-induced disc degeneration model. Intradiscally injection	Wang et al., 2023 [141]
Polyphenol	Resveratrol	Human NP cells	IL-6/JAK/STAT3 pathway	Cell apoptosis and cell cycle arrest↓; maintain the stability of intervertebral disc ECM	NULL	Wu et al., 2021 [132]
Polyphenol	Tea polyphenols	NP cells; Sprague–Dawley rats	Keap1/Nrf2/ARE pathway	ROS↓	Needle-puncture-induced disc degeneration model. Intradiscally injection	Song et al., 2021 [146]
Polyphenol	Resveratrol	NP cells	AKT-FoxO1-SIRT1 axis	Senescence of rat NP cell↓	NULL	He et al., 2019 [133]
Polyphenol	Resveratrol	NP cells of human; Rabbits	Autophagy activation	Mitochondrial dysfunction, cell apoptosis↓	Needle-puncture-induced disc degeneration model. Intradiscally injection	Zhang et al., 2017 [131]
Polyphenol	Cordycepin	NP cells; Sprague–Dawley rats intervertebral disc organ	NF-κB pathway	Anti-inflammatory and anti-catabolic effects	Disc organ culture model; Intervertebral disc injection	Li et al., 2016 [145]
Polyphenol	EGCG	Human NP cells;	IRAK-1, p38, JNK and NF-κB pathway	Anti-inflammatory and anti-catabolic effects; the analgesic properties	NULL	Krupkova et al., 2014 [138]
Polyphenol	Resveratrol	Rabbits	NF-κB pathway	ECM-degrading enzymes↓; maintain the stability of intervertebral disc ECM	Needle-puncture-induced disc degeneration model. Intradiscally injection	Kwon et al., 2013 [127]

antioxidants under certain conditions, and demonstrate potential applications in orthopedic research [153]. For instance, Xiao and co-workers [154] developed a FPR-1 targeted C_{60} nanoparticle with powerful free radical scavenging capabilities to treat IVDD through systemic administration. Building upon this foundation, three years later, the research team combined two elements, Sc and Gd, and two groups, carboxyl and amino, to synthesize four functional metallic fullerenes, all of which have the ability of scavenging oxygen radical, thereby offering a fresh avenue for IVDD treatment [155]. Nonetheless, some studies suggest that pure crystalline C_{60} seems to have a strong ability to promote oxidation, resulting in rapid death of necrotic cells [156]. In addition, nano bismethanophosphonate fullerene may potentially induce matrix protein denaturation through ROS-dependent IL-1 signaling pathway, thereby leading to certain side effects [157]. Therefore, fullerenes exhibited different biological effects under different conditions, highlighting the importance of considering the conditions and forms of fullerenes when applying them to the treatment of IVDD.

MnO_2 is also widely used in biomedical research due to its robust antioxidant properties. MnO_2 is commonly synthesized in the form of nanoparticles and integrated with hydrogels to exert its antioxidant function [158]. MnO_2 nanoparticles can also be encapsulated in polymer microcapsules to prepare synthetic antioxidant microreactors, which can effectively reduce ROS and protect cells from oxidative stress damage [159]. Moreover, MnO_2 can also be prepared to reduce ROS in the form of MnO_2 nanosheets [160], which have superoxide dismutase-like and catalase-like activities and can be integrated into microreactors to combat ROS [161]. In the field of orthopedics, Kumar and co-workers [162] developed MnO_2 nanoparticles with the ability to remove ROS, which can reduce oxidative stress damage and contribute to the treatment of conditions like osteoarthritis. Based on the fact that manganese dioxide can alleviate the oxidative stress response of organisms, Zhang and co-workers [163] found that MnO_2 can provide oxygen equivalent to cells and improve the low oxygen concentration and low pH state in the intervertebral disc microenvironment. Furthermore, MnO_2 has been constructed as a hollow nano platform for the delivery and release of TGF-β3, providing a new strategy for tissue regeneration under local oxidative stress and acidic microenvironment of the intervertebral disc [95]. Other researchers developed nanomaterials MnO_2@TMNP by wrapping MnO_2 nanoparticles in TRKA-overexpressed macrophage cell membranes (TMNP). The material was effective in clearing intracellular ROS, preventing M1 polarization, and it was further found that MnO_2@TMNP could prevent disc inflammation and promote matrix regeneration [164]. In the latest study, researchers have developed carbonized Mn-containing nanodots (MCDs) as catalytic biomaterials to remove ROS, suppress pyroptosis of NP cells, and effectively alleviate IVDD [165].

Additionally, there are other antioxidant inorganic materials with potential applications in the field of IVDD, although their utilization in research remains relatively limited. Black phosphorus, a novel nonmetallic nanomaterial, has shown low cytotoxicity and good biocompatibility to cells and living organisms, garnering significant interest in the field of nanomedicine and inorganic materials. Li and co-workers innovatively combined black phosphorus quantum dots (BPQDs) with chitosan nanoparticles and hydrogel microspheres, exhibiting robust reducibility. This novel approach enables the continuous regulation of imbalanced oxygen metabolism in IVDD through an antioxidant mechanism, offering a promising avenue for IVDD treatment (Fig. 9) [166].

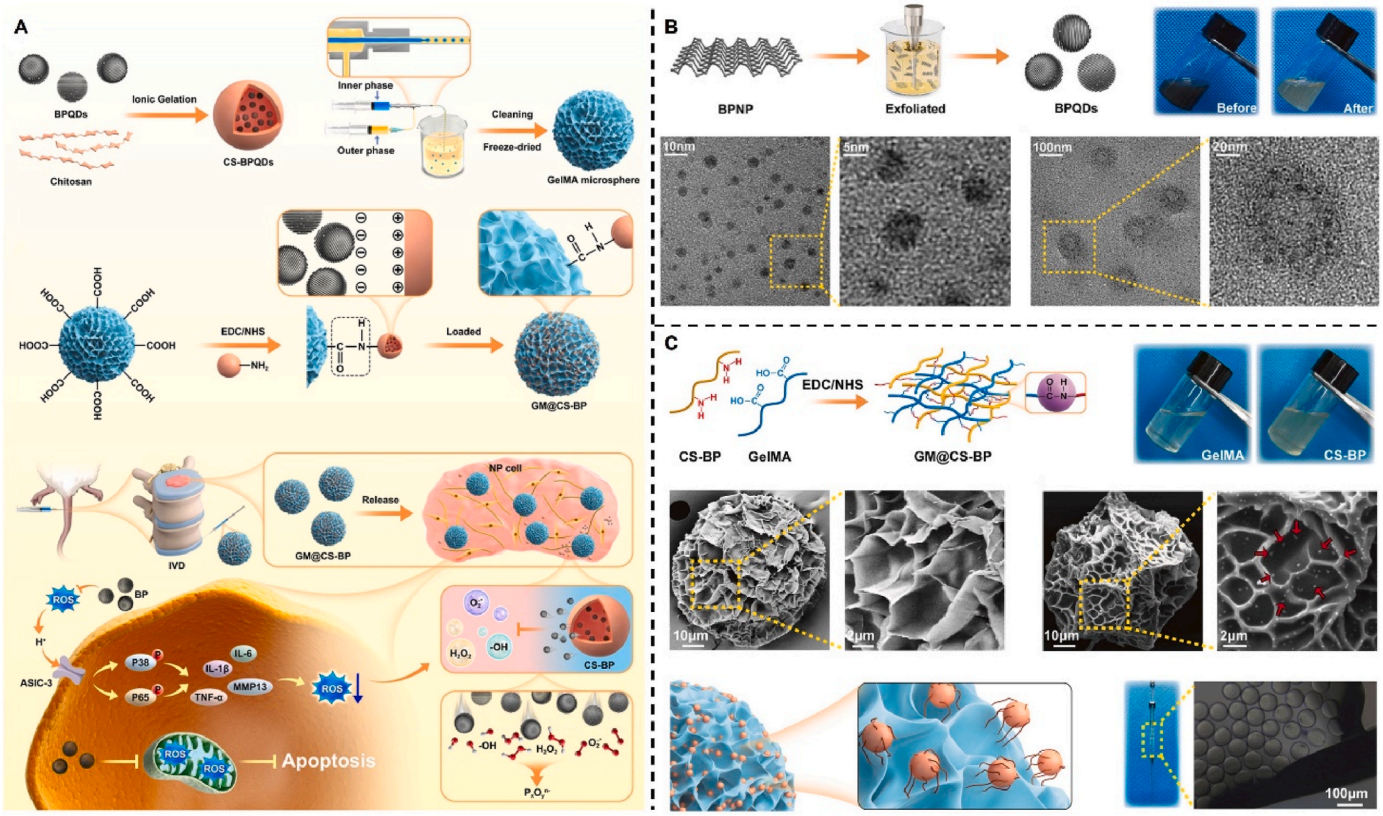


Fig. 9. Preparation process and application of GelMA@ chitosan-BPQDs (GM@CS-BP).
A. The preparation, function and application of GM@CS-BP in the treatment of intervertebral disc degeneration. The team prepared GM@CS-BP microspheres to maintain a balance between ECM synthesis and degradation by regulating the positive feedback between unbalanced oxygen metabolism and inflammation in intervertebral disc. B. Preparation and characterization of BPQDs. C. Preparation and characterization of GM@CS-BP. Reproduced with permission [166]. Copyright 2022, Z. Li et al.

Carbon point (CD) has the advantages of ultra-small size, excellent water solubility, easy modification, good biocompatibility, and has the ability to clear free radicals [167]. PBNPs have also been shown to relieve oxidative stress in intervertebral discs and increase intracellular antioxidant enzyme activity [76]. Therefore, Shi and co-workers combined Prussian blue (PB) with carbon point, which has excellent antioxidant enzyme activity, and further combined with Triphenylphosphine (TPP) to prepare CD-PB-TPP, which has mitochondrial targeting potential, and can effectively reverse mitochondrial dysfunction by clearing accumulated ROS, thus inhibiting cell senescence [168]. It happens that there is a similar case. Chen and co-workers synthesized polygallic acid-manganese (PGA-Mn) nanoparticles by self-assembly polymerization of gallic acid in water medium, and introduced mitochondria-targeting peptide (TPo4) onto the nanoparticles by Schiff base linkage to obtain PGA-MN-TPo4 nanoparticles. This nanoparticle has a strong REDOX ability, which can effectively reduce the damage of mitochondrial ROS to cells, thus reducing the oxidative stress of NP cells, maintaining the vitality of NP cells, and then maintaining the hydration of NP tissue and the height of intervertebral disc, delaying IVDD [169]. What's more, cerium dioxide has strong antioxidant properties effectively scavenging ROS. Notably, cerium dioxide nanoparticles can be fixed on silica nanoparticles, which can take advantage of the antioxidant properties of cerium dioxide but reduce its toxic effects [170]. However, despite these promising attributes, their application in the treatment of IVDD remains underexplored. In recent studies, adsorption of silica nanoparticles and titanium dioxide nanoparticles can cause molecular structure perturbations of antioxidant enzymes, resulting in loss of enzyme activity and thus oxidative stress [171]. Nevertheless, Rasool and co-workers performed sulfhydryl functionalization on the surface of mesoporous silica nanoparticles to develop thiolated, bioactive mesoporous silica nanoparticles, which showed good antioxidant activity and could neutralize ROS formed in cells [172]. Regrettably, such advancements have not yet been employed in the realm of IVDD research. The characteristics of the above inorganic materials research are shown in Table 4.

3.2. Advantages and limitations of antioxidant biomaterials

As an emerging research field in recent years, antioxidant biomaterials provide new ideas and methods for IVDD. Antioxidant biomaterials can reduce oxidative stress response, neutralize or remove ROS, promote cell proliferation and differentiation, maintain ECM stability, and promote ECM synthesis, so as to protect intervertebral disc cells from oxidative damage and promote tissue repair. At the same time, antioxidant biomaterials have anti-inflammatory effects, which can effectively relieve pain and discomfort in the process of IVDD by attenuating the inflammatory response caused by oxidative stress. The diverse range of available antioxidant biomaterials enhances the

Table 4
Inorganic materials for IVDD.

Category	Antioxidant biomaterials	Experimental subject	Mechanism	Biological effect	In vivo model and administration method	Reference
Inorganic materials	Fullerenes (C60; C80)	B6 mice; Raw 264.7 cells	Target to highly expressed FPR-1 receptors	ROS, inflammation↓	Needle-puncture-induced disc degeneration model. Intradiscally injection	Xiao et al., 2019 [154]
Inorganic materials	Fullerenes (C60; C80)	C57BL/6 mice; macrophages Raw 264.7 cells	P38 MAPK/NF-κB p65 pathways	ROS, inflammation↓;	The coccygeal disc is implanted in the L4/5 space.	Xiao et al., 2022 [155]
				the analgesic properties	The drug soaked the coccygeal disc	
Inorganic materials	Manganese dioxide	NP cells;	Apoptotic gene BAX↓; proliferative genes MCL1 and BCL2↑	ROS↓;	Needle-puncture-induced disc degeneration model.	Zhu et al., 2022 [95]
		rats		maintain the stability of intervertebral disc ECM	Intradiscally injection	
Inorganic materials	Black phosphorus quantum dots	NP cells;	Acid-sensitive ion channel-3	ROS↓;	Needle-puncture-induced disc degeneration model.	Li et al., 2023 [166]
		Sprague–Dawley rats		maintain the stability of intervertebral disc ECM	Intradiscally injection	
Inorganic materials	Prussian blue nanoparticles	NP cells;	The ubiquitin-proteasome pathway	ROS↓;	Needle-puncture-induced disc degeneration model.	Zhou et al., 2022 [76]
		Sprague–Dawley rats		intracellular activities of antioxidant enzymes↑	Intradiscally injection	
Inorganic materials	MnO_2@TMNP	NP cells, annulus fibrosus cells (AFC), cartilage end plate cells (CEPC), and ganglion cells;	NULL	ROS↓;	Needle-puncture-induced disc degeneration model.	Yang et al., 2024 [164]
		Sprague–Dawley rats		maintain the stability of intervertebral disc ECM	Intradiscally injection	
Inorganic materials	carbonized Mn-containing nanodots	NP cells;	NULL	ROS, pyroptosis↓;	Needle-puncture-induced disc degeneration model.	Sun et al., 2024 [165]
		Sprague–Dawley rats		maintain the stability of intervertebral disc	Intradiscally injection	
Inorganic materials	CD-PB-TPP	NP cells;	NULL	ROS, inflammation↓;	Needle-puncture-induced disc degeneration model.	Shi et al., 2024 [168]
		Sprague–Dawley rats		maintain the stability of intervertebral disc	Intradiscally injection	
Inorganic materials	PGA-Mn-TPo4	NP cells;	NULL	Oxidative stress, mitochondria damage↓; maintain the stability of intervertebral disc	Needle-puncture-induced disc degeneration model.	Chen et al., 2024 [169]
		Sprague–Dawley rats			Intradiscally injection	

prospects of providing patients with a wider array of treatment options for IVDD. Among various antioxidant biomaterials, antioxidant hydrogels have good cellular compatibility [79] and excellent antioxidant properties [166], and through tissue engineering design, they can improve the release kinetics of drugs [80] and have good drug slow release. At the same time, when coupled with nano-enzymes, hydrogels have the characteristics of multi-function and cost-effectiveness, and can solve the problem of surface leakage of nanomaterials [18]. In addition, the antioxidant coverage of nanomaterials is wide [90], which can enhance the endogenous repair of intervertebral disc [95]. In the latest research, the application of carbon point nano-enzymes has brought new ideas, which is a promising nanomaterial with simple preparation process, high enzyme-like activity and good biocompatibility [107]. Polyphenols have excellent antioxidant function, and they have the characteristics of low separation cost, safety and good tolerance, and are also used in the research of IVDD.

However, antioxidant biomaterials still have many limitations. At present, most studies of antioxidant biomaterials in the treatment of IVDD are confined to animal experiments [81] or in vitro experiments using human nucleus pulposus cell, Consequently the exact therapeutic effect of antioxidant biomaterials is still uncertain. Moreover, the research cycle for antioxidant biomaterials is short, and its long-term therapeutic efficacy, safety and possible side effects have not been effectively evaluated and demonstrated [112,146]. Given the diversity of antioxidant biomaterials and cell types used, variations in outcomes are anticipated. Further exploration and research are warranted, particularly considering individual differences among patients in future clinical applications. Poor in vitro stability and short in vivo half-life remain an ongoing challenge in the study of hydrogel-bound nano--enzyme [18]. In addition, some studies did not actually measure the level of oxidative stress in the animal models, and only assessed the antioxidant effect of the material by the repair effect of the disc [82]. To gain a comprehensive understanding of their efficacy, some more rigorous approaches to assessment are needed. For instance, current studies employ Lipo@HRP&ABTS nanoprobes for the quantification of H_2O_2 levels in animals, while the total antioxidant capacity assay kit (Beyotime Technology) can be utilized to assess the antioxidant capacity of biological materials [80,93]. Additionally, electron spin resonance (ESR) method enables the determination of hydroxyl radicals and superoxide anions scavenging activity by materials. Furthermore, the colorimetric titanium sulfate assay kit (Solarbio Life Sciences) can be employed to evaluate the H_2O_2 scavenging capacity of materials [173]. Consequently, with advancements in science and technology, a plethora of kits are now available on the market to comprehensively evaluate various aspects in animals, cells, and biological materials pertaining to their antioxidant capacity. In the study of nanomaterials, there is a problem of only using a single dose of materials for research [90]. Nanoparticles are prone to surface leakage, and within the high pressure environment of intervertebral disc, nanoparticle loss can accelerate [166], therefore, its controlled release needs to be further improved [95]. Although there has been a lot of research on nanomaterials in the field of medicine, it is still in the initial stage and the depth of research is insufficient. The deep molecular mechanism and principle of antioxidant nanomaterials in the treatment of IVDD have not been clarified and need to be further explored [107,110]. More large animal models and clinical trials are needed to refine the research of antioxidant biomaterials in the treatment of IVDD [105]. As a branch of antioxidant nanomaterials, the safe source and immunogenicity of extracellular vesicles and exosomes need further studies [108]. In addition, the application mode of polyphenol EGCG is still controversial [137]. While most current studies and experimental data suggest that antioxidant biomaterials hold promise for treating IVDD, it is crucial to acknowledge that confirming their therapeutic efficacy necessitates more comprehensive research and clinical evidence.

4. Conclusion and perspective

As a common spinal ailment, IVDD brings great pain and injury upon individuals. The appearance of antioxidant biomaterials brings newfound promise for the treatment of IVDD. In the process of IVDD, amount of ROS is produced, and the ROS will exacerbate the damage of disc caused by oxidative stress. Nevertheless, neither current conservative nor surgical treatments have the capacity to reverse the damage of IVDD. For this situation, many research teams have developed biomaterials with excellent antioxidant properties. At present, the research of antioxidant hydrogels is mainly based on the hydrogels prepared by GelMA and chitosan. Chitosan has good antioxidant properties, while hydrogels have good processability and controllable release of bioactive molecules [71]. Therefore, hydrogel can load more antioxidant bioactive molecules, enhance its overall antioxidant performance, effectively remove ROS in intervertebral disc tissue, reduce oxidative stress damage, and facilitate the repair and regeneration of intervertebral disc tissue. With the rise of nanomaterials, the application of antioxidant nanomaterials to IVDD has gradually increased, such as nanoparticles, nano-micelles, nanofiber scaffolds, nano-enzymes, exosomes, and so on. Antioxidant nanomaterials have stronger drug targeting and controllable release, and better biocompatibility. At the same time, nano-enzymes have low cost, multiple functions, and can also reduce the surface leakage of nanoparticles, which have a wide range of antioxidant properties. As a class of antioxidant organic materials, polyphenols have the characteristics of low separation cost, safe and good tolerance, but their application mode and long-term efficacy are still controversial. What's more, some inorganic materials also have excellent antioxidant properties and have been widely used in the field of medicine, but there is still a lack of antioxidant materials in the treatment of IVDD. Other substances with antioxidant capacity, including biomacromolecular materials, natural extracts, and synthetic polymeric materials, their applications and functions often overlap with those of hydrogels, nanomaterials, polyphenols, and inorganic materials. These biomaterials frequently serve as foundational components or are integrated within these categories, making them an intrinsic part of the broader material classes already discussed. Presently, there are limited antioxidant hydrogels poised for clinical research. In nanomaterial exploration, a prevalent issue persists: insufficient research duration to ascertain long-term safety and side effects. Moreover, understanding the safe sourcing and immunogenicity of nanomaterials requires further investigation, alongside the imperative need for enhanced control over nanoparticle release mechanisms.

More importantly, researchers should further explore the principle and molecular mechanism behind the treatment of IVDD with antioxidant biomaterials to identify key pathways and provide insights into the pathogenesis of IVDD. For example, ROS accumulation plays a critical role in the deterioration of nucleus pulposus cells by triggering various pathway, including apoptosis, senescence, necrosis, and other forms of programmed cell death. ROS-mediated dysfunction in nucleus pulposus cells is a central factor in the cascade of cellular and molecular events leading to disc degeneration, and understanding how ROS drives this dysfunction will be crucial for developing targeted antioxidant therapies. Recent studies have shown that excessive ROS levels induce senescence in nucleus pulposus cells, and targeting this process can reverse ROS-induced dysfunction [117]. Thus, identifying how antioxidant bioactive materials regulate these ROS-driven mechanisms may offer novel approaches to halt or reverse disc degeneration.

Future research on antioxidant biomaterials in the treatment of IVDD should focus on combining various types of materials. For example, combining the machinability of hydrogels with the versatility of nanomaterials, dispersing antioxidant bioactive molecules in the hydrogels in the form of nanoparticles, which may make the biomaterials have good biocompatibility at the same time. It greatly enhances its antioxidant properties and controllable release properties. The combined utilization of hydrogels and nanomaterials should focus on improving the

mechanical properties and biocompatibility of antioxidant biomaterials, enhancing the antibacterial characteristics and drug release capacity of materials, enabling responsive drug release, as well as facilitating anti-inflammatory and immune regulation. Furthermore, it is crucial to progressively incorporate multiple functionalities while preserving their antioxidant attributes in order to comprehensively develop multifunctional hydrogels. In addition, combining polyphenols with hydrogels or nanomaterials may reduce their long-term side effects. At the same time, there is very little research on antioxidant inorganic materials in the treatment of IVDD, and it is also a development direction in the future.

The intervertebral disc is the largest avascular structure in the human body, which severely limits the delivery of therapeutic agents, including anti-oxidation bioactive materials. Nutrient supply to the disc primarily occurs through diffusion from surrounding capillaries, and this poses a significant challenge for drug delivery. For antioxidant therapies to be effective, they must penetrate the dense extracellular matrix of the annulus fibrosus and reach the nucleus pulposus. The lack of direct blood flow means that traditional drug delivery methods (oral or systemic administration, and so on) are largely ineffective, as therapeutic concentrations are difficult to achieve at the target site. Even if antioxidants can be delivered into the IVD, they must remain effective in a harsh, oxidative environment. The degenerating disc is characterized by a low-oxygen, acidic microenvironment with a high concentration of ROS. Antioxidant materials need to withstand these conditions and remain bioactive over extended periods. However, achieving sustained release of antioxidants and ensuring their long-term efficacy is challenging. Many biomaterials degrade quickly or lose their activity, necessitating repeat treatments or additional interventions, which is impractical for chronic diseases like IVDD. Besides, IVDD is driven by multiple pathological processes, including oxidative stress, inflammation, extracellular matrix degradation, and cell apoptosis. While oxidative stress plays a significant role in disc degeneration, targeting it in isolation may not be sufficient to halt or reverse the degenerative process. To achieve effective clinical outcomes, anti-oxidant therapies likely need to be combined with other treatments, such as anti-inflammatory agents, growth factors, or regenerative strategies (stem cells or tissue-engineering scaffolds, and so on), to address the multifactorial nature of IVDD. This presents a challenge in both designing combination therapies and translating them into clinical practice. Besides, there is often a gap between promising results observed in preclinical animal models and the outcomes seen in human trials. The anatomy, cellular composition, and regenerative capacity of animal intervertebral discs differ significantly from those of humans, making it difficult to translate successful animal studies into clinical practice. They also pose important challenges to human biosafety and immunogenicity. Additionally, many animal models do not fully replicate the chronic and progressive nature of human IVDD, which can lead to overestimation of the potential efficacy of antioxidant therapies. Moreover, research should not be limited to animal cells and animal models, we should conduct as many human cell research and clinical studies as possible. In a word, the development of antioxidant biomaterials has brought new hope for patients with IVDD, and we should combine biomaterials with basic research to jointly promote its development and progress.

CRediT authorship contribution statement

Yingjie Mai: Writing – original draft, Data curation. **Siying Wu:** Writing – original draft, Data curation. **Penghui Zhang:** Writing – review & editing. **Ningning Chen:** Writing – review & editing. **Jun Wu:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Fuxin Wei:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization.

Ethics approval and consent to participate

The manuscript entitled “The Anti-oxidation related bioactive materials for Intervertebral Disc Degeneration Regeneration and Repair”, co-authored by Yingjie Mai, Siying Wu, Penghui Zhang, Ningning Chen, Jun Wu, Fuxin Wei, submitted for evaluation to Bioactive Materials, is a literature review work, and thus no in vivo evaluations on animal model or clinical trials were performed in this scope. Therefore, our work does not fall into the incidence of ethical approvals and patient consents.

Declaration of competing interest

The authors declare that they have no known competing/conflicting financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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