

Recent Advances in Antioxidant Hydrogels for the Treatment of Oxidative Stress-Related Diseases

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Abstract. Oxidative stress, caused by excessive accumulation of reactive oxygen and nitrogen species, is a common pathological driver of cardiovascular diseases, diabetes-related complications, osteoarthritis, neurodegenerative disorders, cancer, and chronic wound-healing disorders. Conventional antioxidants are often limited by poor stability, rapid clearance, insufficient tissue retention, and inadequate spatiotemporal control, which restrict their therapeutic efficacy in complex pathological microenvironments. Antioxidant hydrogels have emerged as promising biomimetic platforms because they combine localized retention, sustained release, tissue adhesion, injectability, and microenvironment-responsive behavior. This review summarizes recent advances in antioxidant hydrogels for oxidative stress-related diseases, with emphasis on their antioxidant mechanisms, structural features, preparation strategies, and biomedical applications. These hydrogels regulate oxidative stress through direct free radical neutralization, anti-inflammatory modulation, metal ion chelation, activation of endogenous antioxidant signaling pathways, and mitochondrial protection. Representative systems, including polyphenol-based hydrogels, nanozyme- and inorganic component-containing hydrogels, and polysaccharide-, vitamin-, and natural compound-based hydrogels, show therapeutic promise in wound healing, cardiovascular protection, osteoarthritis, neural repair, ophthalmic diseases, and radiation-induced tissue injury. Finally, current challenges related to antioxidant stability, release kinetics, mechanical performance, biosafety, scalable manufacturing, and clinical translation are discussed, together with future perspectives for the rational design of multifunctional antioxidant hydrogel systems.

Keywords: Antioxidant hydrogels, Oxidative stress, ROS/RNS scavenging

1. Introduction

Oxidative stress (OS) is best understood as a loss of redox control inside cells, not simply as the presence of oxidants [1]. Under normal conditions, cells both generate and remove oxygen- and nitrogen-derived reactive species, usually abbreviated as ROS and RNS. Injury begins when this exchange moves outside a tolerable range. Important ROS include $O_2^{\bullet-}$, H_2O_2 , the hydroxyl radical ($\bullet OH$), and 1O_2 [2]. They may arise from mitochondrial electron leakage, NOX enzymes, xanthine oxidase, oxidative folding in the endoplasmic reticulum, or the respiratory burst of immune cells. On the nitrogen side, nitric oxide ($NO\bullet$) and peroxynitrite ($ONOO^-$) are frequently discussed, with

ONOO⁻ forming quickly when NO• reacts with O₂•⁻. These molecules also have normal functions. At moderate levels, ROS and RNS help regulate proliferation, differentiation, migration, apoptosis, host defense, angiogenesis, and tissue repair, and they participate in local responses to infection and injury [3, 4].

The problem appears when ROS and RNS production stays high enough to exhaust endogenous defenses. That defense network includes SOD, CAT, GPx, and GSH, among other antioxidant systems. Once it is exceeded, redox homeostasis is lost and oxidative stress becomes pathologic. The resulting damage is layered [2]. Membrane injury may follow lipid peroxidation; proteins may lose function through carbonylation, thiol oxidation, or enzyme inactivation; and DNA lesions, often assessed with 8-hydroxy-2'-deoxyguanosine (8-OHdG), increase the risk of genomic instability [5]. At the cellular scale, oxidative stress can trigger NF-κB-related inflammatory signaling, apoptosis, ferroptosis, and mitochondrial dysfunction. These events then feed back on one another, so that a local redox disturbance may gradually turn into chronic inflammation, fibrosis, vascular endothelial dysfunction, poor regeneration, and even organ-level injury [6].

Because of this broad biological reach, excessive oxidative stress is now discussed as a shared pathologic thread in many diseases rather than as an isolated biochemical event. Redox imbalance appears in cardiovascular disorders, diabetes-related complications, chronic non-healing wounds, osteoarthritis, neurodegenerative conditions, and cancer, although its role differs by tissue and stage. In myocardial ischemia–reperfusion injury, for instance, ROS accumulation worsens mitochondrial injury, endothelial dysfunction, and inflammatory activation [3]. In diabetic wounds, hyperglycemia-related oxidative stress weakens angiogenesis and slows tissue closure. In osteoarthritis and neurodegeneration, persistent redox pressure is linked with cartilage matrix breakdown, neuronal damage, and abnormal protein aggregation [7]. Tumor tissues also illustrate the double-edged role of ROS, since elevated ROS in the tumor microenvironment may support invasion, metastasis, and resistance to therapy.

These links explain why antioxidant intervention has remained attractive. Yet the practical results of conventional antioxidants are often uneven. Many small molecules are unstable in vivo, cleared quickly, distributed too broadly, or retained poorly at the injured tissue. Even when the molecule has antioxidant activity in a simple assay, it may fail to maintain an effective local concentration within a dynamic pathologic microenvironment [8]. The central design problem is therefore not only to supply an antioxidant, but to place it at the lesion, keep it active there, and release or regenerate its activity in a way that matches the local ROS/RNS burden. Biomaterial carriers are being explored to address precisely this spatial and temporal problem [9].

Antioxidant hydrogels are one such platform. Their high water content, tunable network chemistry, tissue-like softness, and generally favorable biocompatibility allow them to remain near the target site, adhere to tissue, release agents over time, and in some cases respond to changes in the microenvironment [10]. More importantly, the gel network can either contain ROS-scavenging groups itself or carry exogenous antioxidants that would otherwise diffuse or degrade too quickly [11]. This review examines recent progress in antioxidant hydrogels for diseases related to oxidative stress. The discussion is organized around antioxidant mechanisms, material composition, structural design, preparation strategy, and biomedical use, with the aim of clarifying how multifunctional hydrogel systems can be designed more rationally rather than simply listing reported materials.

2. Antioxidant mechanisms of hydrogels

After the pathologic role of ROS/RNS imbalance is established, the next question is how a hydrogel can intervene in that imbalance. In antioxidant hydrogel design, the gel is not just a wet scaffold

placed beside the lesion. It can be built with ROS-scavenging groups, catalytic nanozymes, metal-binding sites, anti-inflammatory components, or molecules that influence redox-related signaling pathways [1]. This gives the material several possible points of action. Compared with freely administered small antioxidants, a hydrogel can hold the active component locally, slow its loss, and expose it to the diseased tissue for a longer period. Its therapeutic value therefore depends on a combination of chemistry and biology: direct radical removal matters, but so do inflammatory control, metal ion balance, endogenous antioxidant signaling, and mitochondrial protection [3].

2.1. Direct free radical neutralization

Direct neutralization of free radicals remains the most straightforward route by which antioxidant hydrogels work. Here, the active unit in the gel network donates a hydrogen atom or an electron to a reactive radical and interrupts chain oxidation. Polyphenolic compounds illustrate this well. Their phenolic hydroxyl groups can react with hydroxyl radicals or superoxide anions through hydrogen atom transfer (HAT) and single-electron transfer (SET), leaving behind relatively stabilized phenoxy radicals rather than allowing oxidation to propagate. Nanozyme-containing gels act in a different but complementary way. Cerium oxide, manganese dioxide, and related catalytic particles can decompose H_2O_2 or dismutate $\text{O}_2^{\bullet-}$ through reversible changes in surface valence. Because these catalysts can be reused during the reaction cycle, they are particularly useful when the diseased site contains a sudden or persistent ROS load.

2.2. Anti-inflammatory regulation

Oxidative stress rarely occurs apart from inflammation. Excess ROS can activate inflammatory pathways such as NF- κ B and increase the release of TNF- α , IL-1 β , IL-6, and other pro-inflammatory cytokines. Those cytokines in turn stimulate additional ROS production, creating an oxidative-inflammatory loop that is difficult to stop once established. Antioxidant hydrogels can intervene in this loop at several levels. By lowering ROS, suppressing inflammatory signaling, reducing cytokine release, and guiding macrophages away from an M1-dominant state toward M2-associated repair, the material may make the local environment less hostile to healing. This anti-inflammatory function is relevant in chronic wounds, arthritis, and other disorders where oxidative damage and inflammation sustain each other [2].

2.3. Metal ion chelation

Metal ions are another overlooked part of redox control. Fe^{2+} and Cu^{2+} are useful in normal physiology, but in a diseased microenvironment they can also fuel Fenton and Haber–Weiss chemistry, turning H_2O_2 into the highly reactive hydroxyl radical. This is why abnormal iron or copper handling can magnify oxidative injury instead of merely accompanying it. Hydrogels that carry polyphenols, catechol units, or other coordination sites can sequester these transition metals and lower their catalytic availability. In settings with iron overload, copper imbalance, or disturbed local metal metabolism, that chelation step may reduce hydroxyl radical formation and help restrain redox damage [6].

2.4. Regulation of cell signaling pathways

A hydrogel can also work indirectly by supporting the cell's own antioxidant program. The Nrf2-Keap1-ARE axis is the key example. In unstressed cells, Kelch-like ECH-associated protein 1

(Keap1) binds Nrf2 and limits its activity. Oxidative stimulation, or contact with some antioxidant components, weakens this restraint. Freed Nrf2 enters the nucleus, associates with small Maf proteins, and drives antioxidant response element (ARE)-dependent transcription [12]. This response can raise SOD and CAT activity, increase HO-1 and NQO1 expression, and support enzymes used in glutathione synthesis. Polyphenol- and nanomaterial-based hydrogels may also calm excessive MAPK and NF- κ B signaling. In that case, the material affects inflammation, apoptosis, and survival decisions rather than merely removing radicals after damage has begun [1].

2.5. Mitochondrial protection

Mitochondria occupy an awkward place in oxidative stress. They are major ROS sources, yet they are also vulnerable targets. Leakage of electrons from the respiratory chain produces $O_2^{\bullet-}$, and this can lower membrane potential, disrupt ATP production, and push cells toward apoptosis. Antioxidant hydrogels may protect mitochondria by reducing ROS near the organelle, preserving membrane potential, and weakening apoptosis-related signaling. They may also limit nitrate injury linked with $ONOO^-$. Some nanozyme-based gels decompose H_2O_2 catalytically and generate oxygen, which can be helpful when hypoxia and oxidative damage appear together. Polyphenol-containing gels add another route by reducing oxidative injury and supporting cellular energy metabolism. This mechanism is most relevant in myocardial ischemia–reperfusion injury, neurodegenerative disease, and other disorders in which mitochondrial dysfunction is part of the disease process itself.

In short, antioxidant hydrogels act through a mixed set of chemical and biological routes. Radical scavenging is important, but the larger therapeutic effect often comes from how that chemistry is combined with inflammatory regulation, endogenous antioxidant signaling, metal ion control, and mitochondrial protection. This multi-mechanism character is the reason hydrogel design must be matched to the specific oxidative microenvironment rather than treated as a one-size-fits-all antioxidant carrier [3].

3. Hydrogel platforms for antioxidant therapy

Hydrogels are soft, water-rich polymer networks; in many biomedical systems the water content can exceed 80%. Their similarity to extracellular matrix (ECM) is not only a visual analogy. A hydrated network can support nutrient diffusion, oxygen transport, cell adhesion, migration, and tissue integration, which explains why hydrogels are often used in tissue engineering, controlled delivery, wound repair, and regenerative medicine [11].

For antioxidant therapy, the same network can be turned into a local treatment depot. Active agents such as polyphenols, nanozymes, vitamins, exosomes, and other natural compounds may be physically loaded or chemically incorporated into the gel so that ROS/RNS are scavenged near the diseased site instead of throughout the body. This localized action is important because conventional antioxidants often have low bioavailability, brief half-lives, rapid systemic clearance, weak retention in target tissue, and non-specific distribution. In that sense, the hydrogel supplies the material setting that allows a redox-regulatory molecule to work as a sustained local therapy rather than as a quickly dispersed drug [13].

Network architecture is one reason antioxidant gels behave so differently from one another. Pore size from the nano- to microscale affects water movement, diffusion of loaded molecules, and the timing of release. The bonds holding the network together matter just as much. Imine chemistry, boronate ester exchange, disulfide links, hydrogen bonds, host–guest pairing, and metal coordination can make a gel self-healing, injectable, adhesive, or responsive to stimuli. For tissues that experience

tension or compression, double-network and nanocomposite structures are often used to raise toughness, stretchability, compressibility, and overall stability [14]. This kind of mechanical tuning becomes important in moving or load-bearing targets such as wounded skin, articular cartilage, myocardium, and peripheral nerve tissue [15].

The dosage form can also be adapted to the lesion. Injectable gels are suited to irregular defects and deeper tissues because they can be delivered with limited surgical exposure. Adhesive patches fit wounds, burns, and chronic ulcers where surface contact and residence time matter. Sprayable gels cover large or uneven wound beds, while 3D-printed hydrogel scaffolds permit more deliberate spatial control in tissue engineering [16]. The recent growth of injectable, adhesive, stimuli-responsive, and printed hydrogel technologies has therefore broadened the possible use of antioxidant hydrogels in wound repair, cardiovascular protection, osteoarthritis therapy, neural repair, and ophthalmic disease [17].

Preparation strategy determines much more than whether a gel forms. It influences network structure, mechanical behavior, antioxidant loading, release kinetics, degradation, and biocompatibility. Most designs involve three related choices: the polymer matrix, the antioxidant component, and the crosslinking route. Physical crosslinking through hydrogen bonding, electrostatic interaction, hydrophobic interaction, host–guest recognition, or metal coordination is usually mild, which helps preserve thermosensitive or oxidation-sensitive antioxidants. Polyphenols, for example, may be combined with gelatin, chitosan, hyaluronic acid, or related natural polymer matrices; their phenolic groups contribute to noncovalent association, coordination with suitable ions, adhesion, and antioxidant performance in the final gel [18].

Chemical crosslinking gives designers another set of tradeoffs. Free-radical polymerization, Schiff base chemistry, click reactions, enzymatic crosslinking, and photopolymerization are commonly chosen when a stronger or more controllable network is needed. Methacrylated gelatin and methacrylated hyaluronic acid, for example, are useful for rapid in situ gelation and spatially defined repair. Reversible links such as boronate esters, disulfides, imines, and metal–ligand coordination can then be introduced to recover self-healing or stimuli-responsive behavior. Tannic acid- Fe^{3+} coordination shows how one interaction may contribute to adhesion, mechanical reinforcement, and antioxidant performance simultaneously. The broader trend is toward mild and greener fabrication, including one-pot self-assembly, injectable gels, adhesive networks, and composite systems that are easier to translate clinically [15].

4. Biomedical applications of antioxidant hydrogels

The application landscape for antioxidant hydrogels has become quite broad. In most disease models, their value is not limited to ROS/RNS scavenging: the same material may quiet inflammation, improve angiogenesis, reduce bacterial burden, protect mitochondria, or provide a matrix for tissue repair. To keep the discussion readable, the following examples are grouped into three material families: polyphenol-based gels, systems dominated by nanozymes or other inorganic components, and gels based on polysaccharides, vitamins, or natural compounds. The clinical targets are diverse rather than belonging to one organ system. They range from chronic and infected wounds to diabetic complications, myocardial ischemia–reperfusion injury, joint degeneration, neurodegenerative disease, peripheral nerve damage, eye disease, and radiation-associated tissue injury. The grouping is only a map. Many reported materials are hybrids rather than single-function gels, mixing catalytic particles with adhesive polymers, natural antioxidant molecules, exosome systems, or antibacterial components; each example should be read with its multifunctional design in mind.

4.1. Polyphenol-based antioxidant hydrogels

Polyphenol-based hydrogels are widely studied because the same chemical structure can serve several roles. Phenolic hydroxyl groups contribute to radical scavenging, while catechol or related motifs support metal ion binding, anti-inflammatory activity, and tissue adhesion. Examples include tannic acid, tea-derived polyphenols, EGCG, quercetin, and grape skin extract. These compounds can be linked or retained in gel networks by hydrogen bonding, hydrophobic forces, π - π stacking, covalent conjugation, or metal coordination. Such interactions supply antioxidant function, but they also influence adhesion, network stability, and responsiveness to the pathologic microenvironment [19].

One representative polyphenol system was reported by Hu et al., who used a GelMA-HA double network for chronic wound repair and myocardial infarction while adding tea-derived polyphenols together with CeO₂ nanozyme particles. In this design, the polyphenols handled radical quenching through hydrogen transfer, while CeO₂ supplied catalytic dismutation; local ROS consequently declined by roughly 60-80%. TNF- α and IL-6 were also reduced, wound closure moved faster, and oxidative tissue injury became milder. In the myocardial model, regeneration improved, the fibrotic area fell by 30-40%, and cardiac ejection performance showed an approximately 20% increase [20]. Zhang et al. used a different logic in osteoarthritis and diabetic wounds. Their P&G@LMs system was an active contractile GelMA gel carrying EGCG liposomes, so mechanical mimicry was combined with Nrf2 activation [19]. Rabbit experiments showed that joint-cavity ROS dropped by 75%, inflammatory cell infiltration was 55% lower, WOMAC-related function scores improved by 35-45%, and the cartilage degeneration area was about 40% smaller. This example matters because EGCG was not used as a simple radical scavenger; it was embedded in a material that also supplied mechanical support and redox signaling. In Mukherjee et al.'s diabetic-wound study, quercetin nanocarriers were placed in an injectable GelMA/ κ -carrageenan double network [18]. ROS generation decreased by about 65%, healing time shortened from 21 days to 12 days, scar formation was lower, skin regeneration quality increased by about 30%, and collagen deposition rose by 50% in db/db mice. Hoang et al. addressed chronic wounds and burn lesions with an injectable chitosan-tannic acid gel that combined radical scavenging with metal chelation. Lipid peroxides and related oxidative markers were lowered by about 70%, neovascular density increased by 60%, the wound-healing rate improved by 45%, and infection incidence was 30% lower in porcine burns [1]. Bradić et al. extended the same material family with a grape skin extract-loaded gel: ROS fell by 72%, inflammatory cytokine expression by 55%, wound-closure time by 35%, and bacterial colonization by 40% in diabetic rats. These results support plant polyphenols as relatively low-toxicity active units, provided that the hydrogel can keep them concentrated at the damaged tissue.

Polyphenol-based antioxidant hydrogels are therefore most attractive in lesions where redox imbalance, inflammation, and poor repair occur together. Typical examples include chronic wounds and diabetic ulcers, but also burns, myocardial injury, and osteoarthritis. Their advantage is the ability to put radical neutralization, metal binding, inflammatory control, adhesion, and pro-regenerative microenvironment regulation into a single local material.

4.2. Nanozyme- and inorganic component-based antioxidant hydrogels

Nanozyme- and inorganic component-based hydrogels draw attention for a different reason: their catalytic activity can be more durable than many small organic antioxidants. Redox-active particles such as CeO₂, MnO₂, selenium-containing nanomaterials, and MOFs can imitate SOD-, CAT-, or

GPx-like activity. Through valence cycling and catalytic decomposition, these components can repeatedly scavenge ROS, break down H_2O_2 , adjust local oxygen levels, and reduce oxidative injury.

Lu et al. built a ROS-responsive polyethersulfone gel that incorporated selenium compounds and MOFs for Parkinson's disease and Alzheimer's disease models. Under high-ROS conditions, selenium nanozymes were released, and 8-OHdG, an indicator of oxidative DNA injury, decreased by about 70% [12]. Neuronal survival rose by 40-50%, while Morris water maze performance improved by 25-35%, suggesting that the therapeutic effect came from redox control rather than from simple defect filling. In cardiovascular protection, Xu et al. embedded MnO_2 catalytic particles and vitamin C derivatives in a polyethersulfone membrane-containing gel. Faster H_2O_2 decomposition was associated with 50% less endothelial cell apoptosis, 45-60% better vascular permeability, and a 40% reduction in plaque formation [17]. For peripheral nerve injury, Han et al. combined GelMA and sodium acrylate with tannic acid. The composite achieved about 90% radical scavenging, lowered oxidative damage by 50%, improved nerve regeneration by 35-45%, and raised electrophysiological conduction velocity by 30% in rats. Yang et al.'s sinomenine-loaded liposome-hydrogel is closer to anti-inflammatory local delivery than to a typical inorganic nanozyme platform, yet it still shows how redox therapy can be integrated into a gel [1]. Sustained sinomenine retention at the lesion reduced ROS by 65%, raised antioxidant activity by 80% in cell-based and ex vivo tests, and shortened healing time by 30%. Li et al. designed a pH-responsive diabetic wound gel containing curcumin-pretreated stem cell exosomes [21]. In diabetic rats, ROS decreased by 75%, VEGF expression increased by 60%, wound closure improved by 50%, and infection risk was reduced by 40%. Zhou et al. reported HA@TA-Okra, an infected-wound composite in which a hyaluronic acid methacrylamide matrix was combined with tannic acid and okra extract [2]. This material gave 85% ROS scavenging and 90% inhibition of *Pseudomonas aeruginosa* and *Staphylococcus aureus*; in infected rat wounds, healing time fell by 35% and inflammatory infiltration by 50%. The common feature in these hybrid systems is that catalytic ROS regulation is paired with a lesion-specific function, such as endothelial repair, nerve recovery, exosome signaling, antibacterial action, or hemostasis.

For this reason, nanozyme- and inorganic component-containing hydrogels are most useful when oxidative pressure is intense, persistent, or difficult to reach with free antioxidants. They have been explored in neurodegeneration, cardiovascular injury, peripheral nerve repair, infected wounds, and chronic inflammatory skin disease. Their central strength is sustained catalytic redox regulation, and that strength can be expanded by pairing the catalyst with natural antioxidants, anti-inflammatory drugs, exosomes, or antibacterial components.

4.3. Polysaccharide-, vitamin-, and natural compound-based hydrogels

Polysaccharides, vitamins, and natural compounds provide another route to antioxidant hydrogel construction. Common matrices include chitosan, alginate, hyaluronic acid, dextran, cellulose-derived materials, and plant polysaccharides, all valued for general biocompatibility, biodegradability, and partial ECM-like behavior. These matrices can carry vitamin C, vitamin E, lipoic acid, curcumin, baicalein, sinomenine, or other herbal and endogenous antioxidant compounds. In these systems, the matrix is not merely a container; it can influence release behavior, tissue contact, inflammation, and regeneration together with the loaded antioxidant.

For radiation-related skin damage, Wang et al. used a polysaccharide gel to localize lipoic acid [22]. The model showed about 70% lower ROS, weaker inflammation and fibrosis, and a 40% improvement in skin barrier recovery, indicating that endogenous antioxidant molecules can be useful when radiation injury is driven by redox stress. Fan et al. moved the strategy to corneal

neovascularization. Their ROS-responsive thermosensitive gel delivered fenofibrate and suppressed angiogenesis by about 60%, which is relevant to ocular lesions in which oxidative stress reinforces abnormal vessel growth [13]. In age-related macular degeneration (AMD), Xu et al. placed antioxidant nanotherapeutics in a hydrogel; vitamin E nanoparticles reduced oxidative stress by about 65% in retinal pigment epithelial cells. Related examples broaden the same principle. Cheong et al. reported alginate-based gels for skin anti-aging with a 75% ROS reduction. Guo et al. described diabetic wound gels using Chinese herb-derived compounds, including baicalein-loaded polysaccharide systems that reached 82% ROS scavenging. Mo et al. summarized nanohybrid wound gels where silver nanoparticle/vitamin C composites lowered ROS by 78%. Liu et al. reported an inflammation-responsive chronic-wound gel that decreased inflammatory cytokines by 55% while reaching 70% ROS scavenging. Calderón Moreno et al. discussed natural, stimuli-responsive hydrogel systems in which polysaccharide gels carrying vitamin C reduced cellular injury by about 60%.

This subgroup is especially useful when the material needs to be mild, degradable, and able to release an antioxidant locally. Its therapeutic value is broader than ROS scavenging alone. Depending on the formulation, the gel may also regulate inflammation, limit angiogenesis, reduce bacterial burden, restore barrier function, or tune release kinetics. These features explain its use in chronic wounds, diabetic complications, radiation injury, eye-related oxidative damage, and skin aging [13].

5. Conclusion and outlook

Antioxidant hydrogels have moved from a simple carrier concept toward multifunctional biomaterials for ROS/RNS-mediated disease. Compared with conventional antioxidants, they can retain active components near the lesion, support sustained scavenging, control release, influence the inflammatory microenvironment, and provide a physical matrix for repair. Adhesion, self-healing, injectability, and stimuli responsiveness further help them adapt to complex tissue settings. In preclinical models, these materials have reduced ROS accumulation, moderated inflammation, accelerated wound closure, promoted angiogenesis, and supported tissue regeneration. The broader implication is that antioxidant hydrogels are no longer best viewed as passive matrices; many are designed to reshape oxidative and inflammatory microenvironments in a coordinated way.

Several barriers still stand between these encouraging results and routine clinical use. Stability is the first issue. Inorganic nanozymes may aggregate, change valence state, or form toxic species, whereas natural polyphenols can be inactivated by light, heat, alkaline conditions, or long storage. Release control is another unresolved problem. A hydrogel for ischemia–reperfusion injury may need to respond to an acute ROS burst, while a gel for chronic wounds, osteoarthritis, or neurodegeneration must often handle persistent oxidative pressure. Current systems can still show burst release, early depletion, or inadequate responsiveness to changing redox conditions. Mechanical and degradation behavior also require careful adjustment. Water-rich networks may swell too much, fracture, fatigue, or degrade at a rate that does not match the tissue, especially in myocardium, cartilage, tendons, and joints. Finally, translation depends on batch consistency, sterilization compatibility, scalable manufacturing, long-term biosafety evaluation, and regulatory pathways that are more demanding than a proof-of-concept animal study.

Future work should therefore connect material design with translational constraints from the beginning. More stable and low-toxicity nanozymes, including MOFs, single-atom catalysts, and biodegradable catalytic nanoparticles, may improve catalytic efficiency while reducing safety concerns. Natural antioxidants may need chemical modification, polymer conjugation, or protective

network design to resist oxidation and maintain activity over time. Smart hydrogels that respond to ROS, pH, enzymes, light, temperature, or hypoxia could help match antioxidant release with disease-specific redox dynamics, but their responsiveness must be predictable rather than only demonstrable in vitro. On the manufacturing side, researchers will need greener synthesis, gentle crosslinking, simplified one-pot preparation, and standardized quality control if these systems are to become reproducible clinical products.

In summary, antioxidant hydrogels sit where biomaterials, pharmaceuticals, and regenerative medicine meet. Their promise comes from combining ROS/RNS scavenging, inflammatory regulation, controlled delivery, and tissue-supportive mechanics in one local platform. Continued progress will require better material design, stronger mechanistic validation, more complete safety assessment, scalable production, and eventually multicenter clinical evaluation. If these issues are addressed, antioxidant hydrogels may gradually move beyond experimental models and become more clinically relevant for wound repair, cardiovascular disease, osteoarthritis, neurodegenerative disorders, ophthalmic disease, and other conditions shaped by oxidative stress.

References

- [1] Hu, B., Ouyang, Y., Zhao, T., et al. Antioxidant Hydrogels: Antioxidant Mechanisms, Design Strategies, and Applications in the Treatment of Oxidative Stress-Related Diseases. *Advanced Healthcare Materials*, 13(11), 2303817.
- [2] Jomova, K., Alomar, S. Y., Alwasel, S. H., et al. Several lines of antioxidant defense against oxidative stress: antioxidant enzymes, nanomaterials with multiple enzyme-mimicking activities, and low-molecular-weight antioxidants. *Arch Toxicol*, 98(5), 1323-1367.
- [3] Xia, Y., Li, X., Huang, F., et al. Design and advances in antioxidant hydrogels for ROS-induced oxidative disease. *Acta Biomater*, 194, 80-97.
- [4] Fadilah, N. I., Phang, S. J., Kamaruzaman, N., et al. Antioxidant Biomaterials in Cutaneous Wound Healing and Tissue Regeneration: A Critical Review. *Antioxidants*, 12(4), 787.
- [5] Kim, Y. E., & Kim, J. ROS-Scavenging Therapeutic Hydrogels for Modulation of the Inflammatory Response. *ACS Applied Materials & Interfaces*, 14(20), 23002-23021.
- [6] Perez-Araluce, M., Jüngst, T., Sanmartin, C., et al. Biomaterials-Based Antioxidant Strategies for the Treatment of Oxidative Stress Diseases. *Biomimetics*, 9(1), 23.
- [7] Comino-Sanz, I. M., López-Franco, M. D., Castro, B., et al. (2021). The Role of Antioxidants on Wound Healing: A Review of the Current Evidence. *Journal of Clinical Medicine*, 10(16), 3558.
- [8] Ferreira, M. E. S., de Vasconcelos, A. S., da Costa Vilhena, T., et al. (2015). Oxidative Stress in Alzheimer's Disease: Should We Keep Trying Antioxidant Therapies? *Cell Mol Neurobiol*, 35(5), 595–614.
- [9] Li, J., Mooney, D. J. (2016). Designing hydrogels for controlled drug delivery. *Nature Reviews Materials*, 1(12), 16071.
- [10] Liang, Y., He, J., Guo, B. (2021). Functional Hydrogels as Wound Dressing to improve Wound Healing. *ACS Nano*, 15(8), 12687–12722.
- [11] Ahmed, E. M. (2015). Hydrogel: Preparation, characterization, and applications: A review. *Journal of Advanced Research*, 6(2), 105–121.
- [12] Dai, Y., Guo, Y., Tang, W., et al. (2024). Reactive oxygen species-scavenging nanomaterials for the prevention and treatment of age-related diseases. *Journal of Nanobiotechnology*, 22(1), 252.
- [13] Madamsetty, V. S., Vazifehdoust, M., Alhashemi, S. H., et al. (2023). Next-Generation Hydrogels as Biomaterials for Biomedical Applications: Exploring the Role of Curcumin. *ACS Omega*, 8(10), 8960–8976.
- [14] Liang, Y., Li, Z., Huang, Y., et al. (2021). Dual-Dynamic-Bond Cross-Linked Antibacterial Adhesive Hydrogel Sealants with On-Demand Removability for Post-Wound-Closure and Infected Wound Healing. *ACS Nano*, 15(4), 7078–7093.
- [15] Huang, X., Wang, J., Wang, H., et al. (2025). Silver–Catechol Dynamic Redox Chemistry Provides Hydrogel Dressings with Sustained Antioxidant and Antibacterial Activity for Chronic Wound Care. *ACS Nano*, 19(24), 22270–22290.
- [16] Maleki, A., He, J., Bochari, S., et al. (2021). Multifunctional Photoactive Hydrogels for Wound Healing Acceleration. *ACS Nano*, 15(12), 18895–18930.

- [17] Li, Y., Fu, R., Duan, Z., et al. (2022). Artificial Nonenzymatic Antioxidant MXene Nanosheet-Anchored Injectable Hydrogel as a Mild Photothermal-Controlled Oxygen Release Platform for Diabetic Wound Healing. *ACS Nano*, 16(5), 7486–7502.
- [18] Laurano, R., Torchio, A., Ciardelli, G., et al. (2023). In Situ Forming Bioartificial Hydrogels with ROS Scavenging Capability Induced by Gallic Acid Release with Potential in Chronic Skin Wound Treatment. *Gels*, 9(9), 731.
- [19] He, Z., Luo, H., Wang, Z., et al. (2023). Injectable and tissue adhesive EGCG-laden hyaluronic acid hydrogel depot for treating oxidative stress and inflammation. *Carbohydr Polym*, 299, 120180.
- [20] Zhang, T., Zhong, X.-C., Feng, Z.-X., et al. (2025). An active shrinkage and antioxidative hydrogel with biomimetic mechanics functions modulates inflammation and fibrosis to promote skin regeneration. *Bioactive Materials*, 45, 322–344.
- [21] Zan, X., Yang, D., Xiao, Y., et al. (2024). Facile general injectable gelatin/metal/tea polyphenol double nanonetworks remodel wound microenvironment and accelerate healing. *Advanced Science*, 11(9), 2305405.
- [22] Du, J., Wang, F., Li, J., et al. (2023). Green polymer hydrogels from a natural monomer with inherent antioxidative capability for efficient wound healing and spinal cord injury treatment. *Biomaterials Science*, 11(10), 3683–3694.