Cell Reports
Physical Science

CellPress
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Review

Polymeric nanogels and hybrid platforms for redox modulation from ROS biology to therapeutic design

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https://doi.org/10.1016/j.xcrp.2026.103446

SUMMARY

Reactive oxygen species (ROS) play a dual role in biological systems. At physiological levels, they act as essential signaling mediators regulating immune responses, metabolism, proliferation, and differentiation. Conversely, excessive ROS production overwhelms antioxidant defenses, driving oxidative stress, inflammation, and tissue damage. Understanding the generation, spatial confinement, and kinetics of ROS is therefore critical for designing effective therapies. Conventional small-molecule scavengers show limited translational success due to poor stability, rapid clearance, and lack of targeting, while synthetic antioxidants, although more versatile, still face delivery constraints. In this context, polymeric nanogels provide hydrated nanoscale networks capable of protecting labile scavengers, hosting catalytic redox centers, and responding dynamically to ROS-rich microenvironments. However, their standalone application is often limited by insufficient retention in dynamic tissues. To overcome these limitations, hybrid systems integrating nanogels within hydrogels or composite matrices have emerged, enabling improved localization and sustained redox modulation.

INTRODUCTION

Reactive oxygen species (ROS) are a category of highly reactive molecules derived from elementary oxygen.[1] These oxidants can be in the form of free radicals, like superoxide ($O_2\cdot^-$), hydroxyl radicals (·OH), and peroxyl radicals (ROO), as well as non-radical compounds, such as hydrogen peroxide (H_2O_2) and singlet oxygen molecules ($^1O_2$).[2] They can be triggered by endogenous (mitochondrial and cellular metabolism or through inflammation) or exogenous (environmental or by delivery of nanomaterial) stimuli.[3] Depending on their concentration in living organisms, they can have dual roles.[4] At a low level, their presence is beneficial for proper physiological processes as signaling molecules that regulate, for example, immune response and cell growth.[5] Through highly specific and reversible oxidation of protein cysteine residues, particularly the conversion of Cys-S^- to sulfenic acid (Cys-SOH), ROS modulate the structure and activity of key regulatory proteins.[6] These redox-dependent modifications influence transcriptional programs, phosphorylation cascades, metabolic fluxes, and multiple intracellular signaling pathways.[7–9] Controlled ROS production is therefore required for optimal immune response activation, where an increase in mitochondrial or nicotinamide adenine dinucleotide phosphate oxidase (NOX)-derived ROS promotes the release of pro-inflammatory cytokines, including interleukin-1β (IL-1β), tumor necrosis factor alpha (TNF-α), and interferon-β (IFN-β), enabling adequate host defense.[10] Similarly, finely tuned redox signals regulate cell proliferation and differentiation. Cancer cells and several stem cell populations maintain slightly elevated ROS concentrations to activate pathways involving hypoxia-inducible factors (HIFs), phosphatidylinositol 3-kinase (PI3K), nuclear factor κB (NF-κB), and mitogen-activated protein kinases (MAPKs), thereby supporting self-renewal and growth.[11] In stem cells, low ROS levels preserve proliferative potential, whereas higher levels activate ataxia-telangiectasia mutated (ATM)-dependent checkpoints that limit renewal.[12]

The therapeutic goal of ROS-modulating biomaterials should not be interpreted as complete ROS elimination. Physiological ROS are essential signaling mediators involved in immune activation, metabolic regulation, proliferation, differentiation, angiogenesis, and tissue remodeling. Therefore, excessive or non-selective ROS depletion may impair host defense, delay tissue repair, alter stem cell behavior, or interfere with redox-dependent signaling cascades. This consideration is particularly relevant for catalytic scavengers, whose activity may persist beyond the initial oxidative insult.[13] Future polymeric systems should therefore be designed to restore redox homeostasis within a defined therapeutic window rather than to suppress ROS indiscriminately. Spatial confinement, disease-triggered activation, degradable architectures, and tunable catalytic or sacrificial capacity are key parameters to minimize interference with physiological signaling while preserving therapeutic antioxidant efficacy. Overall, these observations establish ROS not only as damaging oxidants but as indispensable regulators of cellular homeostasis, proliferation, immunity, and development, provided that their concentrations remain within the physiological redox-signaling range. When antioxidant defenses fail to maintain redox equilibrium, ROS accumulate beyond the physiological threshold and shift from signaling mediators to cytotoxic agents.[14] Under these conditions, highly reactive species, such as hydroxyl radicals, can directly oxidize DNA, RNA, proteins, and membrane lipids, compromising structural integrity and impairing essential cellular functions.[15] The degree of damage strongly depends on the specific reactivity of each ROS and on the availability of labile Fe^{2+}, which catalyzes hydroxyl-radical formation through the Fenton reaction.[16] This iron-dependent amplification of oxidative reactions represents one of the major determinants of ROS-induced toxicity.[17]

Although mammalian cells possess an extensive antioxidant network (including catalase, peroxidases, and glutathione-based systems) these defenses become insufficient when ROS production outpaces scavenging capacity.[18] The resulting accumulation of oxidized nucleic acids and proteins must be counteracted by repair pathways or removed via proteasomal degradation and autophagy.[19] When these compensatory mechanisms are overwhelmed, cellular injury ensues, and oxidative stress becomes a driving force in pathological inflammation, promoting cytokine release and accelerating tissue degeneration.[20] Interestingly, the extreme resilience of organisms such as *Deinococcus radiodurans* illustrates that ROS toxicity is not solely dictated by the amount of oxidants but by the cell's ability to control iron homeostasis, limit endogenous ROS formation, efficiently scavenge radicals, and repair or replace damaged biomolecules.[21] These systems enable some microorganisms to survive even extraordinarily high ROS levels.[22] In mammals and plants, similar principles apply; ROS-induced cellular damage is tightly modulated by antioxidative enzymes, iron-sequestering mechanisms, and robust DNA/protein repair pathways.[23,24] When these layers of protection fail, ROS no longer act as metabolic signals but instead trigger regulated death programs such as ferroptosis or necrosis-like pathways rather than simply causing passive oxidative collapse.[25,26] Excessive ROS accumulation shifts the system from physiological redox signaling to oxidative stress, leading to macromolecular damage and triggering inflammatory cascades that aggravate disease progression.[27] This redox imbalance has motivated intense research into biomaterials able to neutralize ROS or restore homeostasis.[28–30] In recent years, ROS-scavenging technologies have gained growing attention due to their ability to attenuate oxidative injury.[31] Numerous studies have demonstrated the antioxidant efficiency of these materials against oxidative stress as a crucial pathological driver.[14,32]

Targeting ROS provides two complementary opportunities. On one hand, scavenging excessive oxidants can restore redox balance, attenuate inflammation, and protect vulnerable cells, including stem cells, which are particularly sensitive to oxidative microenvironments.[33] On the other hand, the abnormally high ROS levels characteristic of inflamed or tumor tissues can be harnessed for selective and on-demand activation of therapeutic agents, enabling more precise drug delivery while minimizing off-target toxicity.[34] Polymeric nanotechnologies have rapidly emerged as ideal platforms to implement both strategies.[35] Nanoparticles, nanogels, and hydrogels can be engineered to neutralize ROS through catalytic or antioxidant functionalities or to undergo ROS-triggered degradation and drug release via cleavable linkers such as thioketals or boronic esters.[36–38] These smart systems enhance the solubility, stability, and circulation time of therapeutics while providing precise spatiotemporal control over drug activation.[39] Their modular design allows them to function as protective carriers, diagnostic tools, or ROS-responsive prodrugs capable of activating exclusively within oxidatively stressed tissues.[40] For these reasons, polymer-based nanoplatforms are emerging as some of the most powerful strategies to modulate, exploit, or correct ROS-driven biological processes.[41] However, despite rapid progress, the field remains fragmented, with ROS-scavenging systems, ROS-responsive prodrugs, and polymeric nanoarchitectures often discussed separately without a unified framework linking their mechanisms, design principles, and therapeutic potential.[42,43] This review addresses this gap by providing a comprehensive and integrated overview of polymeric nanogels, hydrogels, and hybrid systems engineered either to neutralize excessive ROS or to harness pathological oxidative environments for precise, spatiotemporally controlled drug delivery (Figure 1).

We highlight converging design strategies, structure-property relationships, and emerging biomedical applications across inflammation, cancer, and regenerative medicine, offering a consolidated perspective that is increasingly needed to guide future development of next-generation ROS-targeted therapies.

ROS IN MAJOR HUMAN DISEASES

Given the pervasive involvement of ROS across a wide spectrum of pathological conditions, an effective redox-oriented therapeutic strategy requires a precise understanding of the nature of the oxidant species involved, their spatiotemporal dynamics, and the molecular mechanisms through which they drive tissue damage.[44] Accordingly, the following section outlines how distinct ROS and redox-dependent pathways contribute to major human diseases, not as an exhaustive pathological survey but as a conceptual framework to inform the rational design of polymer-based nanogels, hydrogels, and hybrid systems tailored to

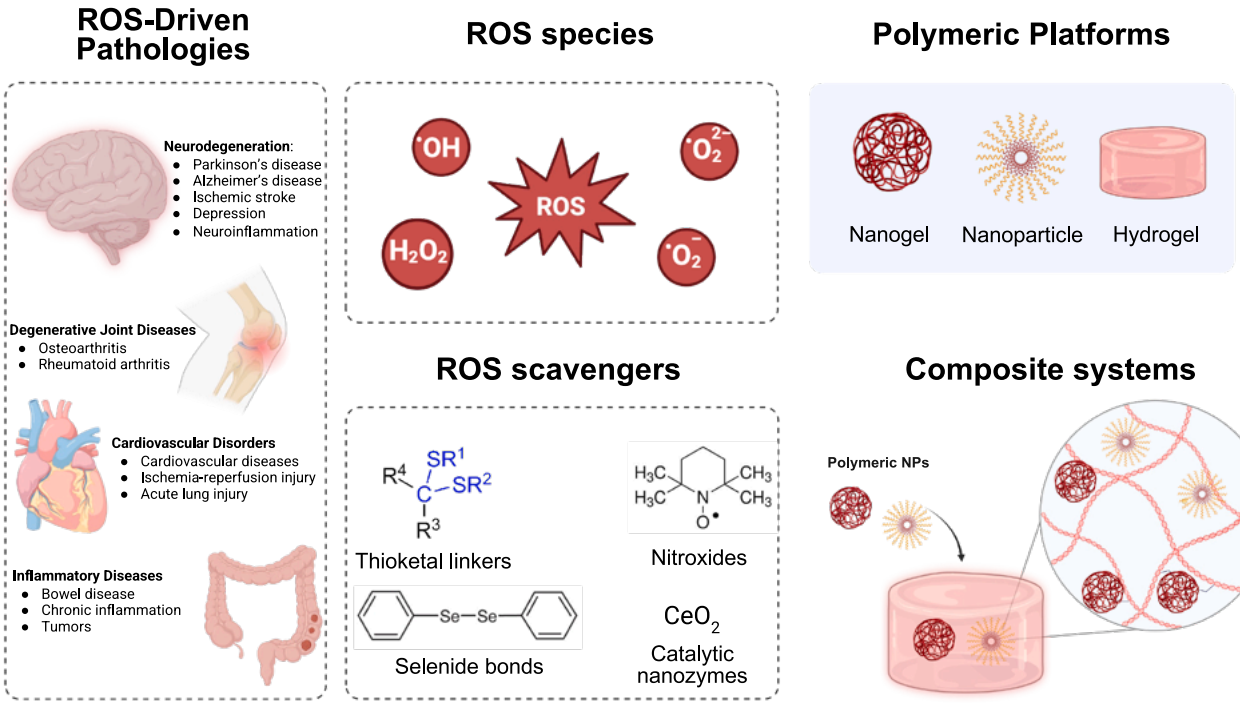

Figure 1. Overview of ROS-driven pathologies and polymeric platforms for redox modulation

Schematic representation of the main elements discussed in the review, including ROS-associated pathological conditions, representative ROS species, ROS-scavenging chemistries, and polymeric delivery platforms.

The figure summarizes how nanogels, nanoparticles, hydrogels, and composite systems can be engineered with antioxidant or ROS-responsive motifs, such as thioketal linkers, nitroxides, selenide bonds, and catalytic nanozymes, to modulate oxidative stress in disease-relevant microenvironments.

specific oxidative microenvironments. ROS are highly reactive oxidants generated during cellular metabolism and in response to environmental cues.[45] When their production exceeds the buffering capacity of endogenous antioxidant systems, oxidative stress arises, leading to damage of nucleic acids, proteins, and membrane lipids.[46] This redox imbalance disrupts signaling networks, sustains inflammation, and directly contributes to the initiation and progression of a broad spectrum of human diseases, including neurodegenerative, inflammatory, metabolic, skeletal, and cardiovascular disorders.[47] Beyond nonspecific macromolecular damage, excessive ROS actively drive regulated cell death programs.[48]

Ferroptosis is a paradigmatic example of ROS-dependent cytotoxicity, relying on iron-catalyzed lipid peroxidation rather than caspase activation.[49,50] The abstraction of hydrogen atoms from polyunsaturated phospholipids initiates self-propagating lipid radical chain reactions that culminate in membrane destabilization.[51] Under physiological conditions, enzymatic antioxidants and lipid-soluble scavengers restrain this process; however, glutathione depletion, glutathione peroxidase 4 (GPX4) dysfunction, or impaired cystine uptake via system Xc^- abolish peroxide detoxification, while expansion of the labile iron pool accelerates radical formation.[52] These converging events establish ferroptosis as a central mechanism linking oxidative stress to tissue degeneration across multiple pathological contexts.[53] Neurodegenerative disorders exemplify the pathological consequences of sustained redox imbalance.[54,55] In Alzheimer's disease, Parkinson's disease, and related dementias, high neuronal oxygen consumption combined with limited antioxidant capacity promotes the accumulation of ROS and reactive nitrogen species, impairing mitochondrial function and proteostasis.[56] In Parkinson's disease, iron deposition in the substantia nigra amplifies oxidative injury and lipid peroxidation, while ROS-mediated modification of α-synuclein enhances its aggregation.[57] Aggregated α-synuclein further compromises mitochondrial respiration, generating a self-reinforcing cycle of oxidative stress, energetic failure, and neuronal loss.[58] Similar interactions between iron dyshomeostasis, mitochondrial dysfunction, and oxidative injury are observed across neurodegenerative conditions.[59] Chronic inflammatory diseases are likewise characterized by persistent, localized oxidative stress.[60] In osteoarthritis and rheumatoid arthritis, excessive ROS production within joint tissues impairs mitochondrial function, induces chondrocyte apoptosis, and sustains inflammatory signaling.[61–64] Upregulation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase isoforms and insufficient antioxidant responses create a redox microenvironment that promotes cartilage degradation and synovial damage.[65–67]

Importantly, disease severity correlates with oxidative dysregulation, underscoring ROS as active drivers rather than secondary byproducts of inflammation.[68] Metabolic disorders further illustrate the pathological impact of prolonged oxidant overload.[69] In diabetes, chronic hyperglycemia enhances mitochondrial ROS generation and activates redox-sensitive pathways,

damaging endothelial cells, reducing nitric oxide bioavailability, and accelerating the formation of advanced glycation end products.[70] These processes contribute to microvascular complications, including nephropathy, neuropathy, and retinopathy, while excessive ROS also impair fibroblast migration and angiogenesis, delaying wound healing.[71] Similarly, in chronic inflammatory bowel diseases, excessive oxidant production by intestinal epithelial cells and infiltrating immune cells overwhelms local antioxidant defenses.[72] ROS and reactive nitrogen species damage mitochondrial enzymes, oxidize lipids, and activate NF-κB and MAPK pathways, sustaining cytokine release, epithelial barrier dysfunction, and chronic inflammation, ultimately increasing the risk of colitis-associated colorectal cancer.[73] Across these diverse pathological settings, a common theme emerges: ROS-driven damage is spatially and temporally confined to diseased tissues, sustained over time, and poorly addressed by systemic antioxidant supplementation. These features highlight the need for strategies capable of locally modulating redox homeostasis, buffering excessive oxidants, and responding dynamically to pathological ROS levels, thereby providing a strong rationale for the development of polymer-based nanogels, hydrogels, and hybrid systems designed to scavenge or exploit ROS. Despite the central role of ROS in disease, direct comparison across studies remains challenging due to the intrinsic heterogeneity of ROS detection methods.[74]

Many commonly used assays rely on indirect or proxy readouts, such as fluorogenic probes or downstream oxidative markers, which differ in sensitivity, specificity, and temporal resolution.[75] As a result, measured ROS levels often reflect integrated oxidative stress rather than individual ROS species or localized redox dynamics.[76] This methodological variability has direct consequences for the interpretation of therapeutic efficacy. Intracellular probes such as dichloro-dihydro-fluorescein diacetate (DCFH-DA) are widely used to estimate global oxidative activity, but their oxidation is indirect; can be influenced by peroxidases, metal ions, light exposure, and cellular uptake; and does not selectively identify a single ROS species.[77] Similarly, dihydroethidium (DHE) and mitochondrion-targeted derivatives such as MitoSOX are commonly used to assess superoxide production, but their interpretation requires caution because non-specific oxidation products can be generated unless appropriate analytical controls are included.[78] Cell-free assays such as 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS) and 2,2-diphenyl-1-picrylhydrazy (DPPH) provide rapid screening of electron- or hydrogen-donating antioxidant capacity, but they are performed under simplified chemical conditions that do not reproduce the spatial confinement, enzymatic regulation, protein corona formation, diffusion barriers, or continuous ROS fluxes present in biological tissues.[79] Conversely, lipid peroxidation readouts such as malondialdehyde (MDA) and thiobarbituric acid reactive substances (TBARS) report downstream oxidative damage rather than the primary ROS species responsible for material activation and can be affected by sample preparation, secondary reactions, and matrix-dependent artifacts.[80] Therefore, a reduction in DCF fluorescence, MDA/TBARS levels, or ABTS/DPPH absorbance should not automatically be interpreted as direct and species-specific ROS neutralization.[81] Future studies should combine complementary readouts, including species-oriented probes, cell-free antioxidant tests, lipid/protein oxidation markers, inflammatory biomarkers, and direct measurement of material degradation or release kinetics.

Importantly, assay conditions should be reported in detail, including ROS source, oxidant concentration, exposure time, probe concentration, calibration strategy, and biological model, to enable meaningful comparison among redox-responsive nanogels and hybrid platforms. In this context, it is also important to recognize that ROS are not interchangeable therapeutic triggers. Although they are often discussed collectively, their biological effects and suitability for material activation depend strongly on chemical identity, lifetime, diffusion range, and subcellular localization.[82] $O_2{\cdot}^-$ is primarily generated by mitochondria and NADPH oxidases and has a short lifetime and limited diffusion because of its charged nature and rapid dismutation.[83] It therefore acts mainly near its site of production and is particularly relevant for catalytic systems able to mimic superoxide dismutase activity, such as manganese-based complexes, cerium oxide, Prussian blue, and nitroxide-bearing materials. H_2O_2 is the most quantitatively tractable species because it is comparatively more stable than radical ROS, can diffuse across biological membranes, and acts as a central mediator of redox signaling.[84] Physiological H_2O_2-dependent signaling is generally associated with low steady-state concentrations in the nanomolar range, commonly reported to be around 1–10 nM, whereas higher concentrations, above approximately 100 nM, are typically associated with adaptive stress responses or oxidative distress.[85] However, even for H_2O_2, these values should be interpreted as order-of-magnitude references rather than universal thresholds because the concentration experienced by a molecular target depends on the compartment; distance from the source; local antioxidant buffering; membrane permeability; enzymatic sinks such as peroxiredoxins, glutathione peroxidases, and catalase; and the analytical method used for detection.[86] For shorter-lived oxidants, this limitation is even more pronounced. ·OH are extremely reactive and react almost immediately at the site where they are formed, typically through Fenton-type chemistry involving labile iron or copper. Therefore, direct "targeting" of ·OH by a material is intrinsically difficult; more realistic strategies aim to prevent its upstream formation by reducing H_2O_2 availability, chelating redox-active metals, or introducing radical-quenching motifs such as nitroxides or polyphenols. Lipid peroxides and lipid-derived radicals are instead spatially confined to membranes and lipoprotein-rich domains and are central mediators of ferroptosis, making lipophilic radical-trapping antioxidants, selenium-containing motifs and GPX-like catalytic systems more appropriate than generic hydrophilic scavengers.[87] Finally, peroxynitrite ($ONOO^-$), generated from the diffusion-controlled reaction between $O_2{\cdot}^-$ and nitric oxide, combines oxidative and nitrative reactivity and is particularly relevant in inflammatory and neuroinflammatory environments, where oxidative and nitrosative stress coexist; in this case, dual ROS/reactive nitrogen species (RNS)-scavenging chemistries may be required.[88] From a materials design perspective, this species-dependent behavior has two important consequences. First, polymeric platforms should not be described generically as "ROS responsive" without specifying the oxidant species, concentration range, exposure time, and detection method

used to demonstrate responsiveness. Many polymer degradation or release studies employ exogenous H_2O_2 challenges in the micromolar to millimolar range to accelerate cleavage, swelling, or payload release.[89,90] These assays are useful to prove chemical oxidizability, but they do not necessarily reproduce physiological redox signaling or the local oxidative microenvironment of diseased tissues. Second, the selection of the responsive chemistry should reflect the spatial and temporal properties of the target oxidant. Catalytic systems are more suitable for sustained and continuously regenerated oxidative stress, whereas sacrificial chemistries such as thioketals, boronic esters, thioethers, selenides, and diselenides are more appropriate when oxidative bursts are intended to trigger network degradation or drug release.

Therefore, the rational design of ROS-modulating polymeric systems requires matching oxidant identity, local concentration, lifetime, compartmentalization, and material-response kinetics rather than relying only on broad antioxidant capacity.

MOLECULES WITH ROS-SCAVENGING ACTIVITY

Understanding the mechanisms through which ROS-scavenging and ROS-responsive molecules operate is essential to rationally design and functionalize polymeric nanosystems. Identifying how different chemical motifs interact with specific oxidant species provides the foundation for tailoring nanogels, hydrogels, and hybrid platforms capable of modulating pathological redox microenvironments. ROS scavengers comprise a wide spectrum of molecules capable of neutralizing oxidative stress, restoring redox balance, and limiting cellular injury. Classically, they are divided into endogenous and exogenous antioxidants.[91] Endogenous scavengers constitute the intrinsic defense network of the organism and include enzymatic systems such as superoxide dismutase, catalase, and glutathione reductase as well as non-enzymatic components such as glutathione, bilirubin, uric acid, melatonin, polyamines, and metal-binding proteins.[92,93] Exogenous antioxidants are predominantly obtained from the diet and encompass vitamins A, C and E together with polyphenols, carotenoids, flavonoids, and trace minerals.[94] Beyond physiological and nutritional defenses, a broad class of synthetic ROS scavengers has gained increasing relevance in biomedical engineering.[95] These compounds are rationally designed to mimic or enhance natural antioxidant functions, with mechanisms that depend on their molecular structure, redox activity, and catalytic properties. Based on their composition, synthetic scavengers can be broadly categorized into inorganic materials and organic small molecules.[96,97]

Importantly, this distinction is not merely chemical but reflects fundamentally different modes of ROS interaction, stability, and turnover, which are directly relevant for their integration into nanoscale delivery systems.[98] Inorganic scavengers introduce a level of catalytic robustness and redox tunability that extends beyond classic organic antioxidants.[99] Manganese-based compounds are a well-established family of catalytic scavengers in which porphyrin ligands stabilize the Mn^{2+}/Mn^{3+} redox cycle, enabling efficient superoxide dismutation and peroxide reduction.[100] Cationic manganese porphyrins have been shown to attenuate oxidative stress and apoptosis in models of spinal cord injury, although without full functional recovery.[101] A related compound, MnTnBuOE-2-PyP^{5+} (BMX-001), demonstrated pronounced anti-inflammatory and antioxidant effects in ischemic stroke by suppressing macrophage-driven oxidative bursts with minimal local toxicity, highlighting the translational potential of catalytic metal-based scavengers.[102] Among inorganic nanomaterials, Prussian blue nanoparticles exhibit enzyme-mimetic activities resembling superoxide dismutase, catalase, and peroxidase, enabling broad-spectrum ROS detoxification.[103] These materials significantly reduce lipid peroxidation and suppress inflammatory mediators such as TNF, IL-1β, IL-6, and inducible nitric oxide synthase (NOS2), protecting tissues from oxidative injury.[104] Similarly, cerium oxide nanoparticles have emerged as highly effective synthetic scavengers owing to their reversible Ce^{3+}/Ce^{4+} redox cycling, sustained by oxygen vacancies within the crystalline lattice.[105] This self-regenerating redox behavior enables catalytic neutralization of superoxide, hydrogen peroxide, and hydroxyl radicals, conferring prolonged activity compared to conventional antioxidants, which are rapidly consumed under oxidative stress.[106] In parallel, organic antioxidants encompass a diverse group of small molecules capable of directly quenching radical species or indirectly restoring redox balance through metabolic and signaling pathways.[107]

Nitroxides such as (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) efficiently neutralize hydroxyl radicals, superoxide, and hydrogen peroxide via a superoxide dismutase-like catalytic cycle without being irreversibly consumed.[108] However, their clinical application is limited by rapid diffusion and a short biological half-life.[109,110] To overcome these limitations, strategies such as tethering TEMPO to biomaterials or confining it within polymeric matrices have been developed.[110] For instance, TEMPO-functionalized hydrogels engineered for cardiovascular implants enable sustained nitroxide retention, reduce hydroxyl radical accumulation, and attenuate pro-inflammatory cytokine secretion, illustrating how material integration can extend antioxidant efficacy.[111] Subcellular targeting further enhances nitroxide performance.[112] Mito-TEMPO, designed to accumulate within mitochondria, mitigates oxidative damage associated with severe hypoglycemia by preserving mitochondrial function, reducing blood-brain barrier leakage, and improving ATP production.[113] Its derivative Tempol, characterized by enhanced water solubility and biocompatibility, has demonstrated protective activity in osteoarthritis by reducing cartilage degradation, restoring endogenous antioxidant enzyme activity, and suppressing inflammatory cytokines.[114] Tempol has also shown neuroprotective effects in cisplatin-induced cerebellar toxicity, where it limits neuronal loss and preserves synaptic organization.[115] Recent advances extend beyond single-function scavengers toward dual-action molecules capable of neutralizing both ROS and reactive nitrogen species. These systems combine antioxidant and NO-scavenging moieties within a single molecular framework, enabling more effective attenuation of oxidative and nitrosative stress.[116] In selenized and thiolated systems encapsulating *trans*-resveratrol for gastrointestinal applications, selenium and thiol groups participate in redox cycles that directly scavenge peroxides and peroxynitrite, reducing inflammation and cytotoxicity in both cellular and animal models.[117,118]

Table 1. Quantitative benchmarking of representative ROS-scavenging and ROS-responsive systems

System	Strategy	Assay/model	Experimental conditions	Quantitative benchmark	Comment
MnTnBuOE-2-PyP^{5+}/BMX-001 manganese porphyrin[102]	catalytic ROS/RNS-scavenging redox modulator	mouse intracerebral hemorrhage model	BMX-001 administered immediately after collagenase-induced ICH; analysis at 72 h	Macrophages in hemorrhagic area decreased from 48 ± 10 to 33 ± 8 cells; Prussian-blue-positive cells decreased from 65 ± 22 to 41 ± 15.	*In vivo* anti-inflammatory/iron-associated oxidative injury endpoint, not direct ROS-scavenging potency.
poly(DMA-co-TEMPO) copolymer, 40T[109]	polymeric ROS-scavenging system	carrageenan-induced air pouch model	5 mg polymer/animal; TEMPO dose matched at 8.48 μmol/animal	After 6 h, retention was 0% for Tempol, ∼12% for 40T, and ∼94% for 100T. 40T reduced O_2^- and TNF-α levels in the air pouch by ∼90% and ∼83%, respectively.	Shows that optimized TEMPO density, rather than maximum TEMPO loading, controls *in vivo* efficacy.
TEMPO-loaded hydrogel-modified pericardium, PSD5:5GM-TEMPO/VEGF[110]	ROS-responsive release + ROS scavenging	H_2O_2-triggered TEMPO release and Fenton-based OH scavenging	TEMPO released under 10 μM H_2O_2; OH scavenging measured using Fenton reaction	TEMPO loading capacity: 10.84 ± 3.79 μg cm^{-2}. Under 10 μM H_2O_2, cumulative TEMPO release reached ∼60% at 96 h and ∼85% at 12 days. Maximum OH scavenging approached ∼70%.	Combines mild H_2O_2-triggered release with radical scavenging.
Tempo-FPF Janus hydrogel[111]	ROS-scavenging hydrogel	DPPH, ABTS, and OH scavenging assays	Hydrogel concentration: 18 mg mL^{-1}; DPPH at 37°C for 60 min; ABTS for 10 min; OH at 37°C for 30 min	DPPH scavenging: 77.8 ± 0.1%; ABTS scavenging: 98.2%; OH elimination: 81.3 ± 0.2%. PFP control: 19.9 ± 0.8%, 24.0% and 24.9 ± 0.6%, respectively.	Strong cell-free antioxidant benchmark.
Selenized thiolated alginate nanogel loaded with *trans*-resveratrol, Ngel-3@Res[117]	ROS-scavenging nanogel	cell-free OH, DPPH, and ABTS assays after simulated gastrointestinal digestion	OH assay based on Fenton reaction; DPPH and ABTS radical assays; *C. elegans* oxidative stress model with 40 mM H_2O_2	After digestion, Ngel-3@Res showed OH clearance of 99.11% ± 0.61%, DPPH clearance of 55.11% ± 0.56%, and ABTS clearance of 59.88% ± 0.80%. Mean survival under H_2O_2 stress increased from 2.00 ± 0.36 h to 3.20 ± 0.32 h.	Good radical-scavenging benchmark, but cell-free and biological survival assays are not directly comparable.

(*Continued on next page*)

Table 1. *Continued*

System	Strategy	Assay/model	Experimental conditions	Quantitative benchmark	Comment
Celecoxib-loaded CMCs/Alg microbeads[118]	anti-inflammatory delivery with indirect redox modulation	LPS-stimulated HCT-116 cells	Cele/CMCs/Alg tested at 100–250 μM; NO measured by Griess assay; ROS assessed by H_2-DCFDA	Mucoadhesivity: 59.32 ± 0.74%. Non-toxic range: 100–250 μM. Cele-250 μM/CMCs/Alg reduced NO generation by 61.14% ± 3.67%. Drug release sustained up to 24 h.	Not a direct ROS scavenger; useful as inflammatory/redox-modulating delivery benchmark.

Values are reported as assay-specific benchmarks and should not be interpreted as directly comparable potency rankings because the cited studies used different ROS/RNS sources, concentrations, exposure times, detection methods, and biological models.

Building on the systems discussed above, ROS-scavenging and ROS-responsive strategies can be regarded as two complementary but mechanistically different approaches to redox modulation. ROS-scavenging systems are designed to directly neutralize excessive oxidants or catalytically convert them into less reactive species, thereby restoring redox homeostasis. This category includes small-molecule antioxidants, nitroxides, polyphenols, manganese porphyrins, cerium oxide, and Prussian blue nanozymes as well as polymeric systems bearing antioxidant or catalytic motifs. Their main advantage is the direct attenuation of oxidative stress, which is particularly relevant in chronic inflammation, neurodegeneration, osteoarthritis, cardiovascular injury, and wound healing. However, excessive or non-localized scavenging may interfere with physiological ROS signaling, and catalytic systems require careful evaluation of persistence, off-target activity, and long-term safety. ROS-responsive systems, in contrast, do not primarily act by continuously removing oxidants but exploit pathological ROS as biochemical triggers for bond cleavage, network degradation, swelling, solubility changes, payload release, or prodrug activation. Typical chemistries include thioketals, boronic esters, thioethers, selenides, diselenides, and other oxidizable motifs. These systems are especially useful when ROS-rich microenvironments are used to achieve spatially and temporally controlled therapy; for example, in inflamed tissues, tumors, or acute oxidative bursts. Their main limitation is that responsiveness depends strongly on the local ROS concentration, exposure time, and oxidant identity, and some systems are activated only under exogenous H_2O_2 concentrations higher than those present in physiological redox signaling. Importantly, the two strategies are not mutually exclusive. Several advanced platforms combine ROS-cleavable linkers with catalytic or sacrificial scavenging motifs, enabling simultaneous oxidative stress attenuation and on-demand therapeutic release. Representative systems and quantitative assay-specific benchmarks are summarized in Table 1.

Collectively, these examples illustrate the chemical diversity and mechanistic versatility of molecular ROS scavengers while also highlighting their intrinsic limitations, including limited stability, rapid clearance, and suboptimal localization. These constraints have driven the development of polymeric and nanostructured ROS-scavenging systems, which offer improved retention, controlled presentation of scavenging motifs, enhanced catalytic turnover, and selective activity within pathological microenvironments.

POTENTIAL POLYMERIC DELIVERY SYSTEMS FOR ROS SCAVENGERS

In recent years, a wide variety of biomaterials have been explored for their ability to scavenge ROS and alleviate oxidative stress-related damage.[119–121] Among these, polymeric systems such as nanoparticles, nanogels, and hydrogels have attracted particular attention (Figure 2).

Their three-dimensional networks and tunable compositions indeed allow incorporation of ROS-scavenging moieties or catalytic nanoparticles while providing controlled therapeutic release.

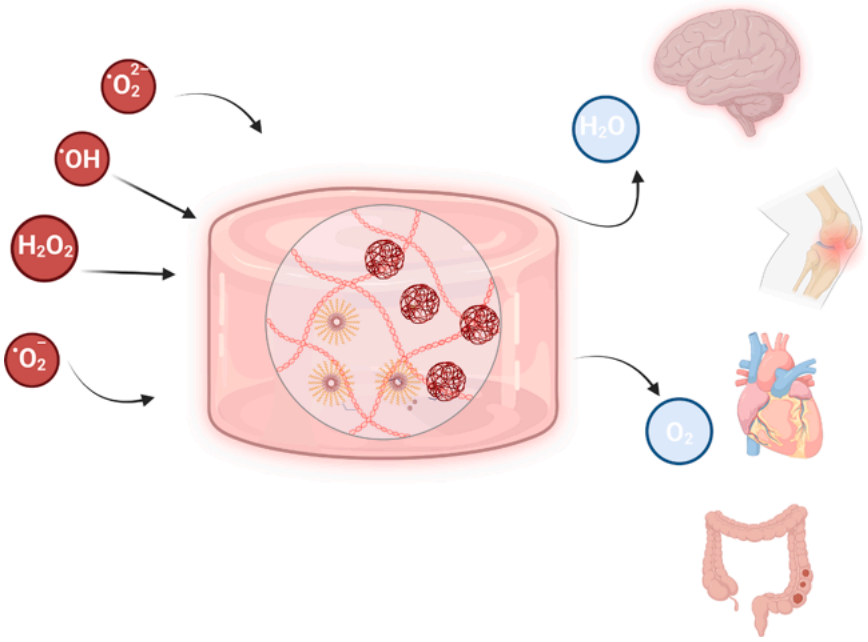

Figure 2. ROS-scavenging composite hydrogel for redox homeostasis restoration

Schematic representation of a polymeric hydrogel/nanogel composite designed to regulate oxidative stress.

Reactive oxygen species, including hydroxyl radicals (OH), superoxide ($O_2^{\cdot-}$), and hydrogen peroxide (H_2O_2), are intercepted by the redox-active network containing embedded nanogels and antioxidant/catalytic components. The platform promotes ROS scavenging or conversion into less reactive species, such as H_2O and O_2, supporting localized redox modulation in pathological microenvironments associated with neurodegeneration, joint inflammation, cardiovascular injury, and intestinal inflammatory diseases.

Metal oxide and polymer-based nanoparticles can mimic antioxidant enzyme activity, and nanogel- or hydrogel-based platforms offer hydrated networks that enable localized and sustained ROS regulation.[122,123] The same polymeric architectures can be readily engineered to respond to additional pathological cues, including pH variations, temperature changes, or enzymatic activity, enabling the development of multi-responsive platforms that integrate redox regulation with broader microenvironmental sensing.[124,125] Before discussing polymeric delivery systems, it is useful to frame the diversity of ROS involved in different pathological contexts and to relate each ROS type to its dominant biological effects, experimental models, and available scavenging strategies. As summarized in Table 2, distinct ROS species differ in reactivity, lifetime, and cellular localization, imposing specific constraints on the chemistry and architecture of polymeric systems designed to modulate oxidative stress.

Nanogels as redox interfaces

Within the broader landscape of redox-modulating strategies, nanogels occupy a specific position that should be distinguished from other antioxidant delivery or ROS-regulating approaches. Small-molecule antioxidants and redox modulators remain attractive because of their chemical simplicity, defined structures, and established pharmacological profiles, but their therapeutic performance is often limited by rapid clearance, poor localization, and insufficient control over the spatial and temporal dynamics of ROS-rich microenvironments.[126] Liposomes and polymeric micelles can improve the solubility and delivery of hydrophobic antioxidants, although premature leakage, dilution-induced instability, and limited control over ROS-triggered degradation may reduce their efficacy unless specific responsive motifs are introduced.[127,128]

Exosomes and extracellular vesicles offer biological communication properties and potential tissue tropism, but their heterogeneity, loading reproducibility, storage stability, and large-scale production remain challenging.[129] Inorganic nanoparticles and nanozymes, including cerium oxide, Prussian blue, and manganese-based systems, provide robust catalytic ROS-scavenging activity, but their long-term persistence, biodegradation, metal-related toxicity, and fate after repeated administration require careful assessment.[130] Finally, gene-based strategies targeting antioxidant pathways such as Nrf2, GPX4, or NOX can modulate redox homeostasis upstream but involve more complex delivery, safety, and regulatory issues and may be less suited to transient, localized ROS buffering.[131] In this context, nanogels offer genuine advantages when redox modulation requires a hydrated, deformable, and chemically tunable nanoscale network rather than only a molecular antioxidant or a passive carrier. Their cross-linked architecture allows the simultaneous incorporation of catalytic centers, sacrificial ROS-cleavable motifs, antioxidant molecules, and therapeutic payloads, while mesh size, charge, degradability, and surface chemistry can be adjusted to control diffusion, retention, and release.[132] Compared with liposomes or micelles, nanogels can provide stronger structural integrity and a more direct coupling between oxidative cues and network swelling, degradation, or payload release.[133,134] Compared with inorganic nanozymes, polymeric nanogels can improve colloidal stability, reduce uncontrolled aggregation, and introduce degradable or excretable components.[135] Compared with free antioxidants, they can enhance local residence time and protect labile scavengers from premature degradation. However, nanogels are not universally superior Their advantages become most relevant when localized, sustained, and disease-responsive redox modulation is required, particularly in tissues where free molecules would be rapidly cleared and where macroscopic matrices such as hydrogels or scaffolds can further improve retention.

For these reasons, nanogels have emerged as some of the most versatile polymeric platforms for the modulation of oxidative stress.[136–138] Nanogels are nanoscale, three-dimensional polymer networks that combine the high-water content, softness, and molecular permeability of hydrogels with the colloidal

Table 2. ROS in physiology and disease: Detection, modulation strategies, and polymeric delivery platforms

ROS species	Physiological role/ pathological context	Representative diseases or conditions	Common *in vitro* ROS models/stimuli	Representative scavengers or redox motifs	Polymeric platforms highlighted in this review
Superoxide (O_2^-)	signaling in immune response and mitochondrial function, excessive levels drive oxidative stress and inflammation	Parkinson's disease, Alzheimer's disease, cardiovascular diseases, ischemia-reperfusion injury	mitochondrial stress, rotenone or MPTP treatment, LPS stimulation	Mn-porphyrins, nitroxides (TEMPO, Tempol), CeO_2 nanozymes	nitroxide-bearing nanogels, ceria-loaded nanogels, nanogel-hydrogel composites for sustained scavenging
Hydrogen peroxide (H_2O_2)	second messenger in redox signaling, high concentrations induce oxidative damage and trigger inflammatory cascades	osteoarthritis, rheumatoid arthritis, depression, acute lung injury, chronic wounds	direct H_2O_2 exposure, NOX activation, inflammatory cytokine stimulation	thioketal linkers, diselenide bonds, boronic esters, selenium-containing motifs	ROS-cleavable nanogels (thioketal, diselenide), H_2O_2-responsive hydrogels, nanogel-hydrogel hybrids
Hydroxyl radical (OH)	no physiological signaling role; highly cytotoxic, induces lipid peroxidation and DNA damage	ischemic stroke, neurodegeneration, acute inflammatory injury	Fenton reaction (Fe^{2+}/H_2O_2), oxidative burst models	nitroxides, polyphenols, catalytic nanozymes	nanogels with sacrificial scavenging motifs, catalytic nanozyme-based polymeric systems
Lipid peroxides/lipid radicals (ROO, LOOH)	minimal physiological role, central mediators of ferroptosis and membrane damage	neurodegenerative diseases, ischemic injury, cardiovascular disorders	erastin-induced ferroptosis, iron overload, oxidative stress models	selenium-based motifs, GPX4-supporting systems; polyphenols	diselenide-crosslinked nanogels, nanozyme-loaded nanogels targeting ferroptotic pathways
Reactive nitrogen species (e.g., $ONOO^-$)	modulate inflammatory signaling; excessive levels cause nitrosative stress	inflammatory bowel disease, rheumatoid arthritis, neuroinflammation	iNOS induction, inflammatory cytokines, NO donors	dual ROS/RNS scavengers, selenium- and thiol-containing systems	dual-function nanogels and hybrid polymeric platforms
Mixed ROS microenvironments	controlled redox signaling vs. pathological oxidative imbalance	tumors, chronic inflammation, diabetic wounds, osteoarthritis	LPS, hypoxia-reoxygenation, chronic inflammatory stimulation	combined antioxidant and catalytic motifs	combined nanogel-hydrogel systems, nanogel-nanofiber scaffolds for prolonged retention and redox control

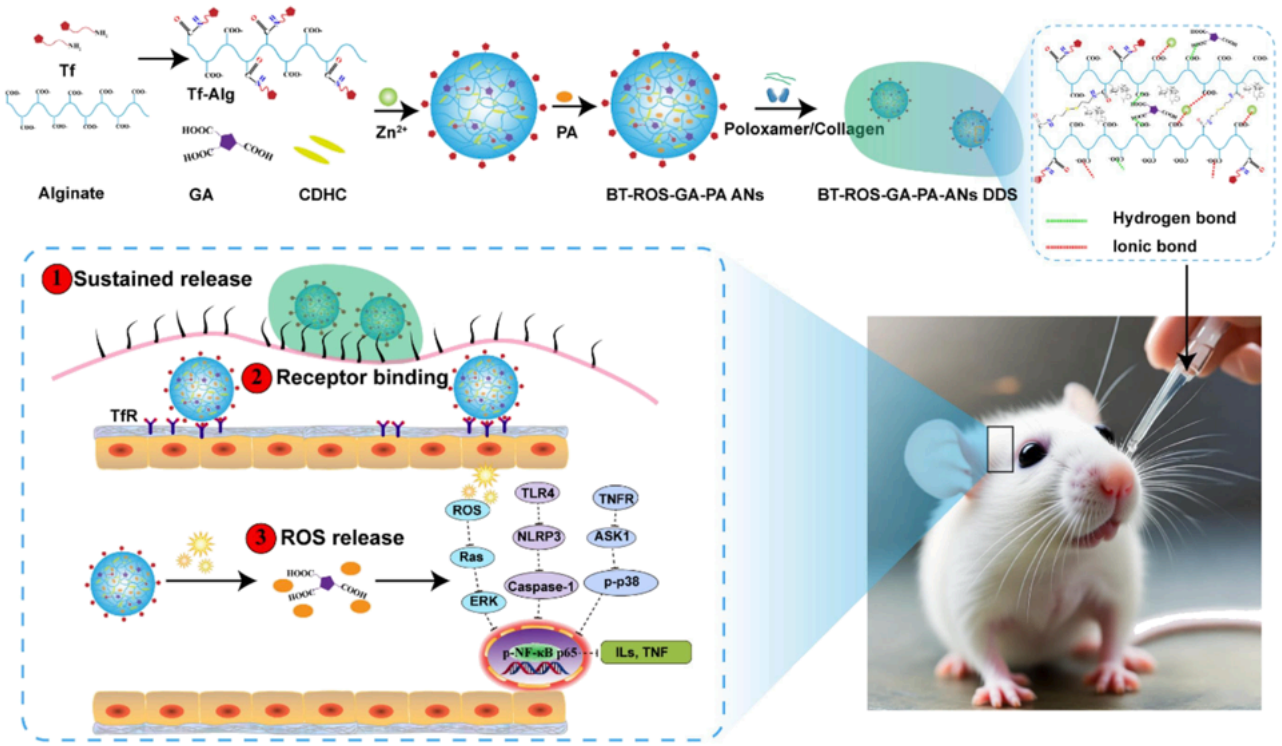

Figure 3. Brain-targeted ROS-responsive polysaccharide nanogels for antidepressant therapy

Schematic representation of a transferrin-modified polysaccharide nanogel designed for nose-to-brain delivery and ROS-responsive drug release in the hippocampal microenvironment.

The nanogel promotes antioxidant and anti-inflammatory effects by reducing ROS levels and inflammatory mediators, thereby contributing to the improvement of depression-related pathological features.

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dimensions and transport properties of nanoparticles.[139] Their highly hydrated crosslinked networks can protect labile antioxidants from premature degradation, while tunable nanoscale dimensions and chemistry enable access to disease-specific microenvironments characterized by elevated superoxide, hydrogen peroxide, and lipid peroxides.[140–142] From a synthesis perspective, nanogels are commonly prepared from natural polymers such as alginate, chitosan, hyaluronic acid, and gelatin or from synthetic building blocks such as polyethylene glycol (PEG), polyvinyl alcohol (PVA), polyethylenimine (PEI)/polyamidoamine (PAMAM) dendrimers, and poly(meth)acrylates, using preparation methods that include covalent or dynamic crosslinking, ionic gelation, and emulsion/inverse emulsion polymerization.[143] Across the available studies, nanogels are not simply passive depots. They function as active redox interfaces that bind, transform, or spatially confine ROS while simultaneously coordinating therapeutic release in response to oxidative or inflammatory cues that characterize each disease setting.[144] Several contributions first establish "platform" nanogels in which the network is intrinsically ROS responsive and already endowed with antioxidant capacity.[145] A closely related strategy is represented by dendrimer-based nanogels in which the crosslinker itself confers ROS responsiveness and intrinsic radical-scavenging activity.[146] In the thioketal-cross-linked platform, generated via flash nanoprecipitation of PAMAM dendrimers with an N-hydroxysuccinimide (NHS)-activated thioketal linker, the resulting compact nanogels undergo fragmentation upon exposure to peroxide-rich environments and simultaneously quench 2,2-diphenyl-1-picrylhydrazyl (DPPH·), hydroxyl radicals, and hydrogen peroxide in dose-dependent scavenging assays.

These nanogels display negligible cytotoxicity in macrophage and lens epithelial cells, confirming that the redox-responsive crosslinking motif enables both ROS-triggered destabilization and antioxidant action without compromising biocompatibility. In a different architecture, nitroxide-bearing reversible addition-fragmentation chain transfer (RAFT)-derived nanogels and related diselenide-crosslinked systems translate the same idea into soft, water-swollen networks.[147] In these platforms, nitroxide or Se–Se motifs act as sacrificial sinks for superoxide and peroxides, while the nanogel matrix behaves as a depot for drugs or genes. Beyond intrinsic ROS-scavenging activity, these nanogels stabilize low-density lipoproteins (LDLs) against oxidation for up to 1 month, a functional outcome that places them among promising candidates for early-stage cardiovascular intervention, particularly in atherosclerosis, where oxidized LDL is a primary pathogenic trigger. These platform studies mainly focus on physicochemical characterization and cell-level oxidative challenges, but they define a design space in which nanogels act as combined sensors and scavengers, loosening or

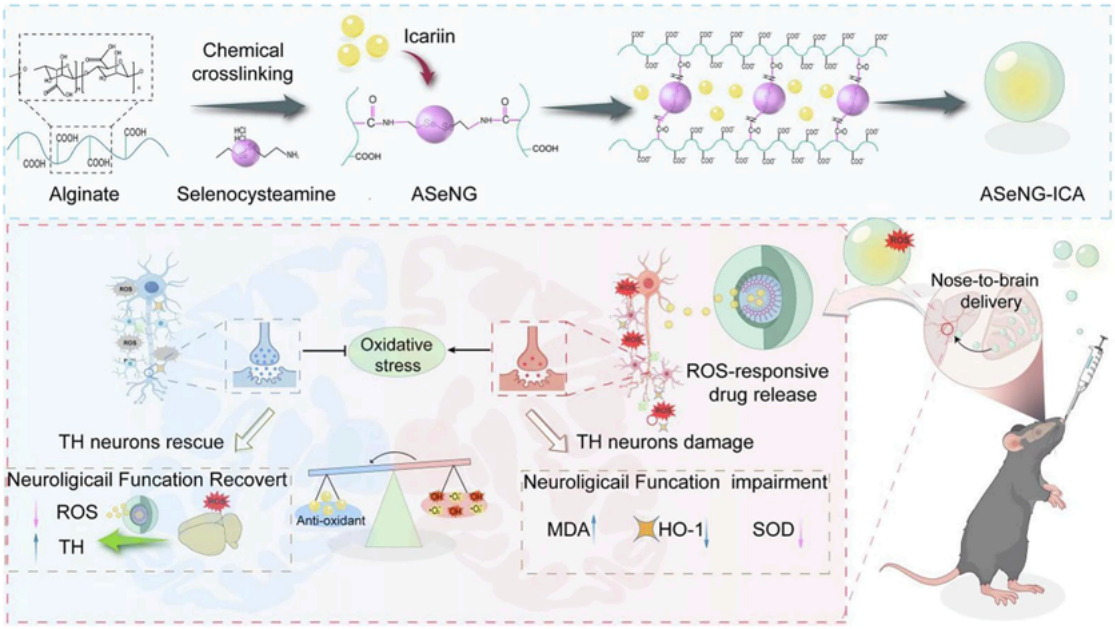

Figure 4. ROS-responsive selenized-alginate nanogels for nose-to-brain delivery in Parkinson's disease

Schematic representation of selenized-alginate nanogels loaded with icariin (ASeNG-ICA) and designed for intranasal administration and brain-targeted delivery. The selenium-containing nanogel network enables ROS-responsive behavior in oxidative microenvironments, supporting drug release, attenuation of oxidative stress and neuroinflammation, and protection of dopaminergic neurons in Parkinson's disease-related pathological conditions.
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disassembling their network as ROS levels rise. Other studies extend this toolbox by matching nanogel chemistry to organ-specific oxidative microenvironments.[148,149] In the central nervous system, a transferrin- and disulfide-modified alginate nanogel (BT-ROS-GA-PA ANs; biotin-conjugated [BT], reactive oxygen species [ROS]-responsive nanogel designed to deliver two active compounds: glycyrrhizinic acid [GA] and paeoniflorin [PA]) was engineered to deliver glycyrrhizic acid and paeoniflorin to the hippocampus in a chronic unpredictable mild stress (CUMS) model of depression.[150] Disulfide bridges impart H_2O_2-sensitive swelling and drug release, while transferrin grafting promotes receptor-mediated transport across the blood-brain barrier and accumulation in ROS-enriched hippocampal regions. Intranasal administration is particularly advantageous for neurological diseases, as it enables direct nose-to-brain delivery while bypassing the blood-brain barrier and reducing systemic exposure.[151]

In vivo, intranasal administration of the thermosensitive BT-ROS-GA-PA nanogel increases hippocampal drug levels compared to oral delivery (Figure 3), lowers ROS content, and decreases IL-6, TNF-α, and prostaglandin E_2 (PGE_2) together with behavioral endpoints of depression, indicating that ROS-responsive release *in situ* can rebalance both oxidative and inflammatory components of the CUMS phenotype.

A complementary nose-to-brain strategy is exemplified by the selenized alginate nanogel developed for brain-targeted delivery of icariin in Parkinson's disease.[152] Here, diselenide crosslinks function as ROS-responsive gates. In peroxide-rich milieus, Se–Se bonds undergo selective cleavage, accelerating drug release while generating transient selenium intermediates that contribute to neutralizing oxidants (Figure 4). This redox-coupled release is paired with improved brain penetration, with biodistribution indicating higher accumulation of icariin in the striatum and substantia nigra compared to the free drug.[153] At the cellular level, the formulation restores mitochondrial homeostasis, recovering membrane potential, complex I activity, and ATP production while reducing DCF-detected ROS and malondialdehyde and increasing superoxide dismutase (SOD) and glutathione peroxidase. In the mitochondrial permeability transition pore (MPTP) mouse model, intranasal administration attenuates dopaminergic neuron loss, preserves helper T cells (TH)-positive fiber density, and improves motor performance across rotarod, pole, and open field tests.

Beyond neurodegeneration, diselenide-rich nanogels have also been adapted to tumor immunotherapy.[154] The platform leverages the dynamic cleavage and re-formation of Se–Se and Se–O bonds to couple ROS-responsive behavior with immunomodulation.[155] Under oxidative stress, abundant in MC38 colorectal tumors, selenium-based bonds undergo reversible scission, promoting siPD-L1 release while attenuating local ROS (Figure 5). This dual action enhances PD-L1 silencing, suppresses autophagy-mediated immune evasion, and boosts $CD8^+$ T cell infiltration. *In vivo*, systemic administration results in significant tumor growth inhibition with reduced oxidative burden and minimal off-target toxicity.

Cerium-based nanosystems appear in mechanistically distinct configurations addressing neurodegeneration and pulmonary inflammation, respectively.[156,157] A catalytic variation of this

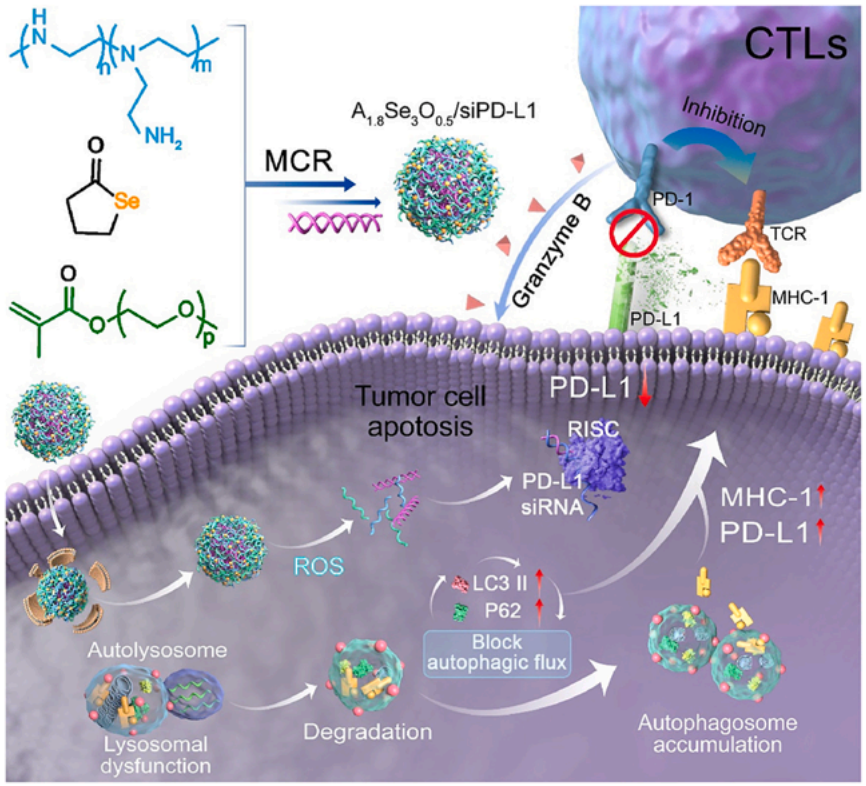

Figure 5. Schematic illustration of the preparation and antitumor mechanisms of the nanogels

Nanogels with three features (ROS sensitivity, proton sponge ability, and biocompatibility) were synthesized using selenol chemistry-mediated multicomponent reaction (MCR) technology with LMW PEI, γ-SBL, and PEGMA. After electrostatic complexation with siRNA, nanogels were formed. These nanogels demonstrated improved uptake by tumor cells and underwent endosomal escape and siRNA release in an intracellular oxidative environment, resulting in the downregulation of PD-L1 and increased expression of major histocompatibility complex class I (MHC-I). Ultimately, CD8+T cells are activated and induce tumor cell death by secreting granzyme B. ROS-sensitive $A_{1.8}Se_3O_{0.5}$/siPD-L1 nanogels: synthesis and antitumor mechanism.

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rationale is represented by hyaluronic acid nanogels co-loading citric acid-coated cerium nanozyme with the neuropeptide chimeric antigen receptor T-cell (CART) for Alzheimer's disease.[158] Here, CeO_2 domains exploit Ce^{3+}/Ce^{4+} cycling to decompose superoxide and hydrogen peroxide, while hyaluronic acid contributes targeting and CART provides neuroprotective signaling (Figure 6). The formulation suppresses $ABTS^+$ and DPPH radical signals and decreases intracellular ROS and lipid peroxidation. It also mitigates ferroptosis-associated readouts such as HO-1 upregulation and iron-induced neuronal loss. In APP/PS1 transgenic mice, treatment reduces amyloid-associated oxidative stress, improves synaptic integrity, and rescues cognitive performance, illustrating how nanozyme-based ROS modulation can be integrated with peptide therapeutics in a nanogel scaffold.[159]

A second, mechanistically distinct cerium-based platform addresses the rapidly escalating oxidative burden characteristic of acute lung injury.[160] Curcumin-loaded ceria nanoenzymes combine Ce^{3+}/Ce^{4+}-mediated detoxification of superoxide and peroxides with the anti-inflammatory action of curcumin, improving curcumin dispersion and retention in inflamed pulmonary tissue. In lipopolysaccharide-induced acute lung injury, the formulated nanoenzymes reduce DHE-detected superoxide and malondialdehyde, restore SOD and catalase activities, and suppress TNF-α, IL-1β, and IL-6. Histologically, they alleviate alveolar wall thickening, edema, and inflammatory infiltration more effectively than free curcumin or CeO_2 alone. Cardiovascular applications highlight the importance of tuning both release and radical selectivity. Alginate-chitosan nanogels loaded with an ethyl acetate fraction of *Olea ferruginea* (EAF-AC-NGs) are designed to stabilize polyphenolic antioxidants and to target ROS-driven cardiac hypertrophy.[161] Encapsulation increases particle size from about 50 to 110 nm and yields high entrapment efficiency, while *in vivo*, the formulation restores superoxide dismutase and catalase activities suppressed in isoproterenol-induced hypertrophy, reduces myocardial H_2O_2 and malondialdehyde, and lowers BAX expression more effectively than the free plant fraction, with histology confirming improved preservation of myocardial architecture (Figure 7). From a formulation perspective, such size ranges and dispersity could be further refined using microfluidic or flow-assisted fabrication strategies, enabling tighter control over nanogel dimensions and batch-to-batch reproducibility[162]

In a murine middle cerebral artery occlusion (MCAO) model, these nanogels accumulate in the ischemic penumbra and thrombus regions enriched in P-selectin.[163]

Upon H_2O_2 exposure, phenylboronic ester and Se–Se motifs undergo sequential cleavage, triggering urokinase release alongside peroxide scavenging.[164] In *in vivo* models, treatment reduces infarct volume on 2,3,5-triphenyltetrazolium chloride (TTC) staining, lowers tissue iron and lipid peroxidation, restores GPX4 levels, and improves neurological deficit scores, indicating combined thrombolytic and anti-ferroptotic activity. Barrier tissues provide further examples of how ROS-responsive nanogels can be adapted to local delivery and retention constraints. In the cornea, a supramolecular hyaluronic acid nanogel assembled through cyclodextrin-adamantane host-guest interactions and thioketal-containing PEG arms yields a dexamethasone (DEX)-loaded construct whose network is cleaved by pathologically high H_2O_2.[165] The formulation remains stable in storage and releases minimal drug in the absence of oxidants but reaches near-complete release in millimolar H_2O_2 while maintaining low cytotoxicity in human corneal epithelial cells (Figure 8). In a rabbit

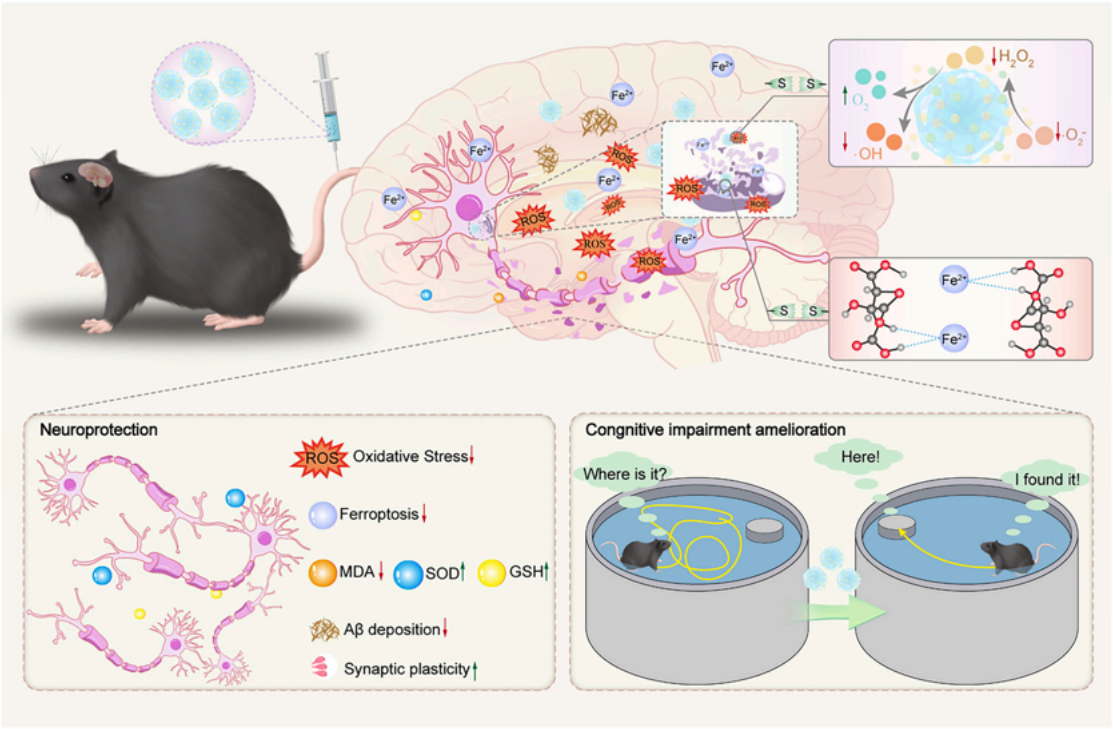

Figure 6. Nanogel-based strategies for the treatment of Alzheimer's disease

Schematic illustration of nanogel platforms designed to modulate Alzheimer's disease-related pathological processes, including oxidative stress, neuroinflammation, and impaired neuronal homeostasis.

The figure highlights how nanogels can be engineered to improve brain delivery, protect therapeutic agents, and promote localized modulation of disease-associated microenvironments.

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chemical burn model, once-daily instillation inhibits corneal neovascularization and reduces local pro-inflammatory cytokines, with efficacy comparable to twice-daily conventional DEX drops.

In the lungs, zinc-alginate curcumin (ZA-Cur) nanogels exploit ionic crosslinking and hydrogen bonding to integrate curcumin within a negatively charged network that can be nebulized as a fine aerosol.[166] The system displays faster release at 37°C, at a mildly acidic pH, and in the presence of monovalent cations, conditions intended to mimic inflamed airways (Figure 9). *In vitro*, ZA-Cur quenches DPPH radicals and reduces intracellular ROS in LPS- or H_2O_2-challenged alveolar cells more efficiently than free curcumin at the same dose.

Finally, non-classic models underline how the same logic can be exported beyond canonical human pathologies. ACC@TBO nanogels, based on azidobenzoyl-modified carboxymethyl chitosan crosslinked under light and loaded with toluidine blue O (TBO), have been used in plant protection as dual photodynamic/Fenton-like antibacterial agents.[167] The mesh architecture protects the photosensitizer, while Fe^{2+}/H_2O_2 in the infected microenvironment promotes network changes and ROS generation, which eradicate phytopathogenic bacteria without damaging the host plant. Although the biological context differs, the design principle remains aligned with the biomedical nanogels above: an oxidatively stressed niche is exploited as both a trigger for release and a target for controlled ROS production or quenching. Taken together, these studies show that nanogels can be programmed to read and reshape highly specific oxidative signatures. Their activity spans hippocampal ROS surges in depression, mitochondrial and neuroinflammatory stress in Parkinson's and Alzheimer's disease, peroxide-driven injury in cardiac hypertrophy and stroke, corneal neovascularization and acute lung injury, and even oxidatively stressed niches in plant infections. By combining ROS-cleavable crosslinkers, catalytic redox centers, and targeting ligands with formulation choices that respect the constraints of each organ and route of administration, nanogels move from generic "antioxidant carriers" to redox devices that localize, modulate, and sometimes exploit ROS in a disease-selective manner. Beyond therapeutic delivery and ROS scavenging, an increasingly important direction is the development of theranostic redox-responsive nanogels, in which diagnostic and therapeutic functions are integrated within the same platform.[168] In this context, imaging is not only used to track nanogel biodistribution but also to report on local oxidative activation, payload release, and treatment response.[169]

ROS-responsive nanogels can be engineered with activatable fluorescent or chemiluminescent probes, ratiometric redox sensors, magnetic resonance contrast agents, photoacoustic components, or catalytic nanozymes with imaging capability.[170,171] In this context, redox-sensitive nanoscale coordination polymers provide a useful example of how diagnostic and therapeutic

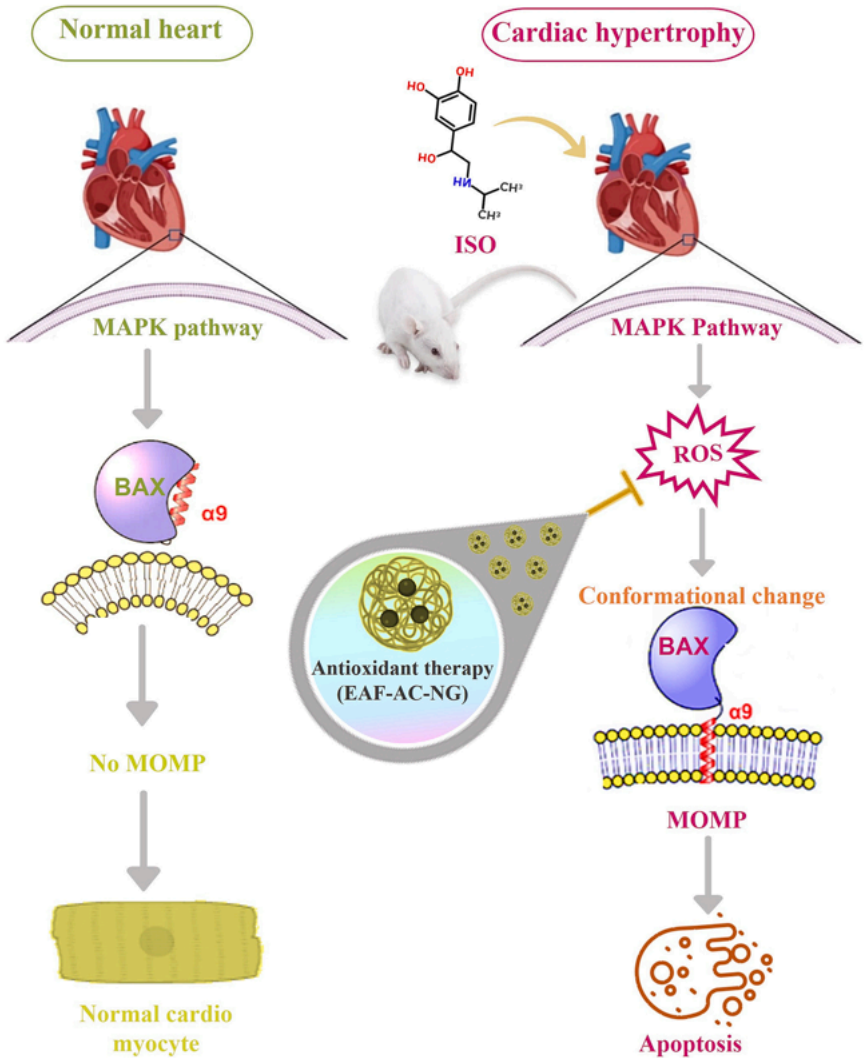

Figure 7. Nanogel-mediated modulation of isoproterenol-induced oxidative stress

Schematic illustration of the oxidative stress pathway activated by isoproterenol and the proposed protective mechanism of EAF-AC-NG.

The nanogel system is presented as a redox-modulating platform able to counteract ROS generation, oxidative damage, and downstream inflammatory/cellular stress responses, thereby supporting tissue protection in the proposed pathological model.

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functions can be combined within a single platform. Zhao et al. developed Mn-SS/DOX@PDA-PEG nanoparticles based on manganese ions and dithiodiglycolic acid as a disulfide-containing bridging ligand.[172] The disulfide bonds within the coordination network were cleaved in the presence of intracellular glutathione, leading to nanoparticle disassembly and accelerated doxorubicin release under reducing conditions. At the same time, the Mn^{2+} centers acted as T1 magnetic resonance imaging contrast agents, allowing the *in vivo* visualization of nanoparticle accumulation in the tumor after systemic administration. This example highlights a key principle of redox theranostics: the same structural element responsible for redox responsiveness can be integrated with imaging-active components, enabling both stimulus-responsive therapy and image-guided monitoring of delivery. Such approaches are important for precision redox modulation because oxidative and reductive stress are spatially heterogeneous, disease dependent, and temporally dynamic.[173] A purely therapeutic nanogel or nanocarrier can scavenge ROS or release a drug, but it cannot indicate whether the platform has reached the pathological site, whether the redox trigger is sufficiently present, or whether the therapeutic response correlates with local redox changes. By incorporating imaging functions, redox-responsive nanogels and related polymeric platforms could be used to monitor accumulation, activation, release, and treatment outcome.

However, this integration also introduces additional challenges, including the need to quantitatively correlate imaging signals with biologically meaningful ROS/RNS or glutathione (GSH) levels, avoid background activation, preserve biodegradability and clearance, and prevent imaging components from increasing long-term toxicity or formulation complexity.

Combined systems: Hydrogels as macroscopic redox matrices

However, standalone nanogels face practical limitations.[174,175] Owing to their small size, which allows rapid vascular/lymphatic clearance, free nanogels can exhibit short residence times following local injection (e.g., intra-articular injection into the synovial joint), diminishing their efficacy at the target site.[176] Moreover, without a supporting matrix, nanogels may lack mechanical integrity under physiological stress and can exhibit burst release.[177] These constraints have motivated hybrid constructs in which ROS-responsive nanogels are embedded within larger biomaterial platforms (hydrogels, nanofibrous scaffolds, or composite dressings), thereby improving retention, robustness, and release control. Hydrogels in particular provide a robust framework. These three-dimensional, crosslinked polymer networks mimic soft tissues due to their high water content, biocompatibility, and tunable mechanical properties, and ROS-scavenging hydrogels have shown promise across multiple oxidative stress-related pathologies.[178] For example, a hyaluronic acid hydrogel chemically conjugated with epigallocatechin gallate scavenged ROS in osteoarthritic joints, supported mesenchymal stem cell viability, and modulated local inflammation by promoting M2 macrophage polarization.[179] Encapsulating nanogels within bulk hydrogel matrices can mitigate premature burst release, enhance mechanical robustness, and prolong intra-

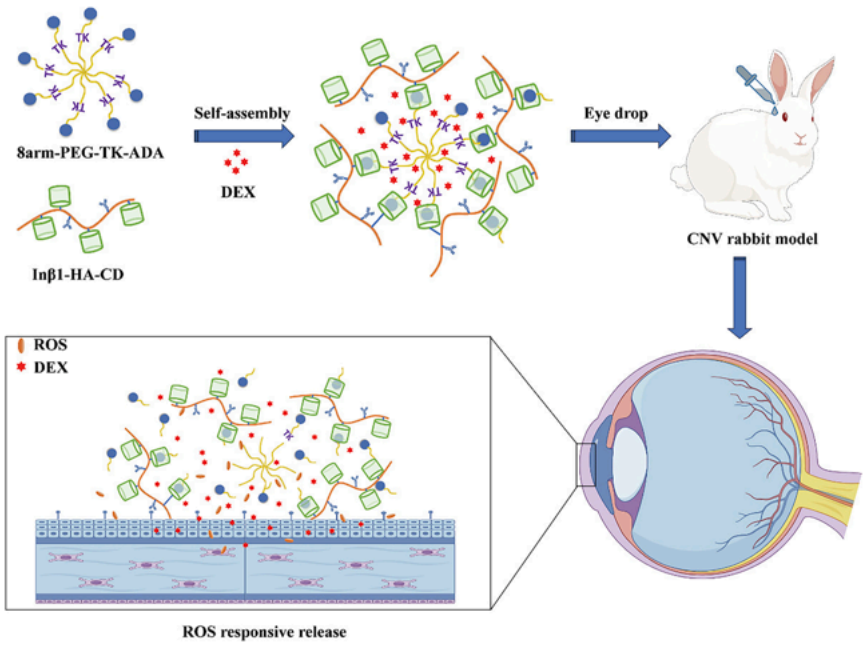

Figure 8. Host-guest-assembled nanogels for ROS-stimulated payload release

Schematic representation of nanogel formation through host-guest interactions and subsequent ROS-triggered release of the encapsulated therapeutic payload.

The figure illustrates how ROS-responsive motifs within the supramolecular nanogel network enable structural changes or degradation under oxidative conditions, promoting controlled drug release in ROS-enriched pathological microenvironments.

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tissue retention.[180] In joint environments, thermosensitive or adhesive hydrogel systems can further improve outcomes by resisting washout and enabling sustained activity over days.[181]

This concept is exemplified by He et al., who developed a bioadhesive and lubricating hydrogel for rheumatoid arthritis, combining dopamine and sulfonated hyaluronic acid networks with copper-based single-atom nanozymes (SANs) and kartogenin.[182] The hydrogel adheres to cartilage via catechol chemistry, resists mechanical washout, and restores lubrication through sulfonate-mediated hydration (Figure 10). Embedded Cu SANs are able to maintain catalase-like activity, scavenging superoxide, hydroxyl radicals, and H_2O_2 *in situ*. The gradual release of kartogenin supports chondrogenic differentiation and cartilage repair. *In vivo*, this multifunctional matrix modulated inflammation, reduced oxidative damage, and reversed cartilage erosion in both early- and late-stage rheumatoid arthritis, enabling extended joint residence and mechanical durability.

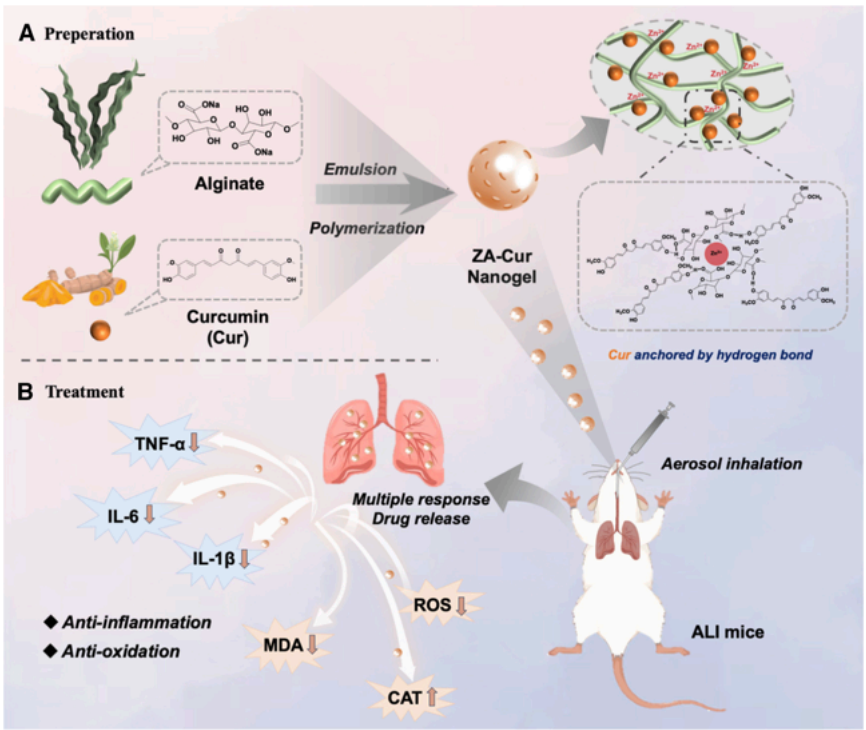

Figure 9. Nanogel synthesis and nanogel-based treatment of acute lung injury

Schematic illustration of the preparation of therapeutic nanogels and their application in a mouse model of acute lung injury.

The figure highlights how the nanogel platform can modulate ROS-associated inflammatory responses, reduce oxidative damage, and support tissue protection in the injured lung microenvironment.

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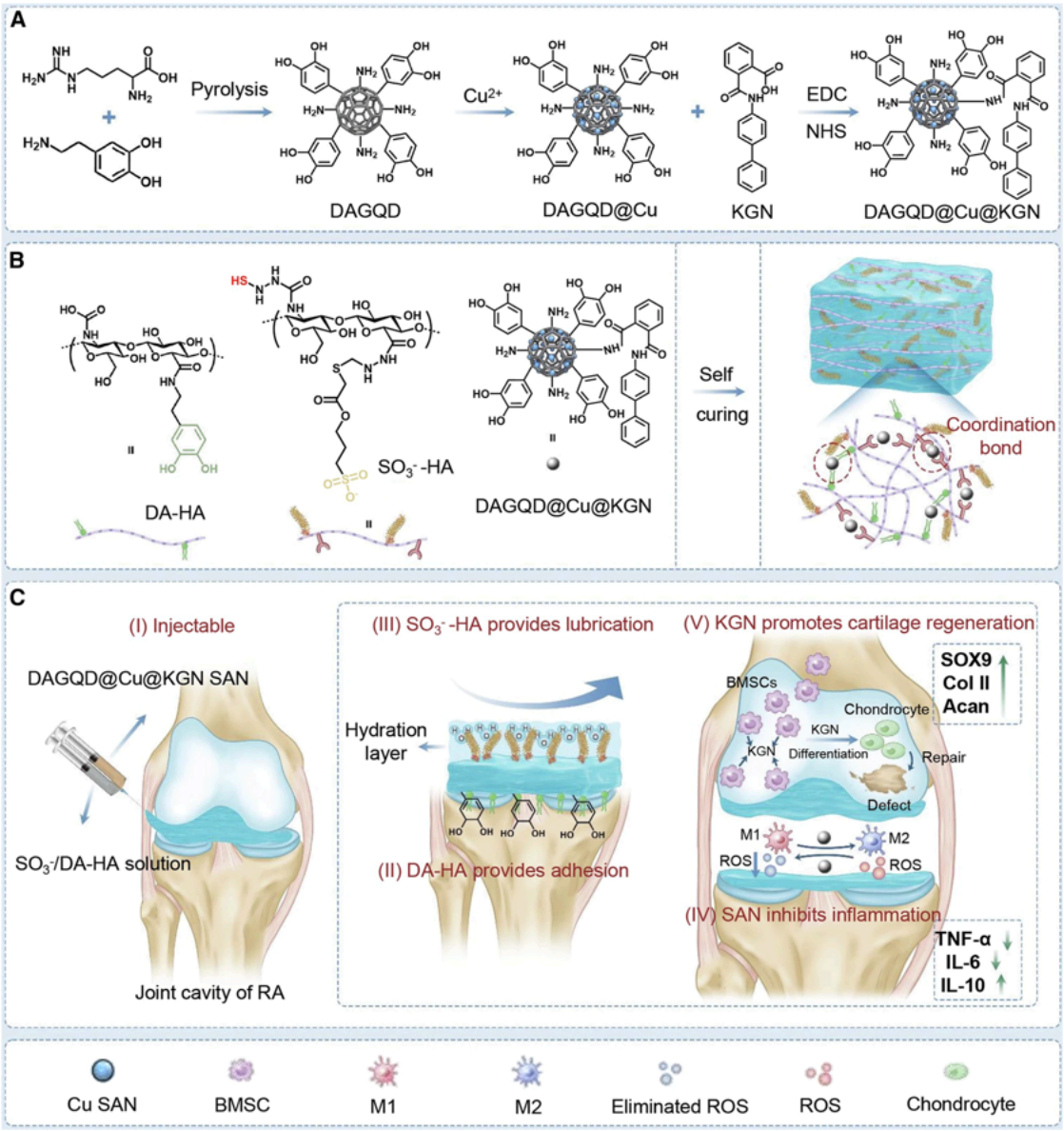

Figure 10. Injectable ROS-scavenging hydrogel for rheumatoid arthritis therapy

(A) Synthesis of DAGQD@Cu SAN and DAGQD@Cu@KGN SAN.

(B) Synthesis of DAGQD@Cu@KGN-SO3−/DA-HA hydrogel.

(C) DAGQD@Cu@KGN-SO3−/DA-HA hydrogel for RA therapy. (I) Hydrogel self-cures *in situ* within the joint cavity; (II, III) DAGQD@Cu@KGN-SO3−/DA-HA hydrogel displays lubrication and adhesion properties; (IV) regulation of inflammatory microenvironment facilitated by SAN with remarkable ROS-scavenging capabilities; (V) kartogenin released from the hydrogel promotes the recruitment of bone marrow mesenchymal stromal cells (BMSCs) and induces their differentiation into chondrocytes, facilitating the repair of cartilage damaged by rheumatoid arthritis.

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The combination of nanogels with scaffolds can also leverage multi-modal triggers for controlled release, pairing hydrogel responsiveness to physiological cues (pH, enzymes, and temperature) with nanogel ROS responsiveness.[183] Zhou et al. exemplified this strategy with a dual-responsive nanohydrogel system (KPP@PLEL) for osteoarthritis therapy, integrating a PAMAM dendrimer functionalized with MMP-13-cleavable peptide linkers and loaded with kartogenin, encapsulated within a thermosensitive poly(D,L-lactide)-poly(ethylene glycol)-poly(D,L-lactide) (PLEL) hydrogel.[184] The *in situ* gelling PLEL hydrogel prolongs intra-articular retention, while MMP-13-sensitive linkers enable localized enzyme-triggered release within the osteoarthritis (OA) microenvironment. *In vitro*, the system was biocompatible, suppressed inflammatory responses, and promoted chondrogenic differentiation.

Table 3. Platform for ROS scavenging

Platform	Primary function	ROS interaction mechanism	Main advantages	Key limitations	Representative applications in this review
Polymeric nanoparticles	systemic or local delivery of redox-active agents	encapsulation or surface presentation of scavengers, catalytic nanozyme activity	small size, tunable chemistry, scalable synthesis	limited tissue retention, rapid clearance	catalytic nanozyme delivery in neurodegeneration and acute inflammation
Nanogels	local and responsive redox modulation	ROS-cleavable crosslinkers, sacrificial or catalytic scavenging motifs	high hydration, chemical versatility, protection of labile scavengers	short residence time *in vivo*, potential burst release	neurodegeneration, cardiovascular disease, ischemic stroke
Hydrogels	local retention and tissue support	immobilized scavengers or redox-active moieties within bulk networks	prolonged retention, mechanical stability, tissue mimicry	limited penetration, slower response kinetics	osteoarthritis, rheumatoid arthritis, wound healing
Nanogel-hydrogel composites	sustained and localized therapy	multi-level ROS responsiveness combining nanogel sensing and hydrogel retention	synergistic redox control, extended therapeutic window	higher formulation complexity	osteoarthritis, rheumatoid arthritis, chronic wounds
Nanogel-nanofiber systems	structural reinforcement and controlled release	ROS-responsive nanogels embedded within fibrous scaffolds	improved mechanical integrity, prolonged retention	fabrication complexity, scale-up challenges	cartilage repair and advanced wound healing

In an OA rat model, it achieved superior cartilage penetration and extended joint residence compared to free kartogenin or hydrogel alone, resulting in enhanced cartilage regeneration and slower OA progression. Beyond joints, numerous studies have demonstrated the effectiveness of ROS-neutralizing hydrogels in promoting wound healing,[185] where sustained oxidative stress impairs regeneration by maintaining inflammation, degrading extracellular matrix components, and inhibiting angiogenesis.[186] Hybrid nanogel-hydrogel dressings can translate antioxidant activity into improved closure rates and tissue quality by combining local retention, infection control, and microenvironmental modulation. In a murine full-thickness wound model, an hyaluronic acid (HA)/PEG hydrogel incorporating chlorhexidine-loaded nanogels (Gel@CLN) promoted markedly faster closure. By day 14, Gel@CLN-treated wounds were essentially healed (~99% closure), whereas wounds treated with unloaded hydrogel or no dressing remained ~85% closed.[187] Histology showed a nearly complete epidermis and organized dermal layers with new capillaries after 2 weeks, in contrast to controls that still lacked continuous epidermis and exhibited persistent inflammatory infiltrates. In diabetic rats, a tannin/small interfering RNA (siRNA)-loaded nanogel-hydrogel composite achieved full closure by day 10 compared to ~18 days in untreated or standard dressing groups, with improved granulation, collagen deposition, and revascularization.[188] Similar trends were reported in additional composite systems, in which reduced inflammatory cytokines and increased angiogenic markers correlated with accelerated granulation and re-epithelialization.[189] Immunohistochemical analyses confirmed that the composite hydrogel significantly reduced proinflammatory cytokines (TNF-α, IL-1β, IL-6, and MCP-1) and upregulated angiogenic markers (CD31 and α-SMA) in the wound bed, correlating with faster granulation and re-epithelialization.

These outcomes underscore that the multi-pronged therapeutic actions of hybrid nanogel systems (infection control, antioxidation, growth factor modulation, and physical support), translate to significantly improved wound closure rates and tissue quality. Finally, nanofiber scaffolds offer a complementary route to address rapid clearance and burst release by providing structural support while retaining nanogel responsiveness.[190] Embedding ROS-responsive nanogels within electrospun nanofibers can improve mechanical stability and extend retention[191] while facilitating controlled release and tissue interaction in dense or highly dynamic environments.[192] Collectively, these hybrid architectures underscore the synergy between structural scaffolds and redox-responsive nanogels. Scaffolds enhance robustness and residence time, while nanogels provide ROS sensing and controlled payload release, improving pharmacokinetics and therapeutic performance in complex oxidative microenvironments. Beyond the individual examples discussed above, several general design principles can be extracted for the rational selection of polymeric redox-modulating platforms. Polymeric nanoparticles are advantageous when systemic administration, small size, and scalable fabrication are required, but their limited tissue retention and rapid clearance may reduce therapeutic efficacy in dynamic or poorly vascularized tissues. Nanogels provide a more versatile redox interface because their hydrated networks can host labile antioxidants, catalytic

nanozymes, or ROS-cleavable linkers while also allowing swelling, degradation, or release in response to oxidative cues. However, free nanogels may still suffer from burst release and insufficient residence time.[139] Hydrogels address these limitations by providing macroscopic retention, mechanical support, and local confinement, but their larger mesh structure and slower diffusion kinetics may limit penetration into dense tissues. Hybrid nanogel-hydrogel or nanogel-nanofiber systems therefore represent an intermediate strategy, combining nanoscale ROS sensing with macroscopic localization and structural stability.

An additional design criterion concerns the choice between catalytic and sacrificial ROS-scavenging mechanisms. Catalytic scavengers, including cerium oxide, Prussian blue, manganese-based nanozymes, and nitroxide-bearing systems, can undergo repeated redox cycles and are therefore particularly attractive for sustained oxidative microenvironments.[193] Their main advantage is prolonged activity, but this also requires careful control over dose, biodistribution, redox cycling, long-term persistence, and possible off-target interference with physiological ROS signaling.[194] In contrast, sacrificial chemistries, such as thioketals, boronic esters, diselenide bonds, and oxidizable polymer segments, directly consume ROS or undergo oxidative cleavage, thereby coupling scavenging with drug release or network degradation.[195] These systems are highly useful for transient oxidative bursts and on-demand activation, but their activity is progressively depleted and may be insufficient in chronic diseases unless supported by a depot-like matrix or combined with catalytic elements.[196] Thus, catalytic and sacrificial strategies should not be considered interchangeable but, rather, complementary tools whose selection depends on ROS intensity, exposure duration, and the desired therapeutic output. As highlighted in Table 3, no single polymeric architecture is universally optimal for ROS modulation. Instead, the choice between nanogels, hydrogels, or combined systems should be guided by the dominant ROS species, target tissue, required residence time, and intended therapeutic window. Hybrid platforms emerge as particularly effective when prolonged retention and multi-modal responsiveness are required, bridging the gap between nanoscale redox activity and macroscopic tissue constraints.

CONCLUSIONS

Polymeric nanogels, hydrogels, and hybrid platforms offer a versatile toolbox for the modulation of oxidative stress, combining nanoscale redox responsiveness with tunable drug delivery, tissue retention, and multifunctional therapeutic activity.

Their ability to incorporate catalytic nanozymes, sacrificial ROS-cleavable motifs, antioxidant small molecules, or biologically active macromolecules makes them particularly attractive for diseases in which oxidative stress is spatially localized and dynamically regulated, including inflammation, neurodegeneration, cancer, osteoarthritis, cardiovascular injury, and chronic wounds. However, despite the rapid growth of the field, the translation of these systems remains limited by several conceptual, methodological, and technological challenges. A first major limitation is the lack of standardized methods to quantify and compare antioxidant performance. Different studies rely on disparate ROS detection assays, including DCFH-DA, DHE, MitoSOX, ABTS, DPPH, lipid peroxidation markers, nitrotyrosine staining, malondialdehyde quantification, or indirect inflammatory readouts. These methods differ in oxidant specificity, sensitivity, subcellular resolution, and susceptibility to artifacts, making it difficult to directly compare the ROS-scavenging capacity of different nanogels or to rank materials across studies. Moreover, many polymer degradation and release assays use exogenous H_2O_2 concentrations in the micromolar to millimolar range to accelerate responsiveness, whereas physiological redox signaling often occurs at much lower and highly compartmentalized oxidant levels. As a result, chemical responsiveness under accelerated *in vitro* conditions does not always predict performance in disease-relevant oxidative microenvironments. Future studies should therefore report not only antioxidant efficiency but also the specific ROS/RNS species targeted, oxidant concentration, exposure time, detection method, material-response kinetics, and the biological context in which redox modulation is evaluated. A second critical issue concerns the balance between therapeutic ROS modulation and preservation of physiological redox signaling. ROS are not only damaging oxidants but also essential mediators of immune activation, angiogenesis, tissue remodeling, proliferation, and differentiation.

Therefore, complete or non-selective ROS depletion may impair host defense, delay tissue repair, or interfere with redox-dependent signaling cascades. This consideration is particularly relevant for catalytic scavengers, whose activity may persist beyond the initial oxidative insult, and for long-retained hybrid matrices designed for chronic diseases. Future redox-modulating platforms should be designed to restore homeostasis within a therapeutic window rather than indiscriminately suppress ROS. Spatial confinement, disease-triggered activation, tunable catalytic turnover, controlled degradability, and localized administration will be essential to minimize off-target interference while maintaining antioxidant efficacy. From a translational perspective, nanogel fate *in vivo* remains a central challenge. Clearance, biodistribution, and tissue retention depend on particle size, surface charge, hydrophilicity, degradability, protein corona formation, and administration route. Very small or highly hydrated nanogels may be rapidly eliminated through renal, hepatic, or lymphatic pathways, whereas larger, poorly degradable, or strongly opsonized systems may accumulate in the liver, spleen, or mononuclear phagocyte system. Immune recognition must also be carefully considered, since surface chemistry, cationic charge, residual monomers or crosslinkers, endotoxin contamination, adsorbed proteins, and repeated dosing can promote complement activation, macrophage uptake, or inflammatory responses. In parallel, long-term toxicity remains insufficiently explored, particularly for redox-active inorganic components or catalytic centers that may persist in tissues, release metal ions, or maintain activity beyond the desired therapeutic window. Accordingly, future investigations should move beyond short-term cytocompatibility and include repeated-dose studies, biodistribution, degradation, excretion, hemocompatibility, complement activation, cytokine release, and chronic toxicity under disease-relevant conditions. Manufacturing feasibility is another decisive barrier.

Many nanogel systems are still prepared using laboratory-scale batch methods that may generate variability in size,

polydispersity, crosslinking density, payload loading, and residual reagents. For clinical translation, critical quality attributes such as particle size distribution, surface chemistry, redox activity, residual monomer/crosslinker content, endotoxin level, sterility, storage stability, and release kinetics must be tightly controlled. Microfluidic and continuous manufacturing approaches may help improve reproducibility, scalability, and batch-to-batch consistency, especially when combined with inline monitoring and standardized purification strategies. However, scale-up should be considered early in material design rather than after biological validation because complex multicomponent architectures may offer excellent laboratory performance but poor manufacturability or regulatory feasibility. Looking forward, the development of next-generation antioxidant polymer materials will likely benefit from the integration of high-throughput experimentation, automated synthesis, advanced characterization, and artificial intelligence-assisted screening. Machine learning and data-driven design can help identify relationships between polymer composition, crosslinking chemistry, particle size, degradability, ROS specificity, payload release, cytocompatibility, and immune response. When coupled with high-throughput ROS assays and disease-relevant biological models, these approaches could accelerate the discovery of materials that respond within physiologically meaningful oxidative windows rather than only under artificially strong oxidant challenges. Importantly, AI-assisted screening will require curated and standardized datasets, including negative results and harmonized reporting of ROS species, oxidant dose, exposure time, and assay conditions. Such tools should therefore complement, rather than replace, mechanistic understanding of ROS chemistry and material-biology interactions.

Overall, polymeric nanogels and hybrid redox-modulating platforms represent a promising direction for antioxidant therapy and ROS-responsive drug delivery. Their future impact will depend not only on increasing chemical sophistication but also on improving comparability, biological relevance, translational safety, and manufacturing robustness. The field should now move from proof-of-concept antioxidant materials toward rationally designed, quantitatively benchmarked, and clinically manufacturable platforms capable of restoring redox homeostasis with spatial, temporal, and disease-specific precision.

ACKNOWLEDGMENTS

This work was partially supported by the European Union's Horizon 2020 Research and Innovation Program under Marie Skłodowska-Curie grant agreement 872648 (RISE-2019 MEPHOS).

AUTHOR CONTRIBUTIONS

G.N., K.F., and G.A. conceptualized, wrote the original manuscript, and edited the manuscript and figures. R.M.P., R.M., Y.K., E.N.Z., and P.D. edited the manuscript. H.K.-M. and F.R. conceptualized, edited the manuscript and figures, supervised the project, and provided funding. All authors contributed to discussions and finalized the manuscript.

DECLARATION OF INTERESTS

The authors declare no competing interests.

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