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ROS-responsive drug delivery systems for chronic wound healing: advances, challenges, and translational perspectives

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Abstract

Chronic wounds pose a substantial global health burden, due to the high incidence and recurrence rates, and associated morbidity. Excessive and sustained production of reactive oxygen species (ROS) is a hallmark of the chronic wound microenvironment, ultimately stalling the repair process. The pathological accumulation of ROS in chronic wounds has motivated the development of ROS-responsive drug delivery systems (DDS), which show considerable potential in improving wound healing outcomes. In this review, we provide a comprehensive overview of the advances in ROS-responsive DDS for chronic wound healing, summarizing the design principles, material chemistry, and underlying ROS-triggered functional mechanisms. Key translational challenges are discussed, including material biocompatibility, stability in protease- and ROS-rich wound exudates, manufacturing scalability, and regulatory considerations. Finally, we outline future perspectives, emphasizing the integration of multi-responsive functionalities, real-time ROS monitoring, and advanced biomaterial engineering to accelerate clinical translation. By aligning therapeutic release with the dynamic redox status of chronic wounds, ROS-responsive DDS holds considerable potential to redefine precision therapy for wound management.

Key words Chronic wounds, Reactive oxygen species (ROS), Drug delivery systems (DDS), Wound microenvironment, Translational medicine

Background

Chronic wounds represent a growing global health challenge [1]. Epidemiological studies suggest that approximately 1%–2% of the global population will experience a chronic wound during their lifetime [2,3]. The prolonged treatment course, which typically involves repeated wound dressing care, systemic antibiotic administration, and other supportive therapies, results in substantial direct healthcare costs. In addition, high recurrence rates and frequent complications further increase the socio-economic burden. Together, these factors highlight the urgent need for more effective and innovative therapeutic strategies [4,5].

Wound healing is a tightly orchestrated, multi-phasic process typically described in 4 overlapping stages: hemostasis, inflammation, proliferation, and remodeling [6,7]. Immediately after injury, hemostasis involves platelet aggregation and fibrin clot formation to arrest bleeding and serve as a provisional matrix, with the release of growth factors that kick-start repair. The inflammatory phase follows as neutrophils and macrophages infiltrate the wound bed, clearing pathogens and debris, while secreting cytokines that orchestrate downstream reparative responses. Next, the proliferative stage is characterized by fibroblast proliferation, collagen deposition, angiogenesis, and re-epithelialization, forming robust granulation tissue. Lastly, during remodeling, collagen fibers are reorganized and matured, and tissue tensile strength is gradually restored [8,9].

Reactive oxygen species (ROS) play context-dependent roles throughout wound healing. When maintained at low to moderate levels, ROS serve as signaling molecules that promote cell proliferation, angiogenesis, and host defense, facilitating effective tissue repair [10]. However, in chronic wounds, an imbalance in ROS homeostasis is evident. Persistent and excessive ROS generation induces oxidative damage to lipids, proteins, and

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nucleic acids, undermining cellular integrity and function [11]. Elevated ROS levels impair fibroblast proliferation, endothelial cell migration, and angiogenic signaling, while promoting matrix degradation and inhibiting collagen deposition, thereby arresting progress at the inflammatory stage or producing dysfunctional granulation tissue [12,13].

Given these pathological characteristics, ROS present an attractive trigger for disease-targeted drug delivery systems (DDS). In this review, we systematically examine the development history of ROS-responsive DDS in the management of chronic wounds during the past years (Fig. 1). First, we introduce and categorize the primary ROS-responsive materials and platforms, highlighting their material chemistry and responsiveness mechanisms. Second, we analyze preclinical evidence detailing how these ROS-responsive DDS behave in chronic wound models, focusing on therapeutic efficacy, kinetics of ROS-triggered release, measures of healing, and mechanistic insights into how local redox modulation promotes wound repair. We then critically assess the challenges hindering clinical translation, such as material biocompatibility, stability in biologically complex wound exudates, manufacturing scalability, regulatory barriers, and user compliance issues. Finally, we project future opportunities by exploring the integration of smart functionalities to advance ROS-responsive DDS toward real-world applications for managing chronic wounds.

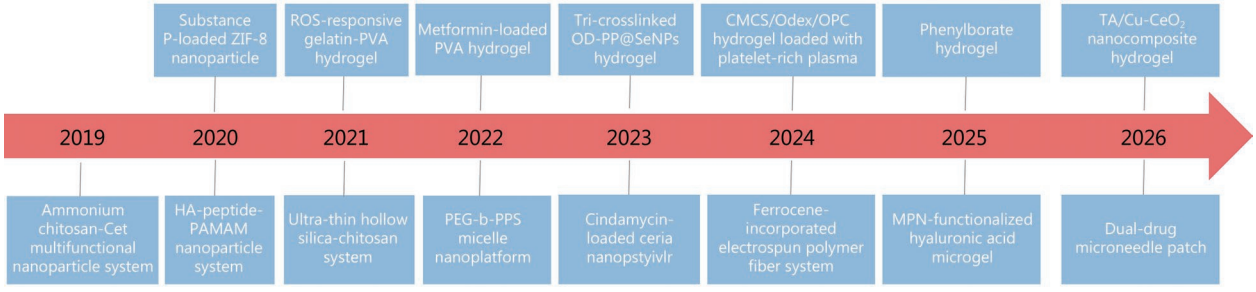


Fig. 1 Generational overview of the ROS-responsive DDS in the management of chronic wound-healing during the past years.

ROS. Reactive oxygen species; DDS. Drug delivery systems; ZIF-8. Zeolitic imidazolate framework-8; PVA. Poly(vinyl alcohol); CMCS. Carboxymethyl chitosan; Odex. Oxidized dextran; OPC. Oligomeric procyanidins; PEG-b-PPS. Poly(ethylene glycol)-block-poly(propylene sulfide); PAMAM. Poly(amidoamine)

Pathophysiology of ROS in chronic wounds

Chronic wounds exhibit a distinctive ROS profile characterized by both elevated concentrations and dysregulated spatiotemporal distribution [14]. The predominant ROS species include superoxide anion radical ($O_2^{\cdot-}$), hydrogen peroxide (H_2O_2), hydroxyl radicals (·OH), hypochlorous acid (HOCl), and peroxynitrite ($ONOO^-$) [11]. Among these, $O_2^{\cdot-}$ and H_2O_2 constitute the major contributors, with levels reported to be several-fold higher in chronic wounds than in acute wounds or healthy skin [15]. Elevated ROS production originates from diverse intracellular sources, including nicotinamide adenine dinucleotide phosphate (NADPH) oxidases (NOX2/NOX4) in neutrophils and macrophages, mitochondrial dysfunction in hypoxic or senescent cells, and sustained myeloperoxidase activity during chronic inflammation, with additional contributions from bacterial infection. These ROS are largely generated by activated immune cells and disturbed mitochondrial metabolism and are typically assessed using fluorescent probes, electrochemical methods, or biosensor-based platforms [16].

The intracellular localization of these ROS further contributes to cellular dysfunction. Mitochondrial accumulation of ROS impairs the generation of adenosine triphosphate and promotes mitochondrial permeability transition, whereas cytosolic ROS activate inflammatory transcription factors [17]. Excessive extracellular accumulation of ROS within the wound exudate also degrades matrix components and inactivates growth factors, collectively reinforcing the non-healing state [18].

In cancer, ROS levels fluctuate dynamically and are buffered by enhanced antioxidant systems to support proliferative signaling [19]. Neurodegenerative diseases primarily involve mitochondrial oxidative injury within defined neuronal populations [20]. Cardiovascular disorders feature NOX-driven ROS surges that are episodic rather than persistent [21]. In contrast, chronic wounds display continuously high ROS levels across both intracellular and extracellular compartments, forming a persistent oxidative-inflammatory loop that lacks effective resolution mechanisms [22]. These distinct features make chronic wounds particularly amenable to ROS-responsive DDS that exploit pathological ROS elevation for selective activation (Fig. 2).

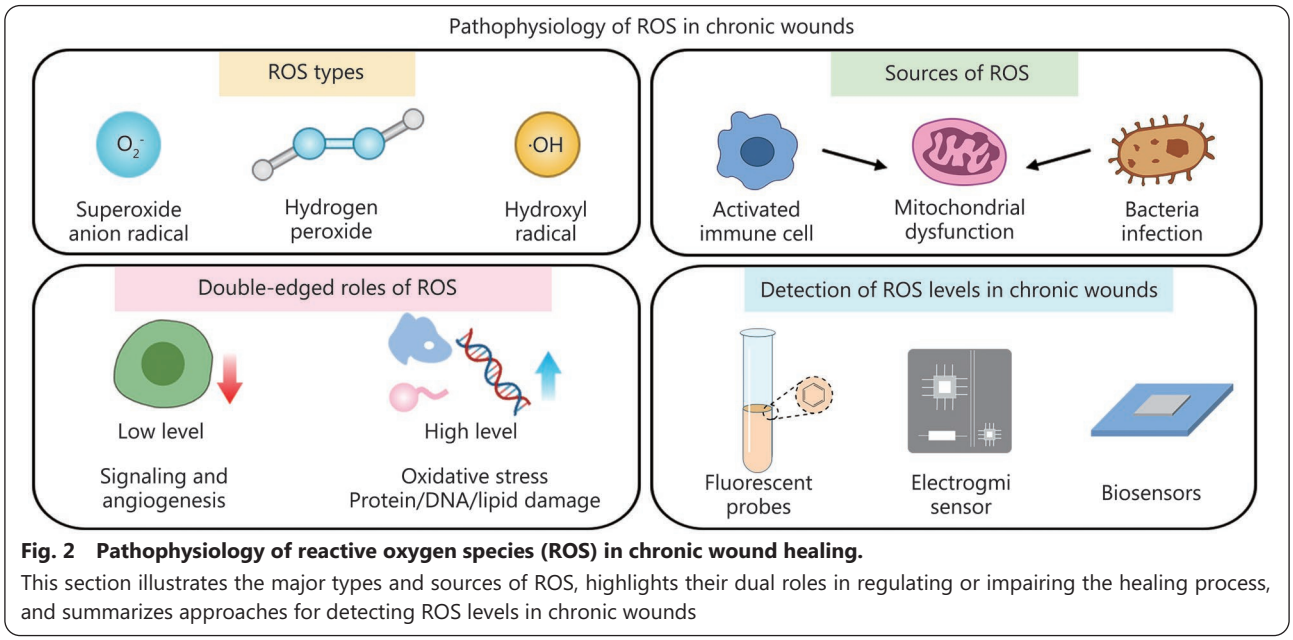


Fig. 2 Pathophysiology of reactive oxygen species (ROS) in chronic wound healing.
This section illustrates the major types and sources of ROS, highlights their dual roles in regulating or impairing the healing process, and summarizes approaches for detecting ROS levels in chronic wounds

Sources of ROS

In chronic wounds, ROS are generated from multiple, often overlapping, sources [23]. Activated immune cells, particularly neutrophils and macrophages, recruited during persistent inflammation, produce ROS via NADPH oxidase-mediated oxidative bursts to kill invading pathogens [24]. Mitochondrial dysfunction in resident cells, such as fibroblasts and keratinocytes, also contributes to sustained ROS production, while impaired electron transport chain activity leads to electron leakage and excessive $O_2^{\cdot-}$ generation [25].

Furthermore, several important enzymatic sources of ROS in non-immune cells also contribute substantially to oxidative dysregulation in chronic wounds. Xanthine oxidase highly active under ischemic and hypoxic conditions, produces $O_2^{\cdot-}$ during purine metabolism and is markedly upregulated in diabetic and ischemic wounds [26]. Cyclooxygenases (COX-1/COX-2) and lipoxygenases, which participate in arachidonic acid metabolism, can generate ROS as by-products while amplifying inflammatory lipid mediator signaling, thereby exacerbating tissue injury, and delaying repair [27,28]. Endothelial nitric oxide synthase, when uncoupled due to limited L-arginine or tetrahydrobiopterin, shifts from producing nitric oxide (NO) to generating $O_2^{\cdot-}$, contributing to endothelial dysfunction and impaired angiogenesis [29]. Incorporating these non-immune enzymatic pathways may provide a more comprehensive understanding of ROS sources in chronic wound microenvironments. It highlights the need for ROS-responsive DDS that can effectively modulate both immune- and non-immune-derived oxidative stress.

Additionally, bacterial infection contributes to excessive ROS accumulation by stimulating immune cell recruitment and activation, while some pathogens directly generate ROS or induce host-derived ROS through virulence factors [30]. Bacterial infection represents a critical aggravating factor in the oxidative microenvironment of chronic wounds. Upon microbial invasion, pathogens stimulate extensive immune cell recruitment, which releases large quantities of ROS as part of the host's antimicrobial defense [31]. Beyond immune activation, certain bacteria can directly induce oxidative stress by secreting redox-active metabolites or virulence factors that trigger NADPH oxidase activity and mitochondrial ROS generation in host cells [32,33]. These cumulative effects lead to sustained overproduction of $O_2^{\cdot-}$ and H_2O_2, amplifying tissue inflammation, extracellular matrix (ECM) degradation, and delayed re-epithelialization [34]. Moreover, biofilm formation creates localized hypoxic and redox-heterogeneous niches that trap ROS and impede antioxidant diffusion, further perpetuating oxidative damage [35].

ROS display a concentration-dependent, double-edged role in wound healing. At low to moderate levels, ROS function as essential second messengers that modulate intracellular signaling pathways, activate transcription factors such as nuclear factor κB (NF-κB) and hypoxia-inducible factor-1α (HIF-1α), and promote processes including angiogenesis, cell migration, and proliferation, critical for progression through the proliferative phase of healing [36,37]. Conversely, at excessively high levels, ROS trigger oxidative stress, overwhelming endogenous antioxidant defenses such as superoxide dismutase and catalase [38,39]. This results in oxidative damage to proteins (oxidation and fragmentation),

DNA (strand breaks, base modifications), and lipids (peroxidation of membrane phospholipids), thereby impairing cellular viability, ECM integrity, and signaling fidelity [40,41]. In chronic wounds, this pathological ROS accumulation perpetuates inflammation, delays re-epithelialization, and disrupts tissue remodeling.

Detection of ROS levels

Accurate measurement of ROS levels is essential for designing ROS-responsive DDS and monitoring redox dynamics in chronic wounds [33]. A variety of sensing platforms have been developed to detect distinct ROS species. Widely used small-molecule fluorescent probes, including 2',7'-dichlorofluorescein diacetate (DCFH-DA) for general ROS [42,43], hydroxyphenyl fluorescein (HPF) for ·OH [44], dihydroethidium (DHE) or MitoSOX for $O_2^{\cdot-}$ [45,46], and boronate-based probes for H_2O_2 [47], primarily detect micromolar to sub-micromolar ROS concentrations. These sensors can be engineered to localize to specific cellular compartments, as DCFH-DA targets the cytosol, MitoSOX accumulates in mitochondria, and lysosome-targeted probes enable assessment of ROS in acidic organelles [48,49]. Extracellular ROS can be monitored using cell-impermeable probes or electrochemical sensors designed to operate in wound exudate [50,51].

In addition to fluorescent reporters, chemiluminescent probes and emerging nanoparticle (NP)-based sensors allow detection of specific ROS with enhanced sensitivity [52,53]. Electrochemical ROS sensors embedded in wound dressings offer real-time, *in situ* monitoring of H_2O_2 and $O_2^{\cdot-}$ in the wound microenvironment [54].

However, current ROS detection methods face significant limitations, as many probes exhibit poor selectivity due to cross-reactivity among ROS species, and some undergo auto-oxidation, generating false-positive signals [55]. Moreover, continuous ROS monitoring is constrained by photobleaching and limited temporal resolution, and probe performance is further compromised by pH variability, metal ions, and protease-rich wound exudates, leading to reduced detection accuracy in chronic wounds [55]. Importantly, most probes provide semi-quantitative rather than absolute ROS measurements, and *in vivo* quantification remains challenging due to attenuation of optical signals in tissue (Table 1) [56-70].

Design principles of ROS-responsive DDS

ROS-responsive DDS for chronic wound therapy is engineered through rational chemical design, tailored release mechanisms, and strategic carrier selection (Fig. 3). Incorporation of ROS-cleavable linkages, such as thioether, selenoether, or boronic esters, enables selective responsiveness to oxidative

Table 1 Overview of ROS sensing modalities

Sensor type	Primary ROS detected	Typical cellular	Advantages	Limitations	References
Fluorescent probes (DCFH-DA)	Broad ROS (H_2O_2, ·OH, $ONOO^-$)	Cytosol (after esterase cleavage)	Widely used; Simple imaging	Poor specificity; Auto-oxidation; PH-sensitive; Semi-quantitative	[56]
H_2O_2-specific probes (Boronate-based fluorophores, hyPer)	H_2O_2	Cytosol, nucleus, and targeted organelles	Higher specificity for H_2O_2; Genetically targetable	Signal saturation; Sensitive to pH; Limited use in protease-rich wounds	[57,58]
Superoxide probes (DHE, MitoSOX red)	$O_2^{\cdot-}$	Cytosol (dihydroethidium), mitochondria (MitoSOX)	Organelle-targetable; High ROS responsiveness	Cross-reactivity; Photo-oxidation; Limited quantification	[59,60]
·OH probes (Hydroxyphenyl fluorescein, aminophenyl fluorescein)	·OH and some $ONOO^-$	Cytosol/whole cell	High sensitivity to ·OH	Not fully selective; Affected by metal ions	[61,62]
HOCl probes (R19-S, MPO-specific indicators)	HOCl	Phagosomes, extracellular space	Measures neutrophil oxidative burst	Overlaps with other ROS/RNS; Rapid bleaching	[63,64]
$ONOO^-$ probes (Boronate-dye conjugates)	$ONOO^-$	Cytosol	Higher selectivity for $ONOO^-$	Reactivity with ·OH causes false positives	[65]
Chemiluminescent probes (Luminol, lucigenin)	$O_2^{\cdot-}$, H_2O_2	Whole wound tissue/exudate	High sensitivity; No excitation light needed	Low selectivity; Signal varies with pH and ions	[66,67]
Electrochemical ROS sensors (H_2O_2 electrodes, graphene/Au nanoprobes)	H_2O_2, $O_2^{\cdot-}$	Extracellular (wound fluid), wound dressings	Real-time, quantitative, continuous monitoring	Limited ROS specificity; Fouling in wound exudate	[68-70]

ROS. Reactive oxygen species; H_2O_2. Hydrogen peroxide; ·OH. Hydroxyl radical; $ONOO^-$. Peroxynitrite; $O_2^{\cdot-}$. Superoxide anion radical; HOCl. Hypochlorous acid; DCFH-DA. Dichlorodihydrofluorescein diacetate; hyPer. Hydrogen peroxide sensor; DHE. Dihydroethidium; MitoSOX. Mitochondria-superoxide indicator; R19-S. Rhodamine 19-sulfide; MPO. Myeloperoxidase; RNS. Reactive nitrogen species

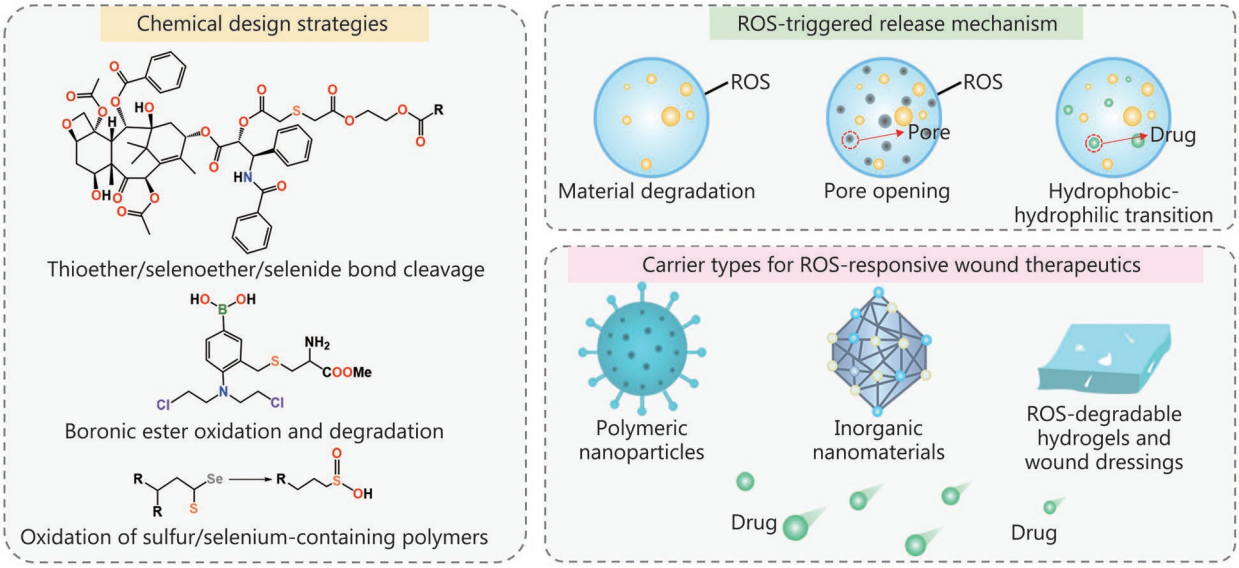


Fig. 3 The schematic illustration of the chemical strategies and release mechanisms of reactive oxygen species (ROS)-responsive drug delivery systems (DDS)

stress, with selenium-containing bonds offering heightened sensitivity suitable for variable ROS levels in chronic wounds [71-73]. ROS-triggered release can be achieved via carrier degradation, nanopore opening, or hydrophobic-hydrophilic transitions, allowing precise modulation of release profiles. A broad spectrum of carriers, including polymeric NPs, inorganic nanomaterials, and ROS-degradable hydrogels, provides structural diversity and functional versatility [37,74,75]. Polymeric platforms offer tunable kinetics and enhanced biocompatibility, while inorganic systems enable multifunctional redox modulation. Hydrogels, particularly when integrated into wound dressings, combine localized delivery with moisture retention and potential ROS-sensing capability [30]. These design strategies lay the foundation for intelligent, site-specific therapies that align drug release with the oxidative dynamics of chronic wounds, thereby enhancing therapeutic efficacy and minimizing off-target effects.

Chronic wounds display heterogeneous pathophysiological characteristics and distinct ROS profiles, which require tailored design strategies for ROS-responsive DDS [76]. Diabetic foot ulcers are marked by sustained intracellular and extracellular ROS accumulation driven by chronic hyperglycemia and persistent inflammation. In this context, high ROS-threshold carriers, such as thioketal-based NPs or hydrogels, are particularly suitable for delivering angiogenic and anti-inflammatory therapeutics [76]. Pressure ulcers experience intermittent ischemia-reperfusion, resulting in transient ROS bursts [77]. Hence, rapid-response carriers, such as boronate-based micelles, are well suited to deliver antioxidants during acute oxidative peaks. Venous leg ulcers display sustained extracellular ROS accumulation, making long-acting, extracellular-targeted hydrogels or fibrous mats optimal for localized anti-inflammatory and pro-healing therapy [78]. Mixed or infected wounds may require multi-responsive DDS capable of sensing ROS alongside pH or enzymatic changes to coordinate antimicrobial, antioxidant, and regenerative functions [79]. This etiology-specific perspective emphasizes the importance of aligning carrier sensitivity, release kinetics, and payload distribution with the unique oxidative and cellular microenvironment of wounds, thereby maximizing therapeutic efficacy and safety.

As an ideal strategy for mild or early-stage wounds, low-threshold systems are designed to respond to lower concentrations of ROS (10–50 μmol/L), allowing for early intervention without premature drug release [11]. In contrast, high-threshold systems are better suited for more severe or infected wounds, where ROS levels can exceed 100 μmol/L. These DDS remain stable under normal oxidative stress and activate only when ROS concentrations reach a pathological threshold, thereby minimizing premature activation [80]. The main challenge in designing effective ROS-responsive DDS for wound healing lies in the variability of ROS levels in the wound microenvironment.

Moreover, although chronic and unresolved hypoxia in diabetic and chronic wounds is well recognized to impair endothelial function, reduce NO bioavailability, and hinder angiogenic sprouting, it is important to distinguish this pathological hypoxia from the transient or moderate hypoxia that naturally arises during early wound repair [22,79].

Physiological hypoxia stabilizes HIF-1α, leading to the transcriptional activation of pro-angiogenic mediators such as vascular endothelial growth factor (VEGF), platelet-derived growth factor B (PDGF-B), and angiopoietin-2, which collectively promote endothelial proliferation, migration, and neovascularization. This adaptive response is essential for normal tissue regeneration [81]. However, in chronic wounds, persistent oxidative stress, inflammation, and metabolic dysfunction suppress HIF-1α signaling and disrupt this beneficial angiogenic cascade [81]. Recognizing this distinction underscores the need for DDS strategies that not only mitigate chronic hypoxia-induced dysfunction but also preserve or mimic the pro-regenerative hypoxic signaling required for effective vascular repair.

Chemical design strategies for ROS responsiveness

A variety of chemical bonds and moieties that respond to ROS have been reported (Table 2) [82-91]. For instance, thioketal bonds exhibit high stability under physiological conditions but cleave rapidly under millimolar H_2O_2 or $ONOO^-$ exposure, making them suitable for targeting severely oxidative wounds [92]. Boronate esters, by contrast, respond to lower micromolar H_2O_2 concentrations, offering higher sensitivity and faster response kinetics ideal for mild-to-moderate oxidative stress microenvironment [93]. Thioether and selenide/tellurium-based linkages show tunable redox sensitivity via heteroatom substitution, enabling gradated responsiveness across different ROS levels [94].

A widely applied approach in ROS-responsive materials involves incorporating thioether, selenoether, or selenide linkages into the backbone or side chains of polymers. These bonds are selectively oxidized by elevated ROS levels to their corresponding sulfoxides/selenoxides or sulfones/selenones, leading to cleavage or conformational changes that trigger drug release [95]. Compared with thioethers, selenium-containing linkages are more redox-sensitive, enabling responsiveness to lower ROS concentrations, which is particularly beneficial for chronic wound environments with variable oxidative stress [96]. However, selenium has a narrow physiological window and excessive exposure can induce cytotoxicity [97]. In ROS-responsive DDS, selenium is typically incorporated at low molar ratios within polymer backbones or side chains, enabling selective oxidation and localized drug release at the wound site while minimizing systemic exposure [79]. Nonetheless, long-term safety and dose optimization remain critical considerations for clinical translation, and careful evaluation of selenium content, degradation products, and local accumulation is essential [79,97].

Table 2 Summary of major ROS-responsive chemical bonds and moieties

Functional group	Mechanism	Primary ROS trigger(s)	Typical sensitivity range	Key features	References
Thioketal [-C(S)-C-]	Oxidative cleavage of C-S bonds forming ketones and sulfoxides	H_2O_2, ·OH, $ONOO^-$	High ROS (H_2O_2 0.1–1.0 mmol/L)	High stability under physiological conditions; Effective in severely oxidative environments	[83,84]
Thioether (R-S-R')	Stepwise oxidation to sulfoxide/sulfone	H_2O_2, ·OH	Moderate-to-high ROS (H_2O_2 10–500 μmol/L)	Gradual oxidation allows tunable responsiveness; Suitable for moderate oxidative stress	[85]
Selenide/tellurium-based linkages	ROS-induced oxidation to selenoxide/telluroxide, triggering bond rearrangement or cleavage	H_2O_2, $O_2^{\cdot-}$	Very low ROS (H_2O_2 1–10 μmol/L)	Extremely high ROS sensitivity; Responsive under mild oxidative stress; Limited by potential cytotoxicity of heavy chalcogens	[86,87]
Boronate ester	Nucleophilic substitution by H_2O_2 yielding phenol and boric acid derivatives	H_2O_2 (selective)	Low ROS (H_2O_2 1–50 μmol/L)	Highly specific to H_2O_2; Fast kinetics; Suitable for precise, early-stage redox sensing and drug activation	[82]
Oxalate ester (-COO-COO-)	H_2O_2-mediated peroxy cleavage generating CO_2 and alcohol	H_2O_2	Moderate ROS (H_2O_2 10–200 μmol/L)	Enables gas-generation (bubble-assisted) and chemiluminescent responses; Applicable to imaging and on-demand release	[88]
Aryl ether	Oxidative elimination via aryl oxidation	HOCl, $ONOO^-$	High ROS (H_2O_2 >100 μmol/L)	Enhances selectivity toward specific ROS species in infected wounds	[89]
Proline or methionine residues in peptides	Oxidative cleavage or modification of side chains	H_2O_2, HOCl	Moderate ROS (H_2O_2 10–100 μmol/L)	Natural, biocompatible ROS-sensitive motifs; Suitable for enzyme-linked systems	[88,89]
Amino Borane/Boronic imidazolate coordination complexes	H_2O_2 oxidation breaks B-N or B-C bonds	H_2O_2	Low-moderate ROS (H_2O_2 5–100 μmol/L)	Emerging hybrid materials with high selectivity and rapid kinetics; Promising for ROS-triggered nanocarriers	[90,91]

ROS. Reactive oxygen species; H_2O_2. Hydrogen peroxide; ·OH. Hydroxyl radical; $ONOO^-$. Peroxynitrite; $O_2^{\cdot-}$. Superoxide anion radical; HOCl. Hypochlorous acid

A second strategy exploits boronic ester oxidation and degradation. Boronic esters and boronic acids are known to undergo rapid oxidative cleavage in the presence of H_2O_2, yielding phenols and boric acid derivatives [98]. This reaction is highly selective and can be tuned by structural modification of the boronic moiety [94]. In DDS, boronic esters may be incorporated as crosslinkers in polymer networks or as capping groups for mesoporous carriers, where ROS-induced cleavage results in carrier destabilization or gate opening [82].

A third approach utilizes sulfur- or selenium-containing polymers that undergo alterations of physicochemical properties upon oxidation, such as poly(propylene sulfide) or selenium-substituted analogs that transition from a hydrophobic to hydrophilic phase, causing polymer swelling, dissolution, or micelle disassembly [99,100]. This transformation can release encapsulated hydrophobic drugs from micellar systems to modulate swelling and release kinetics of bulk materials, such as hydrogels, in response to local ROS levels.

ROS-triggered release mechanisms

ROS can activate drug release through several primary mechanisms [6,101]. Carrier degradation occurs when ROS cleaves specific chemical bonds within the carrier, breaking the structure into soluble fragments that liberate the payload [102]. Nanopore opening is a common feature of inorganic and hybrid carriers, where ROS-sensitive gatekeepers block nanopores until exposed by oxidative cleavage, allowing drug diffusion [103,104]. Hydrophobic-to-hydrophilic transitions of amphiphilic polymers or micelles occur when oxidation of hydrophobic segments increases polarity, destabilizing the core-shell structure of the carrier, thereby facilitating release [105,106]. These mechanisms can operate singly or in combination, depending on the carrier type, desired release profile, and oxidative conditions of the target tissue.

Carrier types for ROS-responsive therapeutics

ROS-responsive carrier systems have been developed across diverse material platforms, each employing distinct activation mechanisms and offering unique therapeutic advantages (Table 3) [6,101,106-115]. Polymeric NPs are among the most extensively studied carriers, with poly (lactic-co-glycolic acid) (PLGA), polyethylene glycol (PEG)-modified polymers, and block copolymers serving as versatile platforms [116-118]. Incorporation of ROS-cleavable linkages or pendant groups enables precise control over release kinetics in response to local oxidative stress, while PEGylation improves stability, circulation, and biocompatibility.

Inorganic nanomaterials offer structural tunability and

Table 3 Characteristics of representative ROS-responsive carrier systems and their characteristics

Type	Responsive moieties	Advantages	Limitations	References
Polymeric nanoparticles	Thioketal, thioether, boronic ester	Excellent structural tunability; Stable in circulation; Precise control of degradation kinetics; High drug-loading capacity	Requires complex synthesis; Potential burst release at excessively high ROS; Degradation by-products must be biocompatible	[107]
Polymeric micelles	Thioether, selenide, boronate	Rapid, reversible response to low-moderate ROS; Suitable for hydrophobic drugs; Scalable self-assembly	Limited stability in protein-rich fluids; Possible premature disassembly; Small payload volume	[106]
Hydrogels	Thioketal, aryl boronate, oxalate	Excellent wound conformity; Prolonged local retention; Can serve as moist dressing with controlled release	Slower ROS diffusion may delay response; Potential incomplete degradation in low-ROS regions	[108]
Liposomal systems	Thioether, selenide, vinyl ether	Biocompatible and clinically familiar; Suitable for combined antioxidant-drug delivery	Membrane oxidation may compromise stability during storage; Limited control of release kinetics	[115]
Dendrimers and hyperbranched polymers	Boronate, thioketal, amino-borane	Precise molecular architecture; Multivalent surface modification; Good nucleic acid complexation	complex synthesis routes; Potential cytotoxicity at high generation numbers	[109,110]
Inorganic-organic hybrid nanoparticles	MnO_2, CeO_2, Fe_3O_4 integrated with polymer shell	Dual function: ROS scavenging and stimulus-triggered release; Imaging capability	Possible long-term metal residue accumulation; Regulatory challenges for inorganic components	[111-113]
Electrospun fibrous films	Thioketal, boronate, hybrid nanocatalyst	Suitable for chronic wound dressings; Supports cell adhesion; Sustained and spatially localized release	Limited penetration depth; Mechanical fragility under wet conditions	[114]
Nanozymes	MnO_2, Pt, CuO_2, CeO_2	Self-regulating redox balance; Combined therapeutic and diagnostic function	Requires careful dose and redox calibration; Potential oxidative toxicity at excess levels	[6,101]

ROS. Reactive oxygen species; H_2O_2. Hydrogen peroxide; ·OH. Hydroxyl radical; Nanozymes. Nanomaterial-based artificial enzymes

multifunctionality. Metal-organic frameworks (MOFs) can be engineered with ROS-labile linkers or loaded with ROS-scavenging/producing agents, allowing synergistic redox modulation [101]. Mesoporous silica nanoparticles (MSNs) are frequently capped with ROS-degradable polymers or molecular gates to achieve "on-off" release [119,120]. Additionally, nanozymes, nanomaterials with enzyme-like catalytic activity, can modulate ROS levels while simultaneously acting as delivery platforms, making them highly relevant to chronic wound microenvironments [121-123].

ROS-degradable hydrogels and wound dressings represent a particularly promising class for localized therapy. Hydrogels incorporating thioether or boronic ester crosslinks can degrade in oxidative environments and release embedded drugs directly into the wound bed [116,124]. Integration of such hydrogels into wound patches enables sustained, site-specific therapy with the added benefit of maintaining a moist healing environment. Furthermore, these systems can be combined with ROS-sensing elements to create "smart" dressings capable of both monitoring and responding to the oxidative status of the wound [124].

Notably, the cleavage of thioether linkages typically generates sulfoxide or sulfone species, which generally have low toxicity and are readily metabolized through oxidative pathways *in vivo*. Since excessive oxidation may alter local redox balance, thioether-containing systems are usually applied at controlled doses [125]. Similarly, boronic ester or boronate linkages degrade into phenolic derivatives and boric acid, which exhibit both good biocompatibility and rapid renal clearance at therapeutic concentrations [126].

Therapeutic applications in chronic wound healing

Antimicrobial therapy

The management of bacterial infection of chronic wounds, particularly diabetic ulcers, remains a cornerstone of therapeutic strategies due to the high risk of persistent biofilm formation, antibiotic resistance, and exacerbated inflammatory responses [94]. Conventional systemic antibiotics often fail to eradicate pathogens within the dense extracellular polymeric matrix of biofilms, while prolonged usage contributes to antimicrobial resistance [94,101]. Advanced biomaterial-based approaches now offer targeted, sustained, and microenvironment-responsive antimicrobial activity, often combined with complementary functionalities, such as oxygenation, ROS regulation, and immune modulation [127,128]. For instance, a programmed *Haematococcus pluvialis* (HEA)-based hydrogel system demonstrated light intensity-dependent functionalities, where high-intensity irradiation (658 nm) induced potent photothermal antibacterial activity capable of disinfecting wound surfaces, while lower light intensities activated photosynthetic oxygen release to support vascular regeneration [129]. Notably, this dynamic platform enabled sequential modulation of infection, hypoxia, and oxidative stress, resulting in accelerated healing of infected diabetic wounds *in vivo*. Similarly, a bilayer hydrogel incorporating *Chlamydomonas reinhardtii* microrobots in the lower layer for bio-oxygenation and silver-fulvic acid (FA) NPs in the upper layer for photothermal bacterial eradication achieved dual action against biofilms and hypoxia, representing an integrated "three-pronged strategy" for management of chronic diabetic wounds [130].

Recent innovations in antimicrobial therapy for chronic wounds also focus on constructing multifunctional catalytic and supramolecular systems to disrupt bacterial metabolism and quorum sensing while simultaneously enhancing wound repair [111,113]. In one study, a hyperbranched poly-L-lysine (HBPL)-crosslinked hydrogel loaded with MnO_2 nanozymes (HMP hydrogel) displayed broad-spectrum bactericidal activity against methicillin-resistant *Staphylococcus aureus* (*S. aureus*), *Escherichia coli* (*E. coli*), and *Pseudomonas aeruginosa*, with killing efficiencies exceeding 94% even at high bacterial loads (10^9 CFU/ml) [110]. Beyond direct killing, HBPL inhibited bacterial quorum sensing and downregulated virulence gene expression, thereby impairing bacterial communication and biofilm maturation. Such combined antibacterial and quorum-quenching properties resulted in reduced neutrophil infiltration, increased M2 macrophage polarization, and enhanced angiogenesis in infected diabetic wound models. Another example is the guanosine-driven hyaluronic acid (HA) supramolecular hydrogel, which harnessed guanosine self-assembly into G-quartets to load hemin with peroxidase-like activity, enabling localized ·OH generation in the presence of H_2O_2 [131]. Incorporation of glucose oxidase further modulated the wound glucose microenvironment and augmented antibacterial effects, while dynamic crosslinking provided adaptability to the wound's biochemical milieu. These supramolecular and enzymatic strategies underscore the shift from static antimicrobial coatings toward responsive, multifunctional wound dressings capable of counteracting microbial persistence while supporting host tissue recovery.

Balancing antimicrobial potency with preservation of host tissue integrity has become a critical focus of chronic wound therapy, as excessive ROS-mediated bacterial killing can exacerbate inflammation and impede regeneration [110]. To

address this issue, redox-modulatory antimicrobial platforms have been developed to fine-tune oxidative stress within the wound bed. A phytochemical-nanozyme hybrid utilized Ce^{3+}/Ce^{4+} cycling and ferulic acid radical scavenging to exert controlled antibacterial effects against *S. aureus* and *E. coli*, while activating the nuclear factor erythroid 2-related factor 2 (Nrf2)/heme oxygenase-1 (HO-1) antioxidant pathway to promote angiogenesis and collagen deposition [132]. Likewise, a sono-piezodynamic therapy-enabled nanocatalytic membrane composed of black phosphorus/V_2C MXene heterojunctions achieved clearance of drug-resistant bacteria under ultrasound-triggered ROS generation, followed by ROS scavenging when stimulation ceased, thereby preventing excessive oxidative damage [105]. Localized delivery approaches, such as copper-manganese oxide-loaded microneedles, have further demonstrated effective killing of bacteria, ROS scavenging, and regulation of macrophage polarization through combined enzymatic and photothermal mechanisms [128]. Collectively, these advances highlight a paradigm shift in chronic wound antimicrobial therapy from singular bactericidal modalities toward spatiotemporally controlled, microenvironment-adaptive systems that couple infection control with regenerative support.

The management of bacterial infection in chronic wounds, particularly in diabetic ulcers, remains a cornerstone of therapeutic strategies due to the high risk of persistent biofilm formation, antibiotic resistance, and exacerbated inflammatory responses [76]. Biofilms, formed by bacterial colonies encased in an extracellular polymeric matrix, protect the pathogens from host immune cells and antibiotics, making infections extremely difficult to eradicate [133]. Moreover, the prolonged use of antibiotics to combat these infections often leads to the development of antibiotic resistance, further complicating treatment [134]. Recent studies highlight that biofilm-associated infections in diabetic ulcers not only increase the risk of chronic inflammation but also delay wound healing by hindering normal immune response and tissue regeneration [135,136]. These challenges underscore the need for advanced antimicrobial strategies, such as ROS-responsive DDS, which can target bacterial biofilms and modulate the wound microenvironment to improve healing outcomes.

ROS-responsive DDS for antimicrobial therapy represents a promising approach to overcome the persistent challenge of bacterial infections in chronic wounds, particularly in diabetic ulcers [79]. These systems utilize the inherent oxidative stress of the wound environment to release therapeutic agents in a controlled manner, ensuring targeted and sustained antimicrobial activity [105]. The combination of antimicrobial properties with ROS regulation is critical, as it reduces the risk of excessive ROS buildup, which could impair healing [76]. Moreover, photothermal and catalytic strategies illustrate the dual functionality of these systems, providing both infection control and wound regeneration. The ability to simultaneously modulate infection, inflammation, and hypoxia represents a shift toward multifunctional platforms, where the synergy between ROS and therapeutic payloads drives more effective wound healing outcomes [110,112].

Anti-inflammatory modulation

Recent studies have demonstrated that incorporating ROS-responsive or antioxidative components into wound dressings enables precise modulation of the inflammatory phase [137-139]. For instance, a double network hydrogel, combining a gelatin-methacrylate and copper-alginate network with luteolin-loaded NPs (GSC/PBE@Lut), achieved spatiotemporal control over the release of luteolin, a flavonoid with potent anti-inflammatory properties, by exploiting both pH and ROS responsiveness [138]. This system promoted the polarization of macrophages toward the anti-inflammatory (M2) phenotype, while simultaneously attenuating the proinflammatory (M1) response, thereby accelerating the resolution of inflammation. Similarly, a dual-component particulate polyacrylic acid/madecassoside dressing facilitated robust microenvironmental modulation by downregulating inflammatory cytokines and steering macrophage polarization, which synergistically enhanced tissue regeneration [137]. These approaches underscore the importance of integrating immunomodulatory functions directly into wound dressings to actively guide the inflammatory phase toward a regenerative trend.

Beyond passive anti-inflammatory effects, some DDS have been engineered to actively target specific molecular pathways implicated in inflammation [140,141]. The glucose-responsive HA-phenylboronic acid (PBA)-FA/EN106 hydrogel combines HA, PBA, and FA to create a glucose-responsive, antibacterial, and antioxidative environment that promotes healing. The "EN106" component is released in a glucose-dependent manner, stimulating angiogenesis and reducing oxidative stress to accelerate wound repair [140]. The HA-PBA-FA/EN106 hydrogel exemplifies such precise intervention, where controlled release of the fem-1 homolog b-folliculin-interacting protein 1 axis inhibitor mitigated mitochondrial ROS overproduction and rescued angiogenic dysfunction under hyperglycemic conditions [140]. By simultaneously delivering FA, an agent with intrinsic anti-inflammatory and antibacterial properties, this platform provided multifaceted

microenvironmental regulation, breaking the cycle of OS and inflammation [140]. Similarly, ROS-responsive hydrogel matrices embedding lipid NPs for co-delivery of antimicrobial peptides and puerarin effectively suppressed the bacterial burden and modulated vascular inflammation [115]. In another innovative example, a multifunctional microneedle system (CeO_2@Tau@Hydrogel@Microneedle) combined deep-tissue antioxidant delivery with direct inhibition of the ROS/NF-κB axis in macrophages, dampening proinflammatory signaling cascades and preventing chronic immune activation [111]. The spatial precision afforded by microneedle-based penetration ensures that anti-inflammatory agents reach deeper tissue layers where persistent inflammatory cells reside, improving the therapeutic outcomes in otherwise refractory chronic wounds.

A further evolution of ROS-targeted anti-inflammatory DDS is the ability to sequentially and adaptively regulate inflammation in concert with other wound healing phases [142]. This is exemplified by dissolvable dual-layer microneedles incorporating selenium-doped carbon quantum dots for immediate ROS scavenging, followed by sustained release of astilbin to promote M2 macrophage polarization and angiogenesis [141]. Such staged release aligns with the physiological transition from inflammation to proliferation, but reduced early suppression of inflammation, which could hinder pathogen clearance. The multifunctional dihydromyricetin-loaded Pluronic F-127-based hydrogel extends this principle by integrating glycemic control with anti-inflammatory activity, addressing systemic drivers of chronic inflammation in diabetic wounds [142]. Importantly, these platforms combine sustained release kinetics, antioxidant capacity, and macrophage reprogramming, creating a synergistic effect that overcomes the limitations of monotherapy. Collectively, these findings highlight that anti-inflammatory modulation in chronic wound healing is most effective when achieved through multifunctional, ROS-responsive DDS that integrate temporal control, microenvironmental targeting, and combinatorial therapy.

Anti-inflammatory modulation in chronic wound healing is essential to overcome prolonged inflammation and facilitate tissue regeneration. ROS-responsive DDS can fine-tune the wound microenvironment by spatiotemporally controlling the release of anti-inflammatory agents. Systems, such as the GSC/PBE@Lut hydrogel, demonstrate how ROS and pH responsiveness can direct macrophage polarization toward the anti-inflammatory M2 phenotype to accelerate tissue repair. Moreover, these platforms not only mitigate inflammation but also engage with key molecular pathways to precisely modulate mitochondrial ROS production, fostering a regenerative microenvironment [138]. Multifunctional DDS that integrates antioxidant properties with anti-inflammatory interventions are particularly promising by enabling precise, dynamic regulation of the inflammatory response, while preserving immune function and accelerating wound healing.

Angiogenesis and tissue regeneration

Angiogenesis, the sprouting of new blood vessels from the pre-existing vasculature, is indispensable for effective chronic wound repair by ensuring adequate oxygen and nutrient delivery to support tissue regeneration [143]. In chronic wounds, persistent inflammation, pathological ROS accumulation, and hypoxia synergistically impair endothelial proliferation, vessel maturation, and microvascular stability, ultimately delaying or preventing closure [7]. ROS-based DDS have emerged as powerful tools to address these obstacles, enabling precise modulation of the wound microenvironment through targeted oxidative stress regulation, staged release of pro-angiogenic factors, and combination with oxygen delivery or antimicrobial strategies.

Recent biomaterial advances have demonstrated that angiogenesis is most effective when preceded by the resolution of inflammation and normalization of ROS levels. For example, bilayer alginate hydrogels encapsulating polyelectrolyte complex NPs co-loaded with interleukin (IL)-10 and angiogenic growth factors exhibit a temporally programmed release, first releasing IL-10 to suppress inflammation via janus kinase 1/signal transducer and activator of transcription 3 activation, followed by VEGF/PDGF to stimulate vessel sprouting and stabilization in diabetic murine wounds [144]. By using ROS-labile linkages or scavenging moieties within the hydrogel network, such systems can maintain VEGF bioactivity in oxidative environments and prevent premature degradation. Similarly, inflammation- and ROS-responsive hydrogels incorporating Prussian blue NPs with VEGF have been shown to quench excess ROS production, preserve growth factor function, and significantly enhance capillary density in type 2 diabetic wound models [145].

ROS-responsive DDS integration also benefits targeting molecular suppressors of neovascularization [146]. Grancalcin, a proinflammatory protein elevated in diabetic wounds, inhibits angiogenesis via transient receptor potential melastatin 8 channel signaling [147]. Sustained delivery of grancalcin-neutralizing antibodies from gelatin methacrylamide hydrogels restores endothelial activity and vessel formation. When combined with ROS-scavenging components, these hydrogels further relieve oxidative endothelial injury, amplifying

angiogenic outcomes [147]. Likewise, ROS-controlled oxygen delivery systems such as oxygen-generating microspheres embedded in ROS-responsive hydrogels, simultaneously mitigate hypoxia and oxidative stress, while enhancing endogenous expression of angiogenic growth factors [148]. Notably, these oxygenation platforms achieve robust vascular network formation without exogenous pharmacologics, highlighting the efficacy of microenvironmental reprogramming through redox balance restoration.

The integration of extracellular vehicles (EVs) into ROS-adaptive dressings has expanded pro-angiogenic therapy toward more targeted and sustained outcomes [149,150]. EVs from *Lactobacillus rhamnosus* GG (LGG) promote angiogenesis and epithelialization via miR-21-5p-mediated metabolic reprogramming of endothelial and epithelial cells [149]. When incorporated into ROS-scavenging hydrogels, EV bioactivity is preserved under oxidative stress, prolonging their pro-healing effect. Similarly, glycoengineered EVs modified with sialyl Lewis X (sLeX), encapsulated in antibacterial Gel/PL-5 hydrogels, exhibit E-selectin-mediated targeting to inflamed vasculature, accelerating vascular regeneration in infected diabetic wounds [150]. Multifunctional scaffolds embedding adipose-derived stem cells with angiogenic cues such as ginsenoside RG1 and stromal cell-derived factor-1 also demonstrate synergistic neovascularization and neurogenesis, especially when ROS-responsive matrices protect cell viability and modulate local redox homeostasis [151].

Catalytic and enzymatic platforms further illustrate the versatility of ROS-based DDS in coupling infection control with angiogenesis promotion. For instance, glucose oxidase-functionalized copper metal-organic framework (Cu-MOF/GOX) hydrogels consume excess glucose, a metabolic driver of oxidative stress, while generating H_2O_2 and NO *in situ*, the latter acting as a potent vasodilator and pro-angiogenic mediator [152]. Similarly, platinum-armed Fe-based MOF nanozymes (Pt@FeMOF) embedded in ROS-adaptive cryogels achieve rapid hemostasis, eradicate biofilms via synergistic Fenton chemistry, and relieve oxidative stress-induced endothelial senescence, thereby restoring angiogenic capacity [153]. Collectively, these examples emphasize that effective angiogenesis in chronic wounds requires more than isolated growth factor delivery, but also demands multi-pronged, ROS-aware strategies that integrate redox regulation, inflammation resolution, hypoxia mitigation, and infection control.

Angiogenesis plays a central role in wound healing by ensuring an adequate supply of oxygen and nutrients to the regenerating tissue [76,105]. ROS-responsive DDS provides a mechanism for spatiotemporally controlled release of pro-angiogenic factors, such as VEGF and IL-10, while simultaneously modulating oxidative stress to enhance endothelial function and capillary growth [154]. Systems like bilayer alginate hydrogels and Prussian blue NP-based hydrogels demonstrate how ROS scavenging can preserve the bioactivity of growth factors and improve vascular network formation in diabetic wound models [145]. Furthermore, the integration of EVs into ROS-responsive hydrogels exemplifies how cell-based therapies can be incorporated into these systems to enhance tissue regeneration [124]. The multifunctionality of these DDS, combining angiogenesis promotion with oxidative stress management and immune regulation, sets them apart as effective therapeutic options for chronic wound healing.

Multimodal therapy

Chronic wound healing demands therapeutic strategies that address multiple pathological factors in parallel, persistent infection, excessive inflammation, oxidative stress, impaired angiogenesis, and deficits in tissue regeneration [29,79,143]. In this context, ROS-based multimodal DDS offer a unique advantage: they not only act as carriers for diverse therapeutic agents but also actively participate in microenvironmental regulation by scavenging excess ROS or harnessing ROS-triggered release mechanisms [155,156]. This dual capability allows integration of antibacterial, immunomodulatory, pro-angiogenic, and ECM remodeling functions within a single therapeutic platform, achieving superior efficacy compared to monotherapies.

A representative example is the prodigiosin-loaded SN-PB@PG nanocomplex for bacterial-infected chronic wounds [157]. This hybrid system couples sodium nitroprusside with prussian blue NPs, the latter functioning as both ROS scavengers and photothermal agents, followed by loading with the antibacterial pigment prodigiosin (PG). Upon near-infrared (NIR) irradiation, Prussian blue NPs generate mild hyperthermia, which not only enhances biofilm disruption but also facilitates on-demand release of NO and PG [157]. Beyond antimicrobial activities, NO promotes angiogenesis via VEGF and CD31 upregulation, while PG eradicates biofilms and suppresses proliferation of multidrug-resistant pathogens [157]. In diabetic wound models, this ROS-adaptive platform achieved wound area reduction to 10.6% by day 11 and improved flap survival rates, illustrating how photothermal-assisted, gas-mediated, and ROS-regulated release can simultaneously control infection and restore vascular networks [157].

Another notable ROS-related approach employs

ferrocene-HA organic copolymer (FHoC) hydrogels as multifunctional dressings [158]. The inherent redox activity of ferrocene enables modulation of ROS levels at the wound site to reduce OS-driven tissue damage. Fe^{2+} ions released from ferrocene not only participate in mild ROS regulation but also enhance angiogenesis [158]. The HA backbone provides biocompatibility and moisture balance, while the microcrystalline, hydrophobic domains yield exceptional exudate absorption (up to 150-fold of dry weight) without structural collapse [158]. This combination of physical wound protection, oxidative stress modulation, and pro-angiogenic stimulation addresses the common chronic wound issue of excessive exudate, inflammation, and delayed granulation tissue formation, while also offering a scaffold for localized drug or cell delivery.

ROS regulation also plays a key role in biofilm eradication and long-term infection control. Polyurea-based multimodal interaction nanogels employ multiple intermolecular interactions for high-capacity antimicrobial loading, including quorum-sensing inhibitors (QSI) [159]. By disrupting bacterial communication pathways, QSIs prevent recolonization, while antibiotics provide immediate biofilm clearance [159]. When engineered with ROS-responsive elements, such nanogels can release antimicrobials in oxidative infection niches, ensuring localized, on-demand therapy [159]. Similarly, photothermal hydrogels incorporating bacteria-capturing bio-MOFs (QCSMOF-Van) combine vancomycin delivery with ROS-mediated metabolic disruption via Zn^{2+} release, while shifting macrophages toward the pro-regenerative M2 phenotype [155]. The result is a coordinated antibacterial, immunomodulatory, and angiogenic response in complex wound environments.

A further dimension involves immune reprogramming alongside oxidative stress regulation. Self-adapting biomass hydrogels based on carboxymethyl chitosan have been engineered to co-deliver antibacterial peptides and miR-301a-loaded NPs within a ROS-sensitive matrix [160]. This design enables peptide release in oxidative microenvironments, providing sustained clearance of Gram-positive and -negative bacteria, while miR-301a reprograms macrophages toward the anti-inflammatory M2 phenotype via the phosphatase and tensin homolog/phosphoinositide 3-kinase gamma/mammalian target of rapamycin pathway [160]. By attenuating ROS-driven chronic inflammation and simultaneously controlling infection, these hydrogels create a permissive environment for tissue regeneration [160]. Taken together, ROS-based multimodal DDS represent a significant shift from single-target interventions to integrated, redox-aware therapeutic platforms by synchronizing antimicrobial, anti-inflammatory, pro-angiogenic, and regenerative actions in a spatially and temporally controlled manner to address the multifactorial pathology at the biochemical root of chronic wounds.

While we primarily emphasize ROS-responsive DDS designed for exogenous drug delivery, it is indeed important to acknowledge that ROS-responsive materials can also act as bioactive regulators of endogenous repair mechanisms, even in the absence of external therapeutic agents [8,79]. These materials function through intrinsic ROS-scavenging activity, catalytic redox regulation, or fine-tuning of redox-associated signaling pathways, contributing to the restoration of redox homeostasis and subsequent tissue regeneration [79,161]. For instance, nanozymes and ROS-scavenging polymers can neutralize excessive ROS, mitigate oxidative stress and inflammation while enhancing fibroblast proliferation and angiogenesis [121]. Similarly, ROS-degradable hydrogels not only provide a protective, moist environment but also dynamically remodel in response to oxidative cues, facilitating cell migration and matrix deposition [162]. Furthermore, ROS-tunable scaffolds can modulate intracellular redox-sensitive pathways such as Nrf2/antioxidant response element and HIF-1α, thereby stimulating endogenous antioxidant and angiogenic responses [163]. Integrating these self-regulatory, material-intrinsic effects with drug delivery functions represents a promising direction for developing next-generation ROS-responsive biomaterials that both deliver exogenous therapeutics and reprogram endogenous wound repair processes.

Theranostic platforms for chronic wounds

The integration of real-time diagnosis and on-demand therapy, theranostics, represents a paradigm shift in chronic wound management, enabling personalized interventions tailored to the evolving wound microenvironment [164]. In ROS-responsive DDS, theranostic platforms extend beyond ROS neutralization by using aberrantly elevated ROS as a local trigger for therapeutic payload release and concurrent *in situ* monitoring.

As a key differentiator, theranostic platforms integrate diagnostic capability with therapeutic functions [165]. For example, a porous silicon (Psi)-based carrier encapsulating an NIR-active dye (IR820) in a calcium-sealed form (I-CaPSi) is an innovative theranostic approach that uses ROS exposure to modulate the photothermal signal. Upon oxidative degradation of the Psi framework, IR820 is released, reducing photothermal output, which is then detected non-invasively

using a smartphone-based thermal camera, providing a real-time wound monitoring system [166]. This enables continuous assessment of wound status while simultaneously delivering photothermal and photodynamic antibacterial effects and promoting fibroblast migration and angiogenesis via NIR irradiation. This combined approach provides both diagnostic and therapeutic functions in a single, user-friendly platform for chronic wound theranostics [166].

Furthermore, ROS-responsive smart dressings represent another important theranostic development [167]. These dressings integrate ROS-sensitive sensors with therapeutic release capabilities, enabling continuous tracking of wound biomarkers without the need to remove the dressing [168]. These sensors can activate closed-loop or externally triggered release of ROS scavengers, antimicrobials, or pro-angiogenic factors, directly responding to real-time wound conditions and thus providing dynamic therapeutic feedback [164]. The key innovation of these platforms is the combination of diagnostic monitoring with therapeutic action in real-time, enabling personalized treatment adjustments.

Another promising example of theranostics for chronic wounds involves nanomedicine-based systems. For instance, trisulfide-derived lipid NPs encapsulating *IL-4* mRNA can target ROS in the wound environment, enabling the NPs to act both as ROS scavengers and as delivery vehicles for therapeutic mRNA. Upon internalization by macrophages, *IL-4* mRNA is translated to shift macrophages from the proinflammatory M1 phenotype to the pro-regenerative M2 phenotype, which accelerates tissue repair [169]. Coupled with appropriate imaging modalities, such as ROS-activated fluorescent probes or thermal signal transduction, this system not only facilitates therapeutic release but also allows for molecular-level monitoring of both ROS dynamics and therapeutic progress [170]. These examples illustrate that theranostic platforms extend beyond multimodal therapy by integrating diagnostic sensors with responsive therapeutic actions, thus providing real-time feedback and control over wound healing.

Translational considerations and future perspectives

ROS-responsive DDS offers unique advantages in the treatment of chronic wounds, especially in conditions like diabetic ulcers, where ROS accumulation is a hallmark of the wound microenvironment. These systems exploit localized oxidative stress to enable targeted drug release at the wound site, minimizing systemic side effects and ensuring that therapeutic drug concentrations are maintained in the affected area [115]. However, the variability in ROS levels across different wound types presents a challenge to the consistent performance of ROS-responsive DDS, as fluctuations in ROS levels can affect their effectiveness in achieving optimal drug release [170]. In contrast, other stimuli-responsive DDS, such as those triggered by pH, enzymes, or temperature, have also been applied for chronic wound healing [79]. For certain infected or necrotic tissues, pH-responsive systems can release drugs in acidic environments, but lack the specificity of ROS-responsive systems, and the pH in chronic wounds may fluctuate significantly [136,154]. Enzyme-responsive DDS, targeting specific proteases like matrix metalloproteinases, can effectively promote tissue remodeling, but applicability may be limited depending on the wound types [6]. Temperature-responsive systems, which rely on changes in local temperature, may face challenges in chronic wounds due to the lack of consistent temperature variation [79]. While alternative stimuli-responsive DDS offer complementary therapeutic approaches, ROS-responsive systems stand out as highly specific for the unique microenvironment of chronic wounds, demonstrating superior potential in clinical applications [6,71].

Chronic oxidative stress also plays a significant role in driving pathological fibrosis during impaired wound healing, an aspect increasingly recognized as a major barrier to functional tissue regeneration [23,24]. Persistent ROS accumulation activates fibroblasts and myofibroblasts through pathways such as transforming growth factor beta/smad, mitogen-activated protein kinase, and Wnt/β-catenin, leading to excessive ECM deposition and aberrant collagen cross-linking [171]. In chronic wounds, this sustained profibrotic signaling disrupts the balance between ECM synthesis and degradation, resulting in prolonged granulation tissue persistence, stiffened wound beds, and impaired re-epithelialization [172]. Furthermore, ROS-induced oxidative modification of matrix proteins alters their biomechanical properties and perpetuates fibroblast activation in a feed-forward manner [173]. By enabling controlled ROS scavenging and microenvironment modulation, ROS-responsive DDS offer a promising strategy to attenuate fibroblast hyperactivation, normalize ECM remodeling, and reduce fibrosis-related wound chronicity [174]. Incorporating antifibrotic capabilities into ROS-responsive platforms may therefore enhance both structural and functional recovery in chronic wound healing.

Emerging living materials, including living therapeutic materials and living biotherapeutics, offer a promising avenue for chronic wound healing and can be integrated with redox-regulated or ROS-responsive strategies [175]. For example, living hydrogels encapsulating *Lactobacillus rhamnosus*

engineered with intracellular nano-selenium combine antimicrobial activity with ROS scavenging, modulating the inflammatory microenvironment, and promoting repair [176]. Such systems dynamically adapt to the wound milieu, with embedded cells or microbes acting as *in situ* redox regulators by producing antioxidant enzymes, secreting ROS scavengers, or releasing therapeutic payloads in response to oxidative cues [175]. ROS levels can further modulate microbial metabolism, enabling self-regulation of therapeutic activity. Hybrid systems that integrate living materials with synthetic ROS-responsive scaffolds could combine the adaptive, self-renewing properties of living cells with precise release kinetics of engineered polymers, offering sustained, site-specific therapy [177]. Successful translation of these systems requires careful design to balance safety, metabolic load, and responsiveness to pathological ROS, highlighting the potential and challenges of living therapeutics in chronic wound management.

The clinical translation of ROS-based DDS for chronic wound therapy hinges first and foremost on ensuring material safety and biocompatibility [79]. Many current ROS-responsive platforms employ inorganic NPs, MOFs, or organometallic components, which, while effective in laboratory studies, may raise concerns regarding systemic toxicity, metal ion accumulation, and potential off-target redox reactions in human tissues [178,179]. Even naturally derived polymers, such as chitosan or HA, require careful modification and thorough evaluation to avoid eliciting immune hypersensitivity or interfering with normal tissue homeostasis [180-182]. Regulatory agencies will require detailed toxicological profiling, encompassing not only acute and subchronic toxicity but also long-term biodistribution, clearance pathways, and effects on distant organs. Achieving a balance between potent ROS reactivity and physiological safety is thus a central challenge, necessitating iterative material design, surface functionalization to minimize nonspecific interactions, and the incorporation of biodegradable linkages that allow safe metabolic elimination [14].

Beyond safety, the long-term stability and storage conditions of ROS-based DDS remain a critical hurdle for real-world deployment. Many ROS-responsive carriers rely on labile chemical bonds, catalytic NPs, or sensitive biological cargos, which may degrade or lose functionality under ambient conditions [113,183]. Moisture, oxygen, and light exposure can prematurely trigger ROS-scavenging or ROS-generating reactions, depleting therapeutic efficacy before application. For hospital and field settings, particularly in low-resource regions, wound dressings should be stable at room temperature for extended periods, packaged to prevent premature activation, and compatible with sterilization methods such as gamma irradiation or ethylene oxide treatment [76]. Achieving this requires advances in encapsulation strategies and the use of protective coatings or secondary shells that preserve reactivity until contact with the wound microenvironment. Addressing these storage and stability concerns is essential to ensure that ROS-based systems maintain consistent therapeutic performance across diverse clinical scenarios.

Achieving scalable manufacturing while preserving product quality and cost efficiency remains a major translational challenge. Laboratory protocols for synthesizing ROS-responsive nanomaterials often involve multi-step reactions, organic solvents, or specialized equipment that are not readily transferable to large-scale manufacturing [184,185]. Batch-to-batch variability can significantly impact ROS sensitivity, release kinetics, and safety profiles, complicating regulatory approval. Cost considerations are particularly pressing for chronic wound care, where treatments may need to be applied repeatedly over weeks to months [186]. To be commercially viable, production pipelines should integrate high-throughput synthesis, green chemistry approaches, and robust quality control systems. Furthermore, discrepancies between preclinical animal models and human wound microenvironments represent a substantial translational barrier [187]. Common diabetic or ischemic wound models in rodents differ from human wounds in size, chronicity, microbial diversity, and immune responses, leading to overestimation of therapeutic efficacy in early studies [79,188]. Incorporating large-animal models and *ex vivo* human skin cultures, alongside standardized outcome measures, will improve predictive accuracy and accelerate regulatory acceptance.

In the future, the next generation of ROS-responsive systems for chronic wound therapy will likely move toward personalized and precision medicine [189,190]. By profiling an individual patient's wound ROS spectrum, using minimally invasive biosensors, clinicians could select or tune DDS formulations to match the oxidative stress burden and healing phase, avoiding both under- and over-scavenging of ROS [54]. Integration with wearable electronics offers a powerful avenue for continuous ROS monitoring and closed-loop feedback control, where real-time data could trigger on-demand drug release, photothermal activation, or oxygen generation [191]. Coupling these platforms with artificial intelligence-driven wound management systems could enable predictive modeling of the healing period, automated adjustment of therapy regimens, and remote clinical oversight. Moreover, multimodal therapeutic combinations, such as ROS regulation synergized with immunomodulatory cues and regenerative

medicine strategies, may address the multifactorial nature of chronic wounds more effectively than single-modality interventions [192-195]. These convergent approaches will require interdisciplinary collaboration between materials scientists, bioengineers, clinicians, and data scientists, but hold the promise of transforming ROS-based DDS from experimental concepts into adaptive, patient-specific wound healing solutions capable of dramatically improving quality of life for individuals with recalcitrant wounds.

Conclusions

ROS-responsive DDS offer unique advantages in chronic wound management by exploiting the pathological hallmark of sustained oxidative stress for site-specific, on-demand therapeutic release. This strategy enables precise spatiotemporal drug deployment, minimizes systemic exposure, and allows integration of multifunctional capabilities, such as antimicrobial action, immunomodulation, and angiogenesis promotion, within a single platform. Moreover, the potential to couple ROS-responsiveness with diagnostic modalities facilitates theranostic applications, enabling real-time monitoring and adaptive treatment. Nevertheless, limitations remain, including the heterogeneity of ROS levels across wound types and stages, possible off-target activation in inflamed but non-wounded tissues, and challenges in achieving long-term stability, scalable manufacturing, and regulatory approval. Overcoming these barriers requires close interdisciplinary collaboration among materials scientists, clinicians, bioengineers, and regulatory experts to refine design parameters, develop standardized evaluation protocols, and conduct rigorous clinical trials. Ultimately, translating ROS-responsive DDS from bench to bedside will depend on harmonizing innovative material science with clinically relevant outcomes, ensuring that therapeutic efficacy, safety, and cost-effectiveness align with the complex needs of chronic wound care.

Abbreviations

DCFH-DA: 2′,7′-dichlorofluorescein diacetate
DDS: Drug delivery systems
DHE: Dihydroethidium
ECM: Extracellular matrix
EVs: Extracellular vehicles
FA: Fulvic acid
HA: Hyaluronic acid
HBPL: Hyperbranched poly-L-lysine
HIF-1α: Hypoxia-inducible factor-1α
H_2O_2: Hydrogen peroxide
HOCl: Hypochlorous acid
HO-1: Heme oxygenase-1
HPF: Hydroxyphenyl fluorescein
IL-10: Interleukin-10
MOFs: Metal-organic frameworks
MSNs: Mesoporous silica nanoparticles
NADPH: Nicotinamide adenine dinucleotide phosphate
NF-κB: Nuclear factor kappa-B
NIR: Near-infrared
NP: Nanoparticle
Nrf2: Nuclear factor erythroid 2-related factor 2
$O_2^{\cdot-}$: Superoxide anion radical
·OH: hydroxyl radical
$ONOO^-$: Peroxynitrite
PBA: Phenylboronic acid
PDGF-B: Platelet-derived growth factor B
PEG: Polyethylene glycol
PG: Pigment prodigiosin
QSI: Quorum-sensing inhibitors
ROS: Reactive oxygen species
VEGF: Vascular endothelial growth factor

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Authors' contributions

YX, BBM, and MAS designed the framework. HW, YX, and QPW wrote the manuscript. MAS, YX, and BBM revised the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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