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# Ferroptosis in Diabetic Wound Repair: Cell-Specific Mechanisms, Therapeutic Targeting, and Translational Barriers

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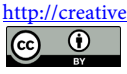



## Abstract

Diabetic wounds, particularly diabetic foot ulcers (DFUs), are sustained by hyperglycemia, ischemia, infection, persistent inflammation, oxidative stress, defective angiogenesis and matrix failure. Ferroptosis—an iron-dependent regulated cell death driven by phospholipid peroxidation—provides a mechanistic link among these abnormalities. A targeted PubMed search through 10 July 2026, supplemented by reference-list screening, identified mechanistic, preclinical and clinical studies relevant to ferroptosis in diabetic wound repair. Evidence was classified as oxidative-injury-associated or ferroptosis-causal according to whether compatible iron/lipid-peroxidation findings were accompanied by ferroptosis-directed rescue, genetic perturbation or orthogonal validation. Iron dyshomeostasis, impaired SLC7A11-GSH-GPX4 activity, altered NRF2 signaling, mitochondrial stress, ferritinophagy, endoplasmic reticulum stress and neutrophil extracellular traps can lower the ferroptotic threshold in macrophages, keratinocytes, fibroblasts and endothelial cells. Current interventions include natural compounds, traditional formulations, extracellular vesicles, platelet-rich plasma, nanozymes and hydrogel-based delivery systems. The evidence supports cell- and stage-specific modulation rather than blanket inhibition: reparative cells generally require protection, whereas selective induction in defined pro-inflammatory or senescent states remains preclinical. The only prospective DFU biomarker evidence is observational, and no controlled DFU treatment study has demonstrated clinical efficacy of a ferroptosis-targeted intervention. Translation is limited by non-specific biomarkers, incomplete causal validation, simplified models and uncertain long-term material safety. Progress requires orthogonal ferroptosis assays,

clinically realistic models, human tissue validation and prospective outcome-linked studies.

## Keywords

Diabetic Foot Ulcer, Ferroptosis, Lipid Peroxidation, Iron Homeostasis, Wound Healing, Translational Medicine

## 1. Introduction

Diabetes mellitus is a chronic metabolic disease defined by sustained hyperglycemia, and its global burden continues to increase. The 11th edition of the International Diabetes Federation Diabetes Atlas estimated that 589 million adults aged 20 - 79 years were living with diabetes in 2024 and projected 853 million cases by 2050. Diabetic foot ulcers (DFUs) are among the most destructive manifestations of diabetic wound disease. They recur frequently, are prone to infection, and carry substantial risks of amputation, high treatment costs and premature death [1]-[3]. A DFU is not simply a local skin defect. Hyperglycemia, ischemia and hypoxia, neuropathy, repeated mechanical loading, microbial colonization, oxidative stress and unresolved inflammation coexist in the wound bed. Consequently, keratinocyte migration, fibroblast matrix production, endothelial angiogenesis and inflammatory resolution fail in parallel. Regulated cell-death pathways, including apoptosis, dysregulated autophagy, pyroptosis, necroptosis, cuproptosis and ferroptosis, are increasingly viewed as active drivers of this failure rather than passive markers of tissue injury [4] [5]. Ferroptosis was originally defined as an iron-dependent, non-apoptotic form of regulated cell death. Its central biochemical event is the accumulation of oxidized phospholipids in membranes enriched with polyunsaturated fatty acids. When lipid hydroperoxides exceed the capacity of antioxidant defense systems, membrane integrity collapses and the cell dies through a process that is biochemically distinct from apoptosis and morphologically different from classic necrosis [6] [7]. The diabetic wound environment is unusually permissive to ferroptosis. Hyperglycemia increases reactive oxygen species (ROS), hypoxia and infection amplify inflammatory signaling, vascular dysfunction restricts oxygen and nutrient delivery, and antioxidant reserves are chronically depleted. Ferroptosis therefore provides more than another pathway label: it links iron handling, lipid metabolism, immune persistence, failed re-epithelialization, poor matrix formation and microvascular injury within a testable framework. Previous reviews have often surveyed programmed cell death broadly or catalogued ferroptosis-related pathways and interventions. The present review uses a different organizing principle. It asks which cell is undergoing ferroptosis, at what stage of healing, whether the evidence demonstrates ferroptotic causality rather than generic oxidative stress, and whether an intervention has a credible route to clinical use. This distinction matters because the desired therapeutic direction may

differ between reparative cells, inflammatory macrophage states and senescent fibroblasts.

## 2. Literature Search and Review Framework

PubMed was searched through 10 July 2026 using three reproducible query blocks. The core wound query was: ("ferroptosis"[Title/Abstract] OR ferroptotic[Title/Abstract]) AND ((diabet*[Title/Abstract] AND wound*[Title/Abstract]) OR "diabetic foot ulcer"[Title/Abstract] OR "diabetic foot ulcers"[Title/Abstract]). The cell-specific query added: AND (macrophage*[Title/Abstract] OR keratinocyte*[Title/Abstract] OR fibroblast*[Title/Abstract] OR endothelial[Title/Abstract]). The translational query added: AND (exosome*[Title/Abstract] OR "extracellular vesicle"[Title/Abstract] OR "extracellular vesicles"[Title/Abstract] OR "platelet-rich plasma"[Title/Abstract] OR hydrogel*[Title/Abstract] OR nanozyme*[Title/Abstract] OR biomarker*[Title/Abstract] OR clinical[Title/Abstract]). Reference lists of relevant primary studies and reviews were screened manually. Priority was given to peer-reviewed English-language studies directly examining diabetic wound repair; studies from other disease settings were used only to explain established ferroptosis biology not yet adequately tested in diabetic wounds.

This review was designed as a targeted narrative review rather than a systematic review. The original search did not prospectively retain a PRISMA-style record-by-record screening log; therefore, exact retrospective numbers of records screened and excluded cannot be verified without rerunning the search, and unverified counts are not reported. The revised review reports the full reproducible search strings above and includes 60 sources in the final reference list. No formal risk-of-bias score or pooled effect estimate was calculated. For cell-specific conclusions, evidence is labeled at two mechanistic levels. “Oxidative-injury-associated” denotes studies showing changes such as $Fe^{2+}$, ROS, MDA, 4-HNE, GPX4, SLC7A11 or ACSL4 without ferroptosis-selective rescue or genetic/pathway perturbation sufficient to establish cell death by ferroptosis. “Ferroptosis-causal” denotes compatible lipid-peroxidation/iron phenotypes accompanied by ferroptosis-directed rescue, genetic manipulation, pathway perturbation or orthogonal validation. Translational relevance is considered separately and requires validation in human tissue, clinically realistic wound models or reproducible delivery systems. Human observational biomarker associations are not classified as ferroptosis-causal in the absence of such evidence.

## 3. Pathobiological Basis of Ferroptosis in Diabetic Wounds

### 3.1. Iron Dyshomeostasis: From Systemic Iron Cycling to the Local Labile Iron Pool

Iron is required for oxygen transport, mitochondrial respiration, DNA synthesis and numerous enzymatic reactions. Systemic iron homeostasis depends on intestinal absorption, transferrin-mediated transport, transferrin receptor-dependent

uptake, ferritin storage, ferroportin-mediated export and macrophage recycling of senescent erythrocytes. During normal repair, adequate iron supports cell proliferation, host defense and collagen synthesis. In diabetic wounds, however, persistent inflammation and oxidative stress can disturb hepcidin, ferroportin, transferrin receptor and ferritin expression, thereby enlarging the local labile iron pool [8] [9]. Excess ferrous iron promotes Fenton chemistry and generates hydroxyl radicals that attack polyunsaturated phospholipids. Iron is therefore a genuine double-edged factor. Indiscriminate chelation could compromise proliferative and antimicrobial functions, whereas uncontrolled iron accumulation amplifies oxidative injury and sensitizes reparative cells to ferroptosis. A rational treatment should reduce the redox-active iron pool without depriving regenerating tissue of iron required for metabolism and matrix formation.

### 3.2. Lipid Peroxidation and the SLC7A11-GSH-GPX4 Axis

Lipid peroxidation is the execution phase of ferroptosis. Membrane phospholipids containing arachidonic or adrenic acid can be oxidized through enzymatic and non-enzymatic reactions. If phospholipid hydroperoxides are not reduced, membrane fluidity declines, permeability rises and organelle function deteriorates. Autophagic degradation, mitochondrial injury, endoplasmic reticulum stress and antioxidant capacity together determine whether an oxidative challenge remains reversible or progresses to ferroptotic death [10] [11]. The SLC7A11-GSH-GPX4 pathway is the best-characterized anti-ferroptotic system. SLC7A11 is the light-chain component of system Xc−, the cystine/glutamate antiporter. Imported cystine is reduced to cysteine and used for glutathione (GSH) synthesis. Glutathione peroxidase 4 (GPX4) then uses GSH to reduce phospholipid hydroperoxides to less reactive lipid alcohols. Reduced SLC7A11 expression, GSH depletion or GPX4 inhibition permits accumulation of lipid ROS, MDA and 4-HNE and lowers the threshold for ferroptosis [12] [13].

### 3.3. GPX4-Independent Ferroptosis Defense Systems

A GPX4-centered model is incomplete. Ferroptosis suppressor protein 1 (FSP1) regenerates reduced coenzyme Q10 at the plasma membrane and can inhibit lipid peroxidation independently of GSH and GPX4. In mitochondria, dihydroorotate dehydrogenase (DHODH) supports a parallel CoQ-dependent defense, whereas GTP cyclohydrolase 1 (GCH1) and tetrahydrobiopterin (BH4) protect selected phospholipid pools through radical-trapping and lipid-remodeling effects [14]-[16]. These backup systems are well established in general ferroptosis biology but have received little direct study in diabetic wounds. This gap has two implications. First, restoration of GPX4 alone may not explain the full response to a treatment. Second, cells that retain FSP1-, DHODH- or BH4-dependent protection may appear resistant despite substantial oxidative stress. Future wound studies should therefore measure more than the canonical SLC7A11-GSH-GPX4 axis and determine whether the relevant defense pathway differs among keratinocytes, fibroblasts, macrophages and endothelial cells.

### 3.4. NRF2 and Metabolic Signaling Networks

Nuclear factor erythroid 2-related factor 2 (NRF2) is a central transcriptional regulator of antioxidant and iron-handling responses. Under basal conditions, NRF2 is restrained mainly by Kelch-like ECH-associated protein 1 (KEAP1)-dependent degradation. Oxidative or electrophilic stress stabilizes NRF2, allowing it to induce HMOX1, NQO1, GCLC, SLC7A11 and GPX4. SLC7A11 also intersects with immune regulation, insulin secretion, mTOR signaling and cellular redox balance [17]-[19]. Experimental diabetic wound models support the relevance of this axis. Early work identified ferroptotic features in diabetic wounds and showed that ferroptosis inhibition reduced inflammatory injury. Bone marrow stromal cell-derived exosomal circular RNA and an MMP-9-responsive cinnamaldehyde hydrogel have subsequently been reported to activate NRF2-related anti-ferroptotic signaling and improve angiogenic repair [20]-[22]. Macrophage and endothelial studies further connect NRF2 with inflammatory resolution and neovascularization. Ferrostatin-1 reduced high-glucose-induced macrophage injury through NRF2 activation, whereas mesenchymal stromal cell-derived extracellular vesicles inhibited neutrophil extracellular trap (NET)-induced endothelial ferroptosis and improved vessel formation [23] [24]. Energy-sensing pathways add another layer of context. Meteorin-like protein attenuated mitochondrial damage and ferroptosis through LKB1/AMPK-related signaling in a diabetic foot ulcer model. In contrast, AMPK activation can promote NCOA4-mediated ferritinophagy and facilitate clearance of senescent cells. AMPK therefore cannot be assigned a uniformly anti- or pro-ferroptotic role; its effect depends on cell identity, metabolic state and wound stage [25] [26] (**Figure 1**).

Hyperglycemia, ischemia, infection and persistent inflammation promote iron dysregulation, mitochondrial/endoplasmic reticulum stress and failure of antioxidant defenses. Lipid peroxidation then impairs macrophage state transitions, re-epithelialization, matrix formation and angiogenesis. Therapeutic direction should be determined by cell identity and wound stage: reparative cells generally require protection, whereas selective elimination of defined pathological cell states remains an experimental strategy. BH4, tetrahydrobiopterin; DHODH, dihydroorotate dehydrogenase; ER, endoplasmic reticulum; FSP1, ferroptosis suppressor protein 1; NETs, neutrophil extracellular traps; PUFA, polyunsaturated fatty acid.

## 4. Cell-Specific Ferroptosis in Diabetic Wound-Healing Failure

### 4.1. Macrophages: Persistent Inflammation and Context-Dependent Targeting

Macrophages coordinate the transition from inflammation to tissue repair. The commonly used M1/M2 terminology is a simplification—wound macrophages occupy a continuum of activation states—but it remains useful for describing the failure of diabetic wounds to move from inflammatory to reparative programs. Persistent inflammatory macrophage states are associated with weak efferocytosis,

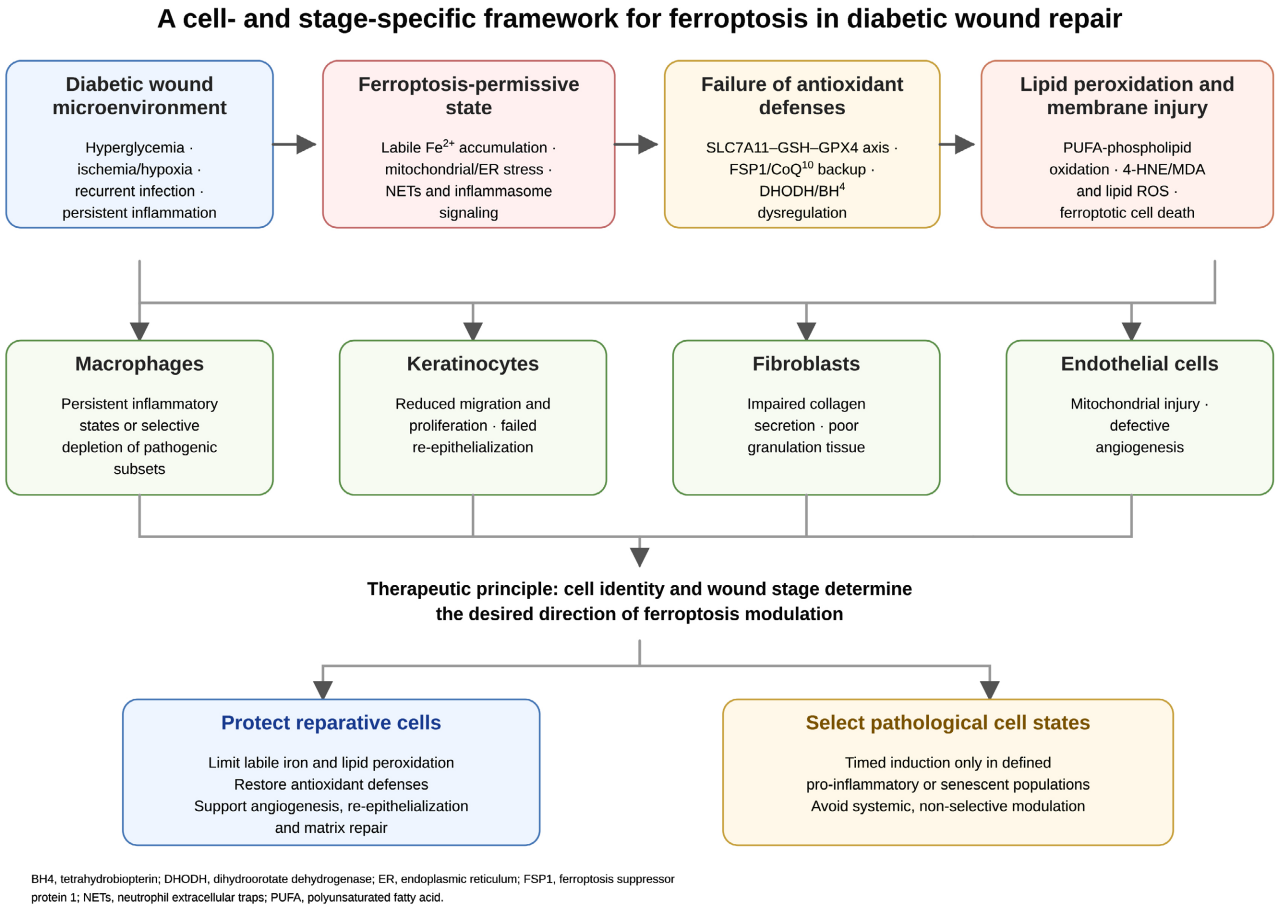


**Figure 1.** Cell- and stage-specific framework linking the diabetic wound microenvironment to ferroptosis and therapeutic direction.

sustained cytokine release and impaired angiogenic and matrix-remodeling support. Iron handling is closely linked to macrophage function, and tissue iron can promote reparative polarization and chemokine programs involved in re-epithelialization [27] [28]. The therapeutic implication is not that all macrophage ferroptosis should be suppressed. In hyperglycemic or infected wounds, iron overload and lipid peroxidation can injure macrophages and prolong inflammation, making ferroptosis inhibition beneficial. Conversely, experimental systems that induce ferroptosis in selected inflammatory macrophage populations have reduced inflammatory burden. Work involving asiaticoside-loaded GelMA and the NINJ1-STAT3 axis illustrates this bidirectionality, but the evidence remains preclinical and does not justify indiscriminate macrophage depletion [29] [30].

Evidence source and causal interpretation. The direct diabetic-wound evidence supporting macrophage ferroptosis is derived from cultured macrophages and diabetic rodent wound models rather than from cell-resolved human DFU intervention studies. The asiaticoside/GelMA and NINJ1 studies used ferroptosis-directed mechanistic perturbation and are therefore interpreted as ferroptosis-causal at the preclinical level [29] [30]. Iron-handling and macrophage-polarization observations without ferroptosis-specific rescue are interpreted as oxidative-injury-associated rather than proof of ferroptotic death [28].

### 4.2. Keratinocytes: Ferroptosis and Failed Re-Epithelialization

Keratinocytes restore the epidermal barrier through proliferation, migration and differentiation. High glucose and advanced glycation end products increase $Fe^{2+}$, ROS and MDA while reducing GPX4 and ferritin expression. Berberine has been reported to activate NRF2 and restore anti-ferroptotic proteins in diabetic skin. More recent studies implicate histone lysine crotonylation, SQSTM1/p62-dependent autophagy, YTHDF2-mediated m6A regulation and ACSL4-dependent lipid remodeling. Keratinocyte ferroptosis is therefore not simply a passive consequence of oxidative stress; it is embedded in epigenetic, post-transcriptional and autophagic control of lipid metabolism [31]-[33].

Evidence source and causal interpretation. The cited evidence consists principally of keratinocyte cultures and diabetic mouse or rat wound models; no study cited here establishes keratinocyte ferroptosis causally in human DFU tissue. Berberine-associated changes in $Fe^{2+}$, ROS/MDA and NRF2/GPX4 are treated as oxidative-injury-associated/ferroptosis-supportive [31], whereas ACSL4/YTHDF2 pathway perturbation and ferroptosis-inhibitor rescue in the mechanistic studies meet the review's ferroptosis-causal criterion at the preclinical level [32] [33].

### 4.3. Fibroblasts: Ferroptosis, Matrix Failure and Granulation-Tissue Quality

Fibroblasts synthesize collagen, organize extracellular matrix and determine the mechanical quality of granulation tissue. High glucose reduces fibroblast proliferation, migration and collagen secretion while increasing $Fe^{2+}$, ROS and MDA. Beta-boswellic acid has been reported to inhibit STAT3-associated fibroblast ferroptosis and improve collagen deposition in diabetic rats. Platelet-rich plasma-derived exosome hydrogels can restore GPX4/SLC7A11 expression, whereas NETs induce fibroblast ferroptosis through IRE1$\alpha$/XBP1-mediated endoplasmic reticulum stress and suppress collagen production. These observations place neutrophil-fibroblast and platelet/exosome-fibroblast crosstalk at the center of granulation-tissue failure [34]-[36].

Evidence source and causal interpretation. These conclusions derive from fibroblast cell culture, including human skin fibroblast preparations, together with streptozotocin-diabetic rodent wound models rather than a clinical fibroblast intervention study. The beta-boswellic-acid study combined human skin fibroblast experiments with a diabetic rat model and showed ferrostatin-1-sensitive effects, supporting a preclinical ferroptosis-causal interpretation [34]. NET/IRE1$\alpha$-XBP1 and PRP-exosome experiments are classified as ferroptosis-causal only where pathway perturbation or ferroptosis-directed rescue accompanies lipid-peroxidation readouts; marker-only changes remain oxidative-injury-associated [35] [36].

### 4.4. Vascular Endothelial Cells: Ferroptosis and Impaired Angiogenesis

Endothelial dysfunction contributes to hypoxia, poor microcirculatory perfusion

and weak angiogenesis in diabetic wounds. High glucose damages mitochondria, raises ROS and promotes phospholipid peroxidation, reducing endothelial proliferation, migration and tube formation. Adipose stem cell-derived apoptotic vesicles can suppress endothelial ferroptosis and improve angiogenesis. The cGAS-STING pathway and CEBPD-dependent CXCL10 transcription have also been linked to $Fe^{2+}$ accumulation, GPX4 loss and impaired tissue regeneration. Endothelial ferroptosis therefore affects both vessel growth and the inflammatory tone of the wound bed [37]-[39].

Evidence source and causal interpretation. The available data are predominantly endothelial-cell culture and diabetic rodent wound studies. Apoptotic-vesicle and cGAS-STING studies include mechanistic perturbation or rescue and are treated as preclinical ferroptosis-causal evidence [37] [38]. CEBPD-CXCL10 findings are interpreted as ferroptosis-causal only to the extent that pathway manipulation is linked to $Fe^{2+}$/GPX4 and functional wound-repair changes; marker associations alone remain oxidative-injury-associated [39]. No cell-resolved human DFU study cited here establishes endothelial ferroptosis causally.

Table 1 summarizes the experimental source, causal grade and therapeutic interpretation for the principal cell-specific evidence.

**Table 1.** Cell-specific evidence, causal classification and therapeutic implications of ferroptosis in diabetic wound repair.

| Cell/evidence source | Representative evidence | Causal label | Therapeutic implication |
|---|---|---|---|
| Macrophages—cultured macrophages and diabetic rodent wounds; no cell-resolved human causal study | Iron handling affects macrophage function; selective targeting of inflammatory macrophage states has shown benefit [28]-[30]. | oxidative-injury-associated [28]; ferroptosis-causal (preclinical) [29] [30] | Use timed, subset-specific modulation rather than global macrophage targeting. |
| Keratinocytes—keratinocyte cultures and diabetic mouse/rat wounds | NRF2/GPX4, ACSL4, YTHDF2 and crotonylation influence lipid peroxidation and re-epithelialization [31]-[33]. | oxidative-injury-associated/ supportive [31]; ferroptosis-causal (preclinical) [32] [33] | Protect migrating keratinocytes and preserve epidermal barrier restoration. |
| Fibroblasts/ER stress—human skin fibroblast/cell culture plus STZ-diabetic rodent wounds | STAT3, PRP-exosome and NET-IRE1*α*/XBP1 pathways alter ferroptosis-related readouts and collagen production [34]-[36]. | Ferroptosis-causal where ferrostatin-1 or pathway rescue/perturbation is shown; marker-only findings are associated | Combine NET/ER-stress control with support for matrix production. |
| Vascular endothelial cells—endothelial-cell culture and diabetic rodent wounds | Mitochondrial ROS, cGAS-STING and CEBPD-CXCL10 signaling impair angiogenic repair [37]-[39]. | Preclinical causal where mechanistic rescue/perturbation is present; no human cell-resolved causal proof | Protect endothelial metabolism and couple ferroptosis control with pro-angiogenic therapy. |
| Antibacterial ferroptosis-like injury—bacteria plus infected diabetic-wound models | Nanozyme systems amplify oxidative membrane damage in bacteria while aiming to preserve host cells [40] [41]. | Not canonical mammalian ferroptosis; retain "ferroptosis-like" terminology for bacteria | Verify host-cell safety and avoid conflating bacterial oxidative death with mammalian ferroptosis. |

## 5. Ferroptosis-Targeted Interventions in Diabetic Wounds

### 5.1. Natural Compounds and Pharmacological Agents

Natural compounds are attractive because many combine antioxidant, anti-inflammatory and pro-angiogenic activity. Hesperetin activates SIRT3 and limits lipid peroxidation, while orientin stimulates NRF2/GPX4 signaling. Dulaglutide, a glucagon-like peptide-1 receptor agonist, restored NRF2, GPX4 and SLC7A11 signaling and reduced keratinocyte ferroptosis in diabetic mice. These studies provide mechanistic leads, but most use a single rodent model and do not compare the candidate treatment with contemporary wound-care standards [42]-[44].

### 5.2. Traditional Medicine-Derived Formulations

Traditional formulations have also generated mechanistic data. Ruan Jian Qing Mai formula attenuated NINJ1-associated macrophage ferroptosis, whereas Chuangling Ye suppressed keratinocyte ferroptosis by inhibiting ACSS2-mediated ACSL4 acetylation. These findings are more informative than generic pathway-enrichment analyses because they include functional validation. Even so, translation requires batch-level chemical characterization, identification of active constituents, dose-response relationships, pharmacodynamic markers and reproducible local-safety assessment [45].

### 5.3. Extracellular Vesicles and Platelet-Rich Plasma

Extracellular vesicles can transport microRNAs, circular RNAs, proteins and mitochondrial components and thereby modify inflammation, angiogenesis and redox metabolism. Bone marrow mesenchymal stromal cell-derived exosomes carrying circ-Snhg11 enhanced SLC7A11/GPX4-dependent protection. Platelet-rich plasma (PRP) has likewise been associated with reduced oxidative and ferroptotic markers and improved healing in diabetic ulcer models. The main obstacle is standardization: vesicle isolation, potency assays, storage, PRP platelet concentration, leukocyte content, activation method and dosing schedule vary substantially across studies [46]-[48].

### 5.4. Nanomaterials, Hydrogels and Antibacterial Synergy

Diabetic wounds commonly contain bacterial biofilms and drug-resistant organisms, but clinical healing is also strongly influenced by devitalized tissue, peripheral artery disease/ischemia and repetitive pressure loading. Contemporary DFU management therefore relies on infection assessment and appropriately targeted antimicrobial therapy, debridement when indicated, vascular assessment and revascularization when needed, pressure offloading, and evidence-based wound-healing care. Ferroptosis-directed materials should be evaluated as adjuncts to, rather than substitutes for, these standards [49]-[53]. Nanomaterials and hydrogels can improve local retention, provide controlled release, maintain a moist environment and combine antimicrobial and regenerative functions. Prussian blue

analogue nanozymes have been designed to reduce $Fe^{2+}$ accumulation and lipid peroxidation while promoting a reparative macrophage phenotype. Ferrous sulfide/glycyrrhizic acid hydrogels can modify ROS and inflammatory conditions in infected diabetic wounds [54] [55]. Newer systems attempt to protect host reparative cells while producing oxidative membrane injury in bacteria. $Fe_3O_4$/MXene heterojunction GelMA microneedles and defect-engineered Fe-WS2@glucose oxidase nanozymes illustrate this approach. Because bacteria lack the canonical mammalian ferroptosis machinery, "ferroptosis-like bacterial death" is the more defensible term. Long-term material retention, degradation products, immunogenicity, activation parameters and batch-to-batch reproducibility remain unresolved [40] [41].

Table 2 compares the translational readiness of the major intervention classes against these clinical-development requirements.

**Table 2.** Translational readiness of major ferroptosis-targeted intervention classes.

| Intervention class | Current evidence | Main strength | Critical limitation | Priority next step |
|---|---|---|---|---|
| Natural compounds/repurposed drugs | Cell and rodent studies [42] [43] | Defined molecules and tractable dosing | Limited head-to-head comparison and uncertain local exposure | Pharmacokinetics, dose optimization and comparison with guideline-based standard care |
| Traditional formulations | Mechanistic animal studies [30] [45] | Multi-target activity in complex wound environments | Composition, batch consistency and active components | Chemical fingerprinting and prespecified pharmacodynamic markers |
| Extracellular vesicles/PRP | Preclinical wound models [46] [48] | Broad regenerative cargo and local delivery potential | Heterogeneous preparation and potency | Consensus manufacturing and release criteria |
| Nanozymes/hydrogels | Predominantly rodent infected-wound models [40] [54] | Combined antimicrobial and regenerative functions | Long-term safety, degradation and manufacturing scale-up | Clinically realistic large-animal models and toxicology |
| Biomarker-guided therapy | One prospective observational study plus transcriptomic discovery [56] [57] | Potential patient selection and response monitoring | Markers are not ferroptosis-specific; no controlled efficacy evidence | Prospective multimodal validation with prespecified thresholds |

## 6. Clinical Translation: Biomarkers, Causal Evidence and Model Validity

For ferroptosis to become clinically useful, it must be measurable, stratifiable and linked to treatment response. Jiang *et al.* conducted a single-center prospective cohort study involving 59 patients with DFU (Wagner grades I - III; 25 men and 34 women; mean age 63.5 ± 15.0 years) and 42 patients with traumatic wounds. Wound exudate was collected after admission before surgical treatment, and 4-HNE, MDA and ROS were assayed. Wound area was recorded at admission and again at 30 days to derive the healing rate. The DFU group

had higher 4-HNE, MDA and ROS, and these markers were inversely associated with 30-day healing [56]. However, the study did not test a ferroptosis-targeted treatment, used oxidative markers that are not specific to ferroptosis, and did not report multivariable adjustment for wound infection status or limb ischemia/peripheral artery disease. Accordingly, it is classified here as oxidative-injury-associated clinical evidence rather than ferroptosis-causal evidence. Machine-learning and transcriptomic studies have identified ferroptosis-related signatures, including MAPK3-associated patterns and CGNL1-positive inflammatory fibroblast states, as candidate diagnostic or prognostic markers [57] [58].

As of the literature-search cutoff of 10 July 2026, no controlled DFU treatment study has demonstrated clinical efficacy of an intervention designed specifically to modulate ferroptosis. Clinical association studies should therefore be distinguished explicitly from therapeutic efficacy evidence.These signals are not specific enough for clinical decision-making. MDA, ROS and 4-HNE vary with infection, ischemia, inflammation, sampling depth and wound-care procedures. Similarly, reduced GPX4 or increased ACSL4 supports a ferroptotic phenotype but does not by itself prove ferroptotic death. Stronger causal inference requires rescue by chemically distinct ferroptosis inhibitors, direct lipid-peroxidation measurements, iron-flux assays, ultrastructural support where appropriate, and cell-specific genetic manipulation [7] [13].

Model validity is an equally serious problem. Most studies use short-term, full-thickness excisional wounds in rodents. Human DFUs are shaped by neuropathy, macro- and microvascular disease, repeated pressure loading, polymicrobial biofilms, debridement and heterogeneous comorbidity. A treatment that accelerates closure in a clean mouse wound may fail in a pressure-bearing, ischemic and infected human ulcer. Future preclinical studies should incorporate at least two clinically relevant stressors and report not only wound area but also epithelial continuity, vascular perfusion, tensile properties, infection burden and recurrence. These features also explain why future ferroptosis studies should benchmark candidate therapies against guideline-based debridement, infection management, vascular care and offloading rather than against untreated controls alone [49]-[53].

Ferroptosis also intersects with cellular senescence. Senescent fibroblasts may resist NCOA4-dependent ferroptosis and persist in the wound, whereas enzyme-responsive nanospheres that selectively target senescent cells have improved healing in preclinical models. This evidence reinforces the central conclusion of the review: the most credible strategy is controlled selection of pathological cell states, not blanket inhibition or blanket induction of ferroptosis [59] [60].

A practical clinical biomarker will probably be composite rather than singular. Wound exudate metabolites, tissue immunostaining, cell-state signatures, perfusion imaging and routine clinical variables could be combined into a ferroptosis-informed risk or response score. Such a score should be developed prospectively,

use prespecified thresholds, and demonstrate incremental value over established measures of ulcer size, ischemia, infection and neuropathy.

## 7. Conclusion and Perspectives

Ferroptosis links iron dyshomeostasis, phospholipid peroxidation, antioxidant failure, mitochondrial stress and persistent inflammation in diabetic wounds. Evidence is strongest for a detrimental role in endothelial cells, keratinocytes and fibroblasts, where ferroptosis impairs angiogenesis, re-epithelialization, collagen production and granulation-tissue quality. Macrophages and senescent fibroblasts are more complex: the consequence of ferroptosis depends on cell state, timing and the surrounding wound environment. The field now needs to move beyond repeated measurement of NRF2, SLC7A11, GPX4, ACSL4, MDA and ROS. GPX4-independent defenses should be tested, ferroptotic causality should be demonstrated with orthogonal methods, and therapeutic studies should use models that reproduce ischemia, pressure, infection and neuropathy. Material-based and biologic therapies require rigorous manufacturing and safety standards. Human tissue studies and prospective clinical cohorts must then determine whether ferroptosis adds useful information to current DFU classification and treatment. Only that evidence chain can convert ferroptosis from an attractive mechanistic narrative into a clinically actionable target. At present, human clinical evidence remains associative, and controlled therapeutic efficacy of ferroptosis-targeted treatment in DFU remains unproven.

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Conceptualization and review design, Yongfu Chen; literature retrieval and screening, Yongfu Chen, Pengyuan He, Wenbo Li, Runze Wu, Jiahui Wang and Dingpeng Ban; evidence synthesis, all authors; writing—original draft preparation, Yongfu Chen; writing—review and editing, Haidong Zhou, Jihua Wei; supervision, Jihua Wei. All authors have read and agreed to the published version of the manuscript.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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## Abbreviations

ACSL4, acyl-CoA synthetase long-chain family member 4;
ACSS2, acyl-CoA synthetase short-chain family member 2;
AMPK, AMP-activated protein kinase;
BH4, tetrahydrobiopterin;
CEBPD, CCAAT/enhancer-binding protein delta;
cGAS, cyclic GMP-AMP synthase;
CXCL10, C-X-C motif chemokine ligand 10;
DFU, diabetic foot ulcer;
DHODH, dihydroorotate dehydrogenase;
ER, endoplasmic reticulum;
FSP1, ferroptosis suppressor protein 1;
GCH1, GTP cyclohydrolase 1;
GPX4, glutathione peroxidase 4;
GSH, glutathione;
4-HNE, 4-hydroxynonenal;
KEAP1, Kelch-like ECH-associated protein 1;
MDA, malondialdehyde;
NETs, neutrophil extracellular traps;
NCOA4, nuclear receptor coactivator 4;
NRF2, nuclear factor erythroid 2-related factor 2;
PRP, platelet-rich plasma;
ROS, reactive oxygen species;
SLC7A11, solute carrier family 7 member 11;
STING, stimulator of interferon genes.