Review

When and How Ferroptosis Becomes Pathogenetic in Psoriasis

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Posted Date: 26 February 2026

doi: 10.20944/preprints202602.1713.v1

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When and How Ferroptosis Becomes Pathogenetic in Psoriasis

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Abstract

Psoriasis is classically framed as an IL-23/IL-17/TNF-driven immune disease, yet durable remission remains elusive for many patients, suggesting that epidermal-intrinsic pathogenic mechanisms shape chronicity and therapeutic escape. Here we propose ferroptosis, viewed as iron-dependent membrane lipid peroxidation coupled to failure of lipid repair, as a unifying, epidermis-centered axis that links metabolic stress to immune amplification in psoriasis. In this review, we synthesize experimental evidence showing that GPX4 suppression, lipid peroxidation accumulation, dysregulated iron handling and PUFA-remodeling programs, together define ferroptosis-permissive niches in psoriatic plaques. We also integrate functional studies demonstrating that ferroptosis modulation reshapes psoriasiform inflammation and discuss why ferroptotic stress can act as a feed-forward amplifier at the immune-epidermal interface, reinforcing IL-17/TNF/IFN-γ circuits and myeloid-Th17 crosstalk. Finally, we highlight ferroptosis-related transcriptomic signatures as a stratification layer that captures metabolic heterogeneity beyond cytokine profiling, with implications for relapse and incomplete response to existing therapies. The translational opportunities and constraints for ferroptosis-targeted interventions are outlined, advocating precision normalization of epidermal redox homeostasis as a new therapeutic frontier in psoriasis.

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1. Introduction

Psoriasis is a chronic, immune-mediated inflammatory disease affecting more than 125 million individuals worldwide, imposing a substantial burden on quality of life and healthcare systems [1–3]. Plaque psoriasis is characterized by the development of well-demarcated, erythematous, scaly lesion that reflects profound alterations in epidermal architecture and function [4–6]. Histologically, psoriatic plaques display marked epidermal hyperplasia (acanthosis), elongated rete ridges, parakeratosis, and a severely shortened keratinocyte turnover time, with differentiation becoming incomplete and spatially disorganized [7,8]. This aberrant epidermal program is accompanied by loss of barrier integrity, altered lipid composition, and increased trans epidermal water [9,10]. Within plaques, the keratinocytes acquire a pro-inflammatory phenotype, producing cytokines, chemokines and antimicrobial peptides that sustain immune cell recruitment and activation [11–13]. Thus, the psoriatic epidermis is not merely a passive target of inflammation but an active driver of disease, in which dysregulated proliferation, differentiation, and barrier metabolism converge to perpetuate the chronic cutaneous inflammation.

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Current pathogenic models frame psoriasis as the product of a self-amplifying dialogue between the immune system and the epidermis, in which genetically primed keratinocytes aberrantly respond to environmental and inflammatory cues, fueling a pathogenic interleukin-23 (IL-23)/interleukin-17 (IL-17)/tumor necrosis factor (TNF) axis that, in turn, sustains chronic inflammation and epidermal hyperplasia [14,15]. Despite the remarkable clinical success of cytokine-targeted therapies, a substantial fraction of patients remains only partially responsive or refractory, and disease frequently relapses upon treatment discontinuation. These limitations indicate that immune dysregulation alone cannot fully explain disease persistence, heterogeneity, and chronicity [15,16].

Increasing evidence points to the psoriatic epidermis as an active pathogenic compartment, characterized by profound alterations in lipid composition, redox homeostasis and differentiation programs, accompanied by impaired barrier integrity and heightened oxidative stress [17]. Within this emerging framework, psoriasis can be reinterpreted not solely as an immune disorder, but rather as a disease in which immune cytokines and metabolic stress converge on intrinsic vulnerability nodes within keratinocytes. One such node is ferroptosis, a distinct, metabolically governed form of cell death driven by iron-dependent lipid peroxidation and collapse of antioxidant defenses [18,19]. This perspective raises a critical question: could ferroptosis constitute a missing mechanistic link between epidermal metabolism and immune activation in psoriasis? Mechanistically, this link is plausible. On the one hand, ferroptotic cells release oxidized lipids and danger-associated molecular patterns (DAMPs) capable of activating innate immune sensors and reshaping tissue microenvironments [20]. On the other hand, in immune-mediated diseases, ferroptosis has been implicated in macrophage polarization, cytokine amplification, and tissue damage, as demonstrated in arthritis and autoimmunity models [21,22]. Thus, ferroptosis is positioned to operate at the interface between metabolic stress and inflammatory amplification.

Over the last few years, converging lines of evidence are placing ferroptosis at the core of psoriatic pathology. Transcriptomic and biochemical analyses of human psoriatic lesions reveal downregulation of glutathione peroxidase 4 (GPX4), accumulation of lipid peroxidation products, and dysregulation of iron-handling genes [18,23,24]. Experimental models demonstrate that pharmacological or genetic inhibition of ferroptosis in keratinocytes attenuates imiquimod (IMQ)-induced psoriasiform inflammation, directly implicating ferroptotic stress in disease propagation [25]. However, despite this rapidly expanding body of primary literature, existing reviews remain largely fragmented, typically addressing ferroptosis in isolation or within broader redox contexts, without integrating epidermal metabolism, immune circuitry, and tissue-level dynamics into a unified pathogenic framework. Here, we synthesize mechanistic, experimental, and systems-level evidence positioning ferroptosis as a pathogenic nexus in psoriasis. We first outline the molecular framework of ferroptosis with an epidermal focus, then we review human and experimental data linking ferroptotic stress to psoriatic inflammation. We also discuss how lipid and iron metabolism rewire keratinocyte vulnerability, how ferroptosis interfaces with immune circuits, and how ferroptosis-related gene signatures enable patient stratification. Finally, we explore the translational implications of targeting ferroptosis in psoriasis, proposing that modulation of epidermal redox death pathways may complement immunotherapy and open new therapeutic horizons. Through this lens, psoriasis emerges not solely as an immune disease, but as a redox–metabolic–immune disorder in which ferroptosis constitutes a central pathogenic axis.

2. Molecular Basis of Ferroptosis: A Skin-Oriented Overview

Ferroptosis is a regulated form of cell death driven by the iron-dependent accumulation of lipid hydroperoxides within cellular membranes [26–30]. Its execution reflects the convergence of three fundamental processes: intracellular iron availability, the enrichment of oxidizable polyunsaturated fatty acid (PUFA)-containing phospholipids, and the failure of lipid peroxide detoxification systems [31–33].

Iron is indispensable for cellular metabolism, yet potentially lethal when present in excess. The ferroptotic cascade is initiated by an expansion of the cytosolic labile iron pool (LIP), which fuels

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Fenton and Haber–Weiss reactions, generating highly reactive hydroxyl radicals. These radicals catalyze the oxidation of membrane lipids, particularly PUFA-containing phospholipids [34–38]. Cellular iron homeostasis is governed by a tightly regulated network involving transferrin receptor (TFRC)-mediated uptake, ferritin (FTH1/FTL)-based storage, and ferroportin (FPN)-dependent export [39–44]. Perturbations of this network, whether through increased iron import, impaired sequestration, or enhanced ferritinophagy, shift cells toward a pro-oxidant state permissive for ferroptosis [45,46]. Ferroptosis is mechanistically rooted in the peroxidation of PUFA-containing phospholipids within cellular membranes. This process is not stochastic but enzymatically primed. Acyl-CoA synthetase long-chain family member 4 (ACSL4) selectively activates PUFAs such as arachidonic and adrenic acid, while lysophosphatidylcholine acyltransferase 3 (LPCAT3) incorporates them into membrane phospholipids. These PUFA-phospholipids constitute the preferred substrates for lipid peroxidation, either through non-enzymatic radical chain reactions or via lipoxygenases. The accumulation of lipid hydroperoxides destabilizes membrane architecture, alters biophysical properties, and ultimately leads to catastrophic membrane failure [47,48]. Thus, ferroptosis is not merely an oxidative event, but the endpoint of a lipid remodeling program that determines which cells become permissive to death. Counterbalancing this pro-oxidant drive is a specialized network of membrane-protective systems, at the core of which lies glutathione peroxidase 4 (GPX4), a selenoprotein uniquely capable of reducing phospholipid hydroperoxides to their corresponding alcohols within membranes [49]. GPX4 activity is critically dependent on reduced glutathione (GSH), whose synthesis requires cysteine availability through the system xc- antiporter (SLC7A11/SLC3A2) [49,50]. Depletion of cysteine, inhibition of GSH synthesis, or direct inactivation of GPX4 leads to unchecked lipid peroxidation and rapid ferroptotic collapse [51]. Genetic ablation of GPX4 is embryonically lethal, and its conditional loss in epithelial tissues precipitates catastrophic barrier failure, underscoring its role as a gatekeeper of membrane integrity [52,53]. In inflammatory contexts, cytokine-driven metabolic stress, oxidative burden, and nutrient competition converge to impair the GPX4-GSH axis, rendering cells vulnerable to ferroptosis. Beyond GPX4, cells deploy auxiliary ferroptosis defense pathways. Ferroptosis suppressor protein 1 (FSP1, formerly AIFM2) operates independently of GSH by reducing coenzyme Q10 (CoQ10) to its lipophilic antioxidant form, ubiquinol, thereby intercepting lipid radical propagation within membranes [54,55]. Additional protective layers include the GTP cyclohydrolase 1 (GCH1)–BH4 axis and endosomal sorting complex required for transport (ESCRT) complex III (ESCRT-III)–mediated membrane repair. These systems confer plasticity to ferroptosis sensitivity and allow cells to buffer transient oxidative insults [56,57]. However, their capacity is finite and context-dependent, and in tissues characterized by sustained oxidative pressure, such as inflamed skin, these defenses may be chronically overwhelmed. Epidermal homeostasis is intrinsically dependent on lipid metabolism, redox regulation, and continuous environmental sensing; therefore, the skin, and particularly keratinocytes, constitutes a biological context where ferroptotic vulnerability acquires direct pathophysiological relevance. Compared with most epithelial lineages, keratinocytes exhibit a membrane architecture optimized for permeability control and interface with the external milieu, inadvertently generating a lipid landscape densely populated by oxidizable substrates. As such, the epidermis is uniquely enriched in PUFA-containing phospholipids that are indispensable for barrier formation, intercellular cohesion, and signal transduction [58]. Furthermore, keratinocytes terminal differentiation entails extensive membrane biogenesis, lipid extrusion, and assembly of the cornified envelope, processes that require high rates of lipid synthesis and remodeling [59,60]. Keratinocyte differentiation, thus, is strictly associated with a profound lipid reprogramming. As basal cells withdraw from the cell cycle and migrate suprabasally, they undergo coordinated shifts in fatty acid composition and phospholipid architecture. This differentiation-associated lipid flux transiently increases PUFA incorporation into membranes, creating physiological windows of heightened ferroptotic sensitivity [61]. This dynamic membrane turnover imposes a continuous demand on lipid-protective systems to preserve phospholipid integrity. Indeed, ablation of GPX4 in keratinocytes causes rapid epidermal degeneration and catastrophic barrier failure [62]. Concomitantly, keratinocytes are chronically

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exposed to both exogenous and endogenous sources of oxidative stress. Ultraviolet radiation, atmospheric pollutants, and microbial products converge on the epidermal surface, while inflammatory cytokines and infiltrating immune cells generate sustained intracellular ROS [63].

Together, these features position keratinocytes at the intersection of lipid metabolism, redox stress, and environmental exposure. As such, epidermis appears as a terrain in which ferroptotic checkpoints are repeatedly challenged, priming keratinocytes for lipid peroxidation–driven death and transforming ferroptosis from a latent vulnerability into a pathogenic effector.

3. Evidence for Ferroptosis in Psoriasis

Over the past 5 years, multiple independent lines of evidence highlight that ferroptosis pathways are engaged in psoriatic skin, with a final destiny towards a pathogenic or a compensatory direction strictly context- and stage-dependent. First, two independent studies highlighted that psoriatic plaques display a coherent ferroptosis-like molecular state characterized by aberrant lipid metabolism and activated lipid oxidation pathways, with GPX4 downregulation across epidermal layers and ACSL4 enrichment in basal keratinocytes, alongside increased lipid-peroxidation by-products such as 4-hydroxynonenal (4-HNE), iron-handling shifts with higher TFRC and lower FTH1/FTL levels, and increased PTGS2 used as inflammatory marker of ferroptotic stress [19,25]. Shou et al. first linked the epidermal lipid oxidation to psoriatic immune polarization at single-cell resolution, identifying a positive association between lipid oxidation in keratinocytes and Th17/Th22-related inflammatory signatures [25]. Later, building on this foundation, Zhou et al. (2022) argue that ferroptotic stress can release DAMPs/alarmins and engage eicosanoid pathways, notably via PTGS2/COX-2, potentially coupling arachidonic acid metabolism to cytokine amplification [19]. Shou et al. also demonstrated that pharmacological ferroptosis blockade using ferrostatin-1 (Fer-1) mitigated IMQ-induced psoriasiform dermatitis, supporting a model in which lipid peroxidation–driven ferroptotic stress amplifies inflammation once disease is established, even if it is not the primary initiating trigger [25]. Zhou et al. emphasized that ferroptosis inhibitors (Fer-1, liproxstatin-1) act as radical-trapping antioxidants that can modulate inflammatory outputs in keratinocytes and psoriasiform models, consistent with the interpretation that lipid peroxidation is both a driver and a readout of inflammatory escalation in psoriasis [19]. In 2022, Liu et al. demonstrated that in psoriatic lesions, ACSL4 expression was increased and positively correlated with inflammatory mediators (e.g., TNF, IL-6, IL-8, IL-17A) and psoriasis area severity index (PASI) score. They showed that erastin promoted inflammatory cytokine expression in keratinocytes, while Fer-1 dampened these outputs; importantly, ACSL4 inhibition reduced both ferroptotic activation and cytokine induction, implicating ACSL4 as a key node through which inflammatory cues can be translated into lipid-peroxidation [64]. Notably, not all mechanistic data point in the same direction. Wu et al. (2024) proposes that ferroptosis induction in keratinocytes may serve a protective, compensatory function in psoriasis vulgaris. The authors showed that while using the GPX4 inhibitor RSL3, HaCaT keratinocytes were highly susceptible to ferroptosis induction, with reduced proliferation and increased ROS and apoptosis [23]. In psoriasis-like in vitro and in vivo settings, RSL3 reduced the hyperproliferation marker KRT6 and increased differentiation markers including filaggrin (FLG). Noteworthy, inflammatory chemokines were also largely reduced in vitro, raising the possibility that within certain “physiological windows,” ferroptotic stress may restrain hyperplasia and partially normalize differentiation other than escalating inflammation, potentially via ROS-triggered antioxidant programs (e.g., nuclear factor erythroid 2-related factor 2, NRF2) [23]. These data contrast with the Shou/Liu model of ferroptosis as an inflammatory amplifier, and highlights the likelihood that dose, timing, and the microenvironment determine whether ferroptosis functions predominantly as injury amplification or as a limiting brake on pathological keratinocyte expansion. Finally, Vats et al. (2024) provided direct proof-of-principle that ferroptosis confined to a minority of keratinocytes can initiate and sustain psoriasis-like, systemic inflammation [65]. In their K14/Gpx4 model, sporadic pro-ferroptotic phospholipid peroxidation in a subset of basal keratinocytes recapitulated key phenotypic, immunological, and multiomic hallmarks of psoriasis and responded to standard

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biologic therapies, arguing that ferroptosis can function as both trigger and driver of chronic inflammatory disease. They propose that ferroptosis generates a spectrum of oxidized free fatty acids and oxidized phospholipids (including oxPE species) with signaling potential, capable of propagating non–cell-autonomous effects, such as increased proliferation in neighboring keratinocytes and dysregulated differentiation, hereby explaining the paradoxical coexistence of cell death and hyperplasia in psoriatic epidermis. They further hypothesize that oxidized lipid species and adducts may be taken up by antigen-presenting cells and potentially function as neolipid antigens, promoting lymphocyte Th1 and IL-23/Th17 responses and establishing a feed-forward epithelial–immune loop that maintains disease [65]. At the systems level, Wu et al. (2023) performed multi-dataset analyses and identified a set of differentially expressed ferroptosis-related genes (DE-FRGs) with diagnostic performance for separating psoriasis from healthy skin, including genes tied to redox control, mitochondrial function, and lipid metabolism (e.g., phosphatidylethanolamine binding protein 1 (PEBP1), protein kinase AMP-activated catalytic subunit alpha 2 (PRKAA2), acyl-CoA synthetase family member 2 (ACSF2), among others). Their pathway analyses connected these markers to innate immune sensing networks (nod-like receptor (NLR), toll-like receptor (TLR), retinoic acid-inducible gene-I (RIG-I)-like receptor (RLR) pathways) and immune-cell infiltration patterns consistent with established psoriasis immunobiology [66]. While these results are inherently associative and limited by bulk-tissue averaging, they support the idea that ferroptosis-related transcriptional states align with psoriatic immune activation and may be exploitable for biomarker development and stratification

Overall, these studies highlight that psoriatic lesion exhibits (i) impaired membrane lipid-peroxide detoxification (GPX4/GSH axis), (ii) increased availability of peroxidizable substrates via lipid remodeling/trafficking (e.g., ACSL4), and (iii) inflammatory iron flux and oxidative pressure, together creating ferroptosis-permissive epidermal niches (Figure 1). Functionally, manipulating ferroptosis can modulate psoriasiform pathology, but the net outcome may depend on whether interventions shift the tissue toward pathological ferroptotic necroinflammation or toward a controlled/physiological ferroptotic restraint of hyperproliferation. Framed this way, the key scientific task ahead is not to ask whether ferroptosis is "present" in psoriasis, but to define where, when, and at what intensity ferroptotic stress becomes immunogenic and disease-sustaining versus homeostatic or therapeutically exploitable.

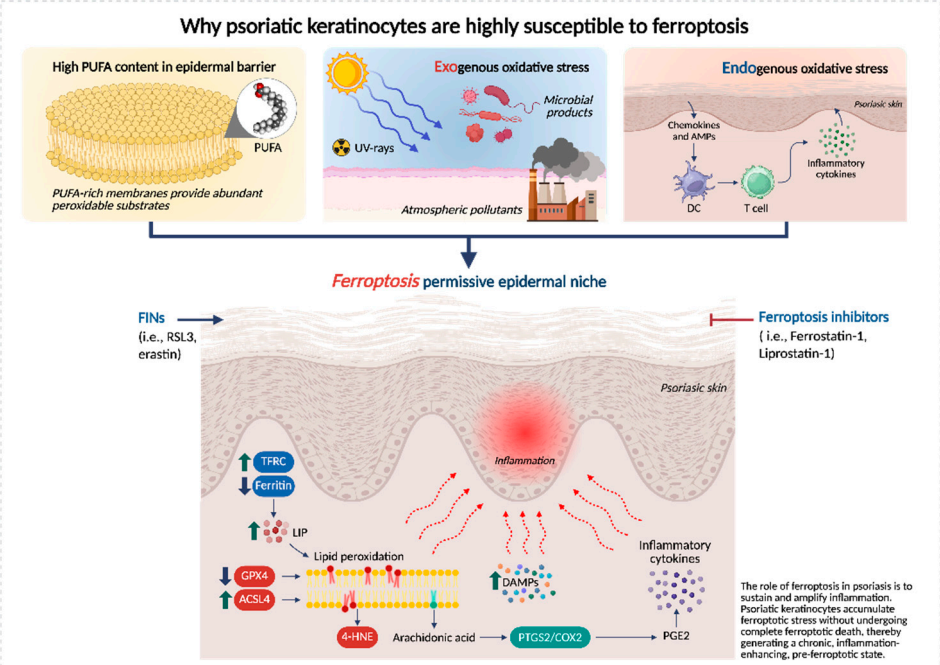

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Figure 1. Keratinocyte-intrinsic determinants of ferroptosis susceptibility in psoriatic skin. Schematic representation of the epidermal metabolic and redox alterations that make psoriatic keratinocytes highly susceptible to ferroptosis. Psoriatic keratinocytes exhibit three major vulnerability factors: (i) high PUFA content, supplying abundant substrates for lipid peroxidation; (ii) exogenous oxidative stress from UV radiation, atmospheric pollutants and microbial stimuli; and (iii) endogenous oxidative stress driven by elevated inflammatory cytokines. These inputs converge to impair antioxidant defenses (reduced GPX4 and glutathione), increase ACSL4-dependent PUFA enrichment, and disrupt iron homeostasis, collectively promoting excessive lipid peroxidation and accumulation of toxic species (e.g., 4-HNE, oxidized phospholipids). Together, these alterations create a ferroptosis-permissive epidermal niche that lowers the threshold for lipid-driven injury and amplifies psoriatic inflammation.

4. Ferroptosis at the Immune-Epidermal Interface

Psoriasis is sustained by a bidirectional crosstalk between keratinocytes and immune cells, in which epidermal stress responses and cytokine-driven inflammation reinforce each other [13]. Within this framework, ferroptosis is best understood not only as a terminal cell-death program but as a microenvironmental event capable of reshaping immune–epidermal communication [65]. The keratinocytes undergoing ferroptotic stress (and, in some contexts, ferroptotic death) generate a distinctive biochemical output characterized by oxidized phospholipids, reactive aldehyde adducts, eicosanoid intermediates, and danger-associated signals, that can engage innate sensing pathways, modulate antigen presentation, and tune cytokine networks [67]. The result is a model in which ferroptosis functions as a "signals generator," converting metabolic redox imbalance into immunological amplification. Again, this interface is context-dependent: depending on magnitude, spatial restriction, and clearance kinetics, ferroptotic signaling can either promote chronic inflammation or, alternatively, limit hyperproliferation through controlled elimination of pathological keratinocyte states.

4.1. Ferroptotic Keratinocytes as Inflammatory Hubs

Keratinocytes are increasingly recognized as active immune effector cells. In psoriasis, they produce cytokines (e.g., IL-1 family members), chemokines (e.g., CXCL1/8, CCL20), antimicrobial peptides, and lipid mediators that recruit and instruct leukocytes [68]. Ferroptosis adds a mechanistically distinct layer to this effector capacity by altering the quality and persistence of epidermal danger signaling. Unlike apoptosis, which is typically immunologically silent, ferroptosis is characterized by extensive membrane lipid oxidation and secondary formation of bioactive lipid species [69]. These products can directly stimulate inflammation, amplify cytokine responsiveness, and potentially generate neo-antigenic lipid-protein adducts [70]. Evidence consistent with this hub model arises from lesion and model systems showing that lipid oxidation programs in keratinocytes correlate with Th17/Th22 inflammatory signatures at single-cell resolution and that ferroptosis modulation affects cytokine output and clinical phenotype in psoriasiform dermatitis [25]. Conceptually, ferroptotic keratinocytes are not merely dying cells; they are metabolically rewired cells that, prior to or during death, shift toward an inflammatory secretory state under redox pressure [71]. This is particularly plausible in psoriasis because keratinocytes already exist in a cytokine-saturated environment and are primed to translate stress into inflammatory transcriptional programs [72]. Ferroptotic stress thus becomes a "multiplier," increasing the probability that keratinocyte-derived signals reach the threshold required to sustain leukocyte recruitment and activation. A further non-intuitive, yet increasingly supported, aspect of this hub model is that ferroptosis in a subset of keratinocytes can reshape the behavior of neighboring cells. Oxidized phospholipids and lysophospholipid derivatives generated during ferroptosis may diffuse locally and act as paracrine mediators, inducing proliferative responses, dysregulation of differentiation, and stress signaling in adjacent keratinocytes [70]. This offers a mechanistic explanation for a classic psoriasis paradox: the coexistence of keratinocyte death signals with marked epidermal hyperproliferation. Rather than being mutually exclusive, localized ferroptosis could generate lipid mediators that stimulate

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compensatory proliferation and aberrant differentiation in surrounding epidermal compartments, thereby reinforcing plaque architecture [65,73].

4.2. Oxidized Lipids as DAMP-like Mediators and Inflammatory Amplifiers

A defining feature of ferroptosis is the accumulation of oxidized PUFA-phospholipids and their downstream breakdown products. These molecules are not inert biomarkers; many of them have intrinsic signaling properties and can function in a DAMP-like manner [74]. Two classes are especially relevant to psoriasis: (i) oxidized phospholipids (oxPLs) and hydroperoxy-PE species, and (ii) reactive aldehydes and protein adducts (e.g., 4-HNE) [75,76]. Ferroptotic execution produces oxidized phospholipids (including oxPE species) that can alter membrane biophysics, disrupt barrier integrity, and engage innate immune sensing indirectly by driving cellular stress pathways [77]. OxPLs can be recognized by pattern recognition mechanisms and can modulate dendritic cell and macrophage activation states. Importantly, oxPLs can also be internalized by antigen-presenting cells, potentially contributing to antigenic diversification [70]. In keratinocyte-rich tissues, lipid oxidation products may therefore function as a bridge between metabolic injury and immune priming. In addition to that, lipid peroxidation generates electrophilic aldehydes such as 4-HNE that covalently modify proteins, altering function and potentially generating neo-epitopes [78]. In psoriasis, elevated 4-HNE has been linked to ferroptosis-associated states and is mechanistically positioned to both propagate ferroptosis (by impairing pro-survival pathways) and promote inflammation (by activating stress kinases and COX-2–linked eicosanoid programs) [79]. These adducts may also be handled by antigen-presenting cells, enabling a route through which ferroptosis could contribute to adaptive immune activation beyond generic DAMP release [80]. A major amplification route connecting lipid peroxidation to inflammation is the eicosanoid axis PTGS2/COX-2, which is often induced during ferroptotic stress and can accelerate conversion of arachidonic acid into inflammatory lipid mediators. While COX-2 induction is not exclusive to ferroptosis, its integration with iron-driven lipid oxidation provides a plausible mechanism by which ferroptotic stress biases the epidermal lipid mediator landscape toward inflammation and leukocyte recruitment [81].

4.3. Cytokine Loops as Both Drivers and Consequences of Ferroptotic Stress

Psoriasis is organized around cytokine feedback loops, particularly IL-17A/F, TNF, and interferon-gamma (IFN-γ), which jointly impose a high-demand inflammatory state on keratinocytes [82]. Ferroptosis intersects these loops in bidirectional ways. (i) Cytokines prime ferroptotic permissiveness: TNF and IFN-γ can induce oxidative stress and remodel metabolism in keratinocytes, increasing ROS production and altering lipid metabolic programs [76]. In parallel, chronic cytokine exposure can impair the GPX4-GSH axis by limiting cysteine availability, altering glutathione metabolism, and imposing endoplasmic reticulum and mitochondrial stress [83]. The net effect is to lower the ferroptotic threshold: membranes become more oxidizable and less repairable. (ii) Ferroptotic stress amplifies cytokine outputs and responsiveness: once lipid peroxidation proceeds, keratinocytes can shift toward enhanced expression of inflammatory mediators and chemokines. Lipid oxidation products and aldehyde stress activate transcriptional regulators (e.g., nuclear factor kappa B (NF-κB)-linked programs) and can increase sensitivity to cytokine signaling [79,84]. Thus, a keratinocyte undergoing ferroptotic stress becomes more responsive to IL-17/TNF/IFN-γ, producing more chemokines, antimicrobial peptides, and inflammatory lipid mediators, further recruiting immune cells that sustain the cytokine milieu [25]. This creates a self-reinforcing circuit: cytokines raise ferroptotic pressure; ferroptotic stress raises inflammatory output and cytokine sensitivity. Importantly, this circuit does not require widespread keratinocyte death to be pathogenic. Sublethal or “pre-lethal” ferroptotic stress states, characterized by lipid peroxide accumulation and redox imbalance, may be sufficient to alter keratinocyte immune function and maintain inflammation. This distinction matters because it reconciles the observation of

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hyperproliferative plaques with ongoing ferroptotic signaling inflammation may be driven by stressed-but-surviving keratinocytes as much as by dying ones.

4.4. Crosstalk with Macrophages, Neutrophils, and Th17 Immunity

Ferroptosis at the immune-epidermal interface must ultimately be understood through cell-cell interactions. In psoriasis, macrophages, neutrophils, dendritic cells, and Th17/Th1 lymphocytes form an interdependent network with keratinocytes [85]. Ferroptotic keratinocytes can shape this network through multiple routes. (i) Macrophages are sensitive to redox and lipid signals, and oxidized lipids can influence their activation and polarization [86]. In the psoriatic dermis, macrophages are exposed to keratinocyte-derived oxPLs, aldehyde adducts, and cytokines, which may bias them toward pro-inflammatory phenotypes and enhance production of TNF, IL-1, and IL-23. In parallel, macrophages act as scavengers for oxidized material; inefficient clearance could prolong antigenic and inflammatory exposure, whereas efficient efferocytosis-like programs could limit it [87]. Given that ferroptosis is not classically apoptotic and may generate debris with distinct immunogenicity, macrophage handling of ferroptotic keratinocytes may be a critical determinant of whether ferroptosis resolves or sustains inflammation [88]. (ii) Neutrophil infiltration is a hallmark of psoriasis [89]. Keratinocyte-derived chemokines represent a key node for neutrophil recruitment, and ferroptotic stress may amplify their production. Neutrophils, in turn, generate ROS and release inflammatory mediators and enzymes that intensify oxidative pressure within plaques, potentially accelerating lipid peroxidation in keratinocytes [90]. This creates a redox escalation loop: ferroptotic stress recruits' neutrophils while neutrophil oxidative burst increases ferroptotic pressure. Furthermore, neutrophil-derived lipid mediators and oxidative enzymes could modify the local lipid oxidation landscape, shaping the pool of oxPLs available for immune recognition and signaling. (iii) The IL-23/Th17 pathway is central in psoriasis. Ferroptotic keratinocytes may contribute to Th17 skewing both indirectly and directly. Indirectly, ferroptotic stress increases keratinocyte production of cytokines and chemokines that recruit and activate dendritic cells and macrophages, promoting IL-23 production and Th17 maintenance. Directly, oxidized phospholipids and lipid-protein adducts derived from ferroptosis may be taken up by antigen-presenting cells and contribute to antigenic landscapes that support T cell activation [91]. Experimental models in which keratinocyte ferroptosis is induced in a subset of basal cells show that this is sufficient to elicit Th1 and IL-23/Th17 responses and psoriasiform dermatitis, highlighting that epithelial ferroptosis can be upstream of canonical adaptive immunity.

Taken together, these findings support an integrated circuit in which ferroptosis sits at the center of immune-epidermal coupling (Figure 2). This immune-epidermal interpretation has clear implications for disease heterogeneity and therapy. It predicts that patients (or plaque regions) with stronger lipid peroxidation, altered iron handling, and weaker GPX4 defenses will exhibit more robust myeloid/Th17 activation and potentially distinct responses to biologics. It also suggests that therapies targeting ferroptosis, either by restoring lipid repair capacity, limiting PUFA peroxidation, or modulating iron flux, could complement cytokine blockade by disrupting the epidermal source of inflammatory reinforcement rather than only neutralizing downstream immune mediators.

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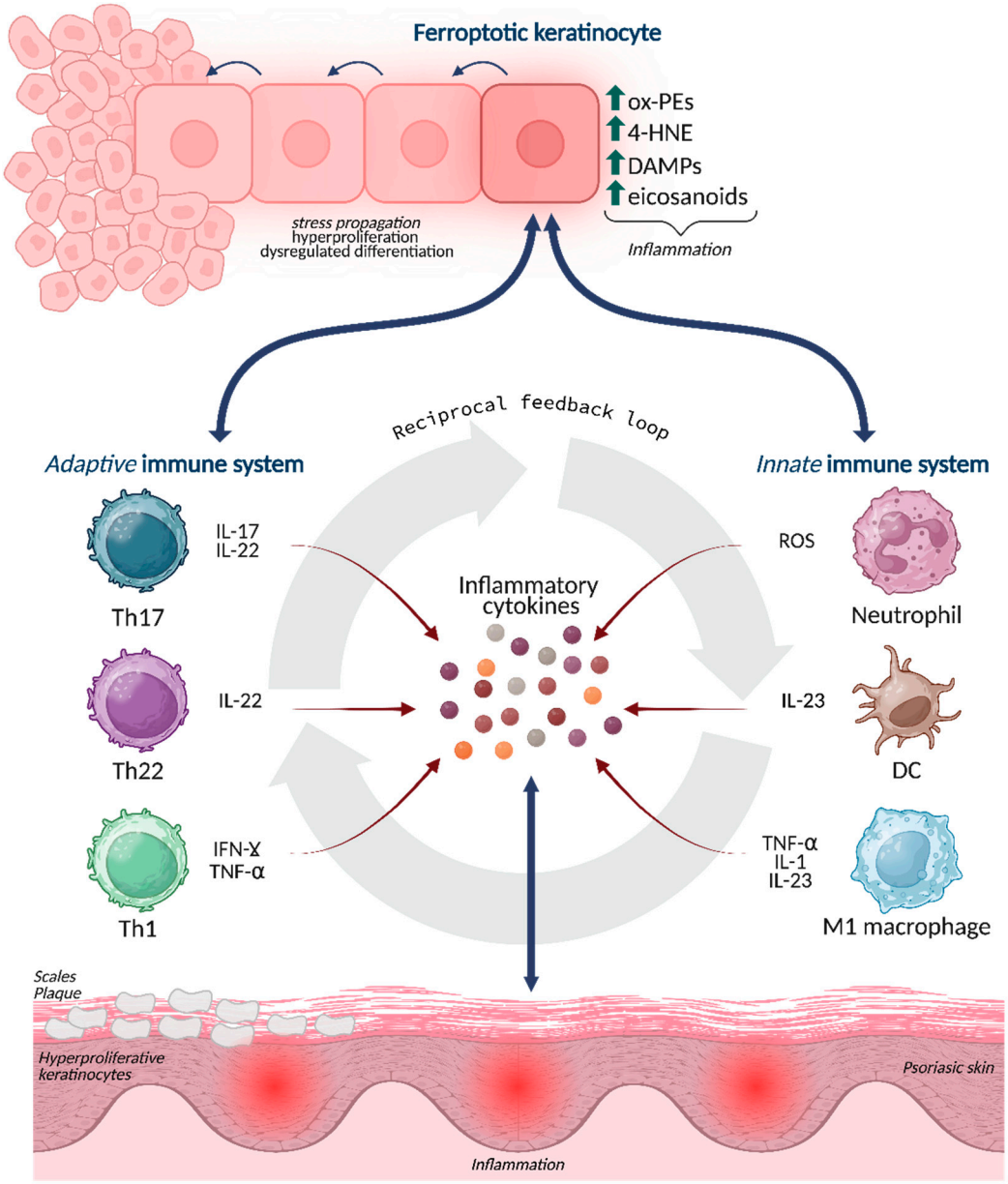

Figure 2. Ferroptosis-driven inflammatory signaling at the immune-epidermal interface in psoriasis. Ferroptotic stress in epidermal keratinocytes leads to the accumulation of oxidized phospholipids, 4-HNE adducts, ROS, and eicosanoid intermediates, which act as danger signals and amplify inflammation. These lipid-based mediators modulate crosstalk with innate (neutrophils, M1 macrophages, dendritic cells) and adaptive (Th17, Th22, Th1) immune cells, promoting the release of IL-17, IL-22, IFN-γ, TNF-α, and IL-23. The figure depicts how ferroptosis enhances immune recruitment, cytokine output, and redox imbalance, establishing a self-reinforcing loop that sustains keratinocyte hyperproliferation, abnormal differentiation, and chronic psoriatic inflammation.

5. Ferroptosis Signatures and Psoriasis Patient Stratification

The recognition that ferroptosis-related pathways are involved in the pathogenesis of psoriasis has opened a new dimension in the clinical stratification of this disease. Rather than viewing psoriasis as a uniform immune-mediated entity, recent transcriptomic and systems-level studies suggest that patients can be stratified according to the degree and configuration of ferroptosis-related metabolic stress within the epidermis. This reframing is conceptually important: it implies that inter-individual heterogeneity in lipid remodeling, redox buffering, and iron handling is not merely a background

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noise, but a biologically meaningful axis that shapes disease severity, immune architecture, and potentially therapeutic responsiveness. Multiple bioinformatic analyses have identified FRG programs that distinguish psoriatic lesions from healthy skin with high fidelity [92,93]. These signatures integrate genes governing glutathione metabolism (e.g., glutamate-cysteine ligase catalytic subunit (*GCLC*), glutathione-specific gamma-glutamylcyclotransferase 1 *CHAC1*), lipid remodeling and trafficking (e.g., *ACSF2*, phosphatidylethanolamine binding protein 1 (*PEBP1*)), mitochondrial and redox control (e.g., CDGSH iron sulfur domain 1 (*CISD1*), translocase of inner mitochondrial membrane 9 (*TIMM9*)), and stress-response regulators (e.g., *PRKAA2*, tribbles pseudokinase 2 (*TRIB2*), mouse double minute 2 (*MDM2*)). Importantly, these FRGs do not operate as isolate actors: functional enrichment analysis linked them to converging biological processes, such as innate immune sensing networks (TLR, NLR, RIG-I–like receptors), cytokine signaling, and epidermal differentiation programs [93]. Clustering approaches based on FRG expression have revealed different molecular subtypes of psoriasis [94]. In these analyses, one cluster typically exhibits high expression of pro-ferroptotic and redox-stress genes (e.g., elevated CHAC1, altered glutathione pathways, lipid metabolic skewing), accompanied by enrichment of pathways related to programmed cell death, negative regulation of epithelial proliferation, and stress signaling [94]. This "ferroptosis-high" state correlates with more severe inflammatory programs and poorer predicted prognosis [94,95]. A second cluster displays a comparatively restrained ferroptotic profile, with enrichment of metabolic buffering and differentiation-related pathways and a more favorable disease phenotype. Immune deconvolution analyses further demonstrate that ferroptosis-defined subtypes profoundly differ in their cellular microenvironment [94,95]. "Ferroptosis-high" plaques show increased infiltration of activated $CD4^+$ T cells, neutrophils, regulatory T cells, and Th17/Th2 subsets, together with heightened expression of immune effector programs [95]. Among FRGs, CHAC1, a glutathione-degrading enzyme that promotes ferroptosis, emerges as a central node, exhibiting strong correlations with neutrophil abundance and activated T-cell compartments. Mechanistically, CHAC1-mediated GSH depletion may act at two levels: in keratinocytes, it lowers the threshold for lipid peroxidation and ferroptotic stress; in immune cells, it may modulate apoptosis and effector function, thereby sustaining inflammatory persistence [94]. From a translational perspective, ferroptosis-based stratification offers several advantages over purely cytokine-centric models. First, it captures upstream metabolic vulnerability rather than downstream immune consequence. Two patients may share comparable IL-17 signatures yet differing substantially in their epidermal redox state, lipid architecture, and ferroptotic readiness, features that may influence chronicity, flare propensity, and response durability [92,93]. Second, ferroptosis signatures may help explain why a subset of patients remains refractory or only partially responsive to therapies: immune blockade may suppress effector cytokines, but if epidermal membranes remain PUFA-enriched, GPX4-deficient, and iron-loaded, the tissue retains the capacity to regenerate inflammatory cues [65]. The key ferroptosis-related genes in psoriasis are summarized in Table 1.

Table 1. Key ferroptosis-related genes in psoriasis and their enrichment in ferroptosis endotypes.

Gene	Core function	Role in ferroptosis	Expression pattern in psoriasis and endotype assignment
GPX4	GSH-dependent detoxification of phospholipid peroxides	Central anti-ferroptotic enzyme maintaining membrane integrity	Decreased in lesions: high-ferroptosis endotype
ACSL4	PUFA activation and incorporation into phospholipids	Generates oxidizable PUFA-PLs that promote lipid peroxidation	Increased in lesions: high-ferroptosis endotype
CHAC1	Intracellular GSH degradation	Enhances lipid peroxidation by reducing GSH availability	Increased in lesions: high-ferroptosis endotype

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PEBP1	Modulator of phosphatidylethanolamine oxidation	Facilitates formation of pro-ferroptotic oxidized PE species	Increased in lesions: high-ferroptosis endotype
CISD1	Mitochondrial iron-sulfur and ROS regulation	Modulates mitochondrial contribution to ferroptotic stress	Increased in lesions: high-ferroptosis endotype
ACSF2	Fatty-acid activation and lipid metabolism	Shapes pools of peroxidizable lipids	Increased in lesions: high-ferroptosis endotype
PRKAA2 (AMPKα2)	Metabolic and stress-response regulation	Influences redox homeostasis and ferroptotic susceptibility	Increased in lesions: high-ferroptosis endotype
GCLC	Rate-limiting enzyme for glutathione synthesis	Supports antioxidant capacity and GPX4 activity	Increased in lesions: low-ferroptosis endotype

Overall, ferroptosis signatures provide a metabolic lens on psoriasis heterogeneity. They formalize the idea that the epidermis is not merely inflamed but metabolically reprogrammed in ways that determine whether immune perturbations are transient or self-sustaining. Just as asthma and atopic dermatitis are increasingly parsed into molecular subtypes with distinct therapeutic trajectories, psoriasis may benefit from classification that integrates immune dominance with epidermal metabolic state.

6. Therapeutic Implications

6.1. Targeting Ferroptosis Vulnerability in Psoriatic Epidermis

Reconceptualizing psoriasis as a disorder in which immune dysregulation converges on epidermal redox–metabolic vulnerability has profound therapeutic implications. From this perspective, ferroptosis is not merely a mechanistic curiosity but, rather, a druggable axis that operates upstream of, and in parallel with, canonical cytokine circuits. Consequently, three major strategies can be identified i) Utilization of lipid peroxidation inhibitors: radical-trapping antioxidants such as ferrostatin-1 and liproxstatin-1 provide proof-of-principle that, by interrupting lipid peroxidation, can attenuate psoriasiform inflammation in vivo [96]. Unlike conventional antioxidants, these agents selectively intercept lipid radical propagation within membranes, the biochemical core of ferroptosis [97]. In experimental psoriasis models, such compounds reduce epidermal hyperplasia, scaling, and inflammatory cytokine production. Although not yet clinically deployable, they establish lipid peroxidation as a tractable target. Clinically viable analogues, topical or systemic, could be designed to restore membrane redox stability without globally suppressing immune function. ii) Utilization of iron modulators and chelators: because iron provides the catalytic force for lipid peroxidation, reshaping epidermal iron flux represents a complementary strategy [98]. Local iron chelation, modulation of TFRC activity, or interference with ferritinophagy could reduce the LIP in keratinocytes, raising the ferroptotic threshold. Importantly, such approaches need not eliminate iron signaling systemically; localized or epidermis-targeted modulation could blunt catalytic redox pressure while preserving systemic iron homeostasis [99]. iii) GPX4 stabilization and redox repair: enhancing the GPX4-GSH axis directly addresses the failure of lipid repair that defines ferroptotic vulnerability. Strategies could include boosting cysteine availability, stabilizing GPX4 protein, or modulating upstream regulators such as NRF2 and mechanistic target of rapamycin kinase (mTORC1) in a tissue-specific manner [100]. Nutritional and endocrine modulators already used in dermatology, such as vitamin D and selenium, are mechanistically linked to GPX4 expression and activity and may exert part of their benefit by restoring epidermal redox competence [101–103].

Ferroptosis-oriented therapies are not positioned to replace cytokine blockade; rather, they offer a means to inhibit the feed-forward loop that persists beneath immune suppression. Anti–IL-17 and anti–TNF agents efficiently neutralize dominant effector pathways, yet a substantial fraction of patients remains partially responsive, experiences relapse or develops secondary resistance [104]. One explanation is that while immune effector signals are dampened, epidermal lipid architecture

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and redox imbalance remain unchanged, allowing the tissue to regenerate inflammatory cues once pharmacologic pressure fluctuates. In this context, ferroptosis may itself represent a mechanism of therapeutic resistance. Therefore, combining immune suppression with ferroptosis-targeted agents could improve depth and durability of response, reduce flare frequency, and potentially enable dose reduction of immunosuppressive agents. However, targeting ferroptosis in a chronic inflammatory disease demands careful consideration of physiological trade-offs. First, ferroptosis participates in antimicrobial defense and inflammatory resolution in certain contexts [105]. Excessive suppression of lipid peroxidation could blunt innate immune sensing and compromise cutaneous defense against pathogens [106]. Therapeutic modulation must therefore aim for normalization rather than ablation, restoring physiological thresholds without creating an immunologically inert epidermis. Second, ferroptosis is a recognized tumor-suppressive mechanism [107]. Chronic inhibition of ferroptotic pathways could, in principle, reduce elimination of premalignant keratinocytes or alter immune-mediated tumor surveillance. This concern is particularly relevant in a tissue with high turnover and cumulative mutational burden [44]. Epidermis-restricted delivery, temporal modulation, or strategies that reinforce repair rather than block execution may mitigate this risk. Third, keratinocyte differentiation involves tightly orchestrated cell death-like programs [108,109]. Interfering indiscriminately with ferroptosis could perturb terminal differentiation, cornification, or barrier renewal. Therapeutic approaches must therefore respect the physiological role of controlled oxidative remodeling in epidermal maturation.

To sum up, by stabilizing membrane integrity, reshaping lipid flux, and restoring redox competence, ferroptosis-oriented therapies could disable the epidermal source of inflammatory reinforcement.

6.2. Natural Ferroptosis Modulators: Phytochemicals as Pleiotropic Therapeutic Candidates

In addition to pharmacological interventions, several recent studies have highlighted the potential of plant-derived bioactive compounds to modulate redox–metabolic imbalance in psoriasis. Current treatments for psoriasis remain largely symptom-directed, and both topical and systemic agents, whether conventional or biologic, may carry significant adverse effects, including immunosuppression and increased cancer susceptibility. These limitations have stimulated interest in phytochemicals, which are generally associated with a more favorable safety profile and have long been recognized for their anti-inflammatory and antioxidant properties. Over the past two years, several reviews and numerous original studies have reported novel compounds or plant extracts with promising activity in vitro and in preclinical models [110], and a few early clinical studies have yielded encouraging results [111]. Anti-psoriatic phytochemicals span a wide range of chemical classes, including flavonoids, phenolic acids, stilbenes, terpenoids, saponins and alkaloids. Despite this diversity, many consistently reduce oxidative stress by stimulating endogenous antioxidant systems such as superoxide dismutase II (SOD2) and catalase, and attenuate inflammation through multiple mechanisms, including inhibition of NF-κB and janus kinase (JAK)/signal transducer and activator of transcription (STAT) signaling, activation of peroxisome proliferator-activated receptor (PPAR) and AMP-activated protein kinase (AMPK) pathways, and suppression of cytokines such as TNF-α and IL-17 [112]. The predominance of anti-inflammatory mechanisms in the literature likely reflects research emphasis rather than the full breadth of biological effects exerted by these molecules. Increasing evidence indicates that their beneficial actions extend beyond classical antioxidant or cytokine-directed pathways and involve additional regulatory dimensions such as ferroptosis, autophagy and epigenetic modulation. Although studies explicitly linking phytochemicals to ferroptosis regulation in psoriasis remain relatively limited, this evidence is rapidly expanding. Several flavonoids, including quercetin and baicalin, attenuate psoriasiform inflammation in murine and keratinocyte models by restoring GPX4 activity, reducing lipid peroxidation and normalizing iron homeostasis [18,113]. Likewise, diterpenoid and triterpenoid compounds such as andrographolide and ursolic acid ameliorate psoriasis-like lesions while modulating NRF2/heme oxygenase-1 (HO-1) signaling and downregulating ferroptosis-related markers [114,115].

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Polyphenol-rich extracts from *Camellia sinensis* and *Curcuma longa* improve histological and molecular features of psoriasis models in parallel with reduced ACSL4 expression and decreased accumulation of oxidized phospholipids [116–118]. Given that more than 40 individual phytochemicals and at least 35 plant extracts have already demonstrated anti-inflammatory activity in psoriasis models, the number capable of inhibiting ferroptosis is likely to grow. This expectation is supported by substantial overlap between compounds known to regulate ferroptosis in other disease contexts and those with established anti-psoriatic properties [25,65,119]. Examples include polyphenols and phenolic acids such as curcumin [120], dihydromyricetin [121], apigenin, luteolin, catechins, kaempferol, gallic acid and ellagic acid [110,112], many of which also modulate autophagy [122] and chromatin structure [123], broadening their mechanistic relevance.

Together, these findings suggest that ferroptosis inhibition represents an underappreciated component of the biological activity of several plant-derived compounds with anti-psoriatic potential. By acting simultaneously on oxidative stress, inflammatory signaling, lipid metabolism, iron homeostasis, autophagy and epigenetic regulation, these agents exert pleiotropic effects that may help stabilize epidermal homeostasis and mitigate the metabolic drivers of chronic inflammation. Table 2 provides an overview of the key therapeutic drug categories designed to target ferroptosis vulnerability in psoriasis.

Table 2. Therapeutic drug classes targeting ferroptosis vulnerability in psoriasis.

Drug class	Representative agents	Evidence in psoriasis / ferroptosis	Potential advantages	Limitations / Considerations
Lipid peroxidation inhibitors	Ferrostatin-1 Liproxstatin-1	Reduce epidermal hyperplasia, scaling, oxidative stress, and inflammatory cytokines in psoriasiform models	High specificity for ferroptosis; potential for topical or localized delivery.	Risk of suppressing physiological oxidative signaling essential for antimicrobial defense.
Iron chelators / iron flux modulators	Topical chelators TFRC modulators ferritinophagy inhibitors	Alleviate redox pressure and normalize iron handling in keratinocytes	Local administration may minimize systemic iron perturbation.	Excessive iron restriction could impair cutaneous innate immunity.
GPX4 stabilizers and redox repair enhancers	GPX4 stabilizers GSH precursors cysteine boosters NRF2/mTORC1 modulators	Improve redox buffering capacity and reduce ferroptotic sensitivity in psoriatic epidermis	Directly addresses a core driver of ferroptotic vulnerability; may synergize with biologics.	Must avoid interfering with physiological keratinocyte differentiation and cornification.
Combined cytokine blockade + ferroptosis modulation	IL-17 inhibitors TNF inhibitors + agents from classes above	May enhance response durability and reduce relapse by correcting persistent metabolic vulnerability	Potential dose-sparing effect for immunosuppressants.	Excessive ferroptosis inhibition could impair antimicrobial defense or tumor surveillance.
Natural ferroptosis modulators (phytochemicals)	Quercetin, Baicalin, Andrographolide, Ursolic acid,	Improve redox homeostasis, reduce inflammatory	Generally favorable safety profile; broad mechanistic spectrum.	Variable bioavailability and standardization;

 doi:10.20944/preprints202602.1713.v1

	Curcumin, Catechins	markers, and modulate ferroptosis-related pathways in preclinical models.	limited clinical data.

7. Discussion

Collectively, this review reframes psoriasis as a redox-metabolic-immune disorder in which ferroptosis constitutes a central pathogenic axis linking epidermal vulnerability to chronic inflammation. Ferroptosis provides a unifying biochemical framework for hallmark features of plaque disease, including barrier failure, lipid remodeling, oxidative stress, iron dysregulation, and the paradoxical coexistence of keratinocyte death signals with hyperproliferation. At the immune-epidermal interface, ferroptotic keratinocytes act as inflammatory hubs, releasing oxidized lipids and aldehyde adducts with DAMP-like activity that bias eicosanoid metabolism and amplify IL-17/TNF/IFN-γ circuits via feed-forward myeloid and T-cell engagement [23,25,65]. In parallel, ferroptosis-related transcriptomic signatures reveal a stratifiable metabolic dimension of psoriasis heterogeneity, identifying "ferroptosis-high" endotypes with distinct immune ecologies and therapeutic liabilities beyond cytokine profiling [92–95]. The critical question thus shifts from whether ferroptosis is present to where, when, and at what intensity it becomes immunogenic and disease-sustaining. Translationally, restoring membrane redox competence, by intercepting lipid peroxidation, modulating iron flux, or reinforcing GPX4-dependent repair, offers a rational complement to existing immunotherapies to disable upstream epidermal amplifiers of inflammation [96,98–100]. Notably, emerging evidence suggests that selected plant-derived bioactive compounds may engage these same redox–metabolic pathways, hinting at a complementary therapeutic avenue to reinforce epidermal resilience in a physiologically aligned manner [110,112,117,119] . Integrating ferroptosis into psoriasis biology therefore establishes a mechanistic foundation for next-generation precision dermatology, positioning epidermal metabolism as a tractable driver of disease persistence and heterogeneity.

Author Contributions: Conceptualization, F.B. and A.M.B.; writing—original draft preparation, E.G., C.G., E.J., A.M.B., F.B.; writing—review and editing, e.g., C.G., G.N., L.P., E.J., M.C.F., F.S.C, A.M.B., F.B.; supervision, E.G., A.M.B., F.B.; funding acquisition, F.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by the Unione Europea—Next Generation Eu, Missione 4 Componente 1, CUP F53D23012280001. PRIN—Progetti di Ricerca di Interesse Nazionale—Bando PNRR 2022—Prot. P2022RBPHH.

Acknowledgments: During the preparation of this manuscript the authors used ChatGpt for grammar check. All schematic figures and graphical illustrations were created with BioRender.com

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

The following abbreviations are used in this manuscript:

IL-23	Interleukin-23
IL-17	Interleukin-17
TNF	Tumor necrosis factor
DAMPS	Danger-associated molecular patterns
GPX4	Glutathione peroxidase 4
IMQ	Imiquimod
PUFA	Oxidizable polyunsaturated fatty acid
TFRC	Transferrin receptor

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FTH1	Ferritin heavy chain
FTL	Ferritin light chain
FPN	Ferroportin
ACSL4	Acyl-CoA synthetase long-chain family member 4
LPCAT3	Lysophosphatidylcholine acyltransferase 3
GSH	Glutathione
SLC7A11	Solute carrier family 7 member 11
SLC3A2	Solute carrier family 3 member 2
FSP1	Ferroptosis suppressor protein 1
CoQ10	Coenzyme Q10
GCH1	GTP Cyclohydrolase 1
ESCRT-III	Endosomal sorting complex required for transport (ESCRT) complex III
ROS	Reactive Oxygen Species
4-HNE	4-Hydroxynonenal
Fer-1	Ferrostatin-1
PASI	Psoriasis Area Severity Index
RSL3	RAS-selective lethal 3
FLG	Filaggrin
NRF2	Nuclear factor erythroid 2-related factor 2
DE-FRGs	Differentially expressed ferroptosis-related genes
NLR	Nod-like receptor
TRL	Toll-like receptor
RLR	Retinoic acid-inducible gene-I (RIG-I)-like receptor
PEBP1	Phosphatidylethanolamine binding protein 1
PRKAA2	Protein Kinase AMP-Activated catalytic subunit alpha 2
ACSF2	Acyl-CoA synthetase family member 2
OxPLs	Oxidized phospholipids
IFN-γ	Interferon gamma
NF-κB	Nuclear factor kappa B
GCLC	Glutamate-Cysteine ligase catalytic subunit
CHAC1	ChaC Glutathione-Specific Gamma-Glutamylcyclotransferase 1
PEBP1	Phosphatidylethanolamine Binding Protein 1
CISD1	CDGSH Iron Sulfur Domain 1
TIMM9	Translocase Of Inner Mitochondrial Membrane 9
TRIB2	Tribbles Pseudokinase 2
MDM2	Mouse Double Minute 2
mTORC1	Mechanistic Target of Rapamycin Kinase
SOD2	Superoxide Dismutase II
JAK	Janus Kinase
STAT	Signal Transducer and Activator of Transcription
PPAR	Peroxisome Proliferator-Activated Receptor
AMPK	AMP-activated Protein Kinase
HO-1	Heme Oxygenase-1

References

1. Armstrong, A.W.; Read, C. Pathophysiology, Clinical Presentation, and Treatment of Psoriasis: A Review. *JAMA* 2020, *323*, 1945–1960, doi:10.1001/JAMA.2020.4006.
2. EClinicalMedicine The Burden of Psoriasis: A Call for Awareness. *EClinicalMedicine* 2021, *38*, 101114, doi:10.1016/j.eclinm.2021.101114.
3. Greb, J.E.; Goldminz, A.M.; Elder, J.T.; Lebwohl, M.G.; Gladman, D.D.; Wu, J.J.; Mehta, N.N.; Finlay, A.Y.; Gottlieb, A.B. Psoriasis. *Nature Reviews Disease Primers 2016 2:1* 2016, *2*, 16082-, doi:10.1038/nrdp.2016.82.
4. Kimmel, G.W.; Lebwohl, M. Psoriasis: Overview and Diagnosis. *Evidence-Based Psoriasis* 2018, 1, doi:10.1007/978-3-319-90107-7_1.
5. Kirby, B.; Burden, A.D. Psoriasis and Related Disorders. *Rook's Textbook of Dermatology* 2024, 1–62, doi:10.1002/9781119709268.ROOK035.
6. Mehta, S.; Sathe, N.C. Plaque Psoriasis. *Psoriasis: Diagnosis and Management* 2025, 57–75, doi:10.12968/pnur.2008.19.11.31631.

 doi:10.20944/preprints202602.1713.v1

7. Moorchung, N.; Khullar, J.S.; Mani, N.S.; Chatterjee, M.; Vasudevan, B.; Tripathi, T. A Study of Various Histopathological Features and Their Relevance in Pathogenesis of Psoriasis. *Indian J. Dermatol.* 2013, *58*, 294, doi:10.4103/0019-5154.113948.
8. Balan, R.; Grigoraş, A.; Popovici, D.; Amălinei, C. The Histopathological Landscape of the Major Psoriasiform Dermatoses. *Archive of Clinical Cases* 2021, *6*, 59, doi:10.22551/2019.24.0603.10155.
9. Nikam, V.; Monteiro, R.; Dandakeri, S.; Bhat, R. Transepidermal Water Loss in Psoriasis: A Case-Control Study. *Indian Dermatol. Online J.* 2019, *10*, 267, doi:10.4103/IDOJ.IDOJ_180_18.
10. Motta, S.; Monti, M.; Sesana, S.; Mellesi, L.; Ghidoni, R.; Caputo, R. Abnormality of Water Barrier Function in Psoriasis: Role of Ceramide Fractions. *Arch. Dermatol.* 1994, *130*, 452–456, doi:10.1001/ARCHDERM.1994.01690040056007.
11. Ye, J.; Lai, Y. Keratinocytes: New Perspectives in Inflammatory Skin Diseases. *Trends Mol. Med.* 2025, *31*, 1103–1113, doi:10.1016/j.molmed.2025.03.012.
12. Ni, X.; Lai, Y. Keratinocyte: A Trigger or an Executor of Psoriasis? *J. Leukoc. Biol.* 2020, *108*, 485–491, doi:10.1002/JLB.5MR0120-439R;PAGEGROUP:STRING:PUBLICATION.
13. Kamata, M.; Tada, Y. Crosstalk: Keratinocytes and Immune Cells in Psoriasis. *Front. Immunol.* 2023, *14*, 1286344, doi:10.3389/FIMMU.2023.1286344.
14. Lowes, M.A.; Russell, C.B.; Martin, D.A.; Towne, J.E.; Krueger, J.G. The IL-23/T17 Pathogenic Axis in Psoriasis Is Amplified by Keratinocyte Responses. *Trends Immunol.* 2013, *34*, 174, doi:10.1016/J.IT.2012.11.005.
15. Vičić, M.; Kaštelan, M.; Brajac, I.; Sotošek, V.; Massari, L.P. Current Concepts of Psoriasis Immunopathogenesis. *International Journal of Molecular Sciences 2021, Vol. 22, Page 11574* 2021, *22*, 11574, doi:10.3390/IJMS222111574.
16. Masson Regnault, M.; Shourick, J.; Jendoubi, F.; Tauber, M.; Paul, C. Time to Relapse After Discontinuing Systemic Treatment for Psoriasis: A Systematic Review. *Am. J. Clin. Dermatol.* 2022, *23*, 433, doi:10.1007/S40257-022-00679-Y.
17. Jang, J.; Park, M.; Kim, H.J.; Jung, Y.J. Reprogramming Immunity at the Metabolic–Epidermal Interface in Obesity-Associated Psoriasis. *Cytokine Growth Factor Rev.* 2026, *88*, 32–46, doi:10.1016/J.CYTOGFR.2026.01.003.
18. Li, S.; Luo, X.; Zhang, S.; Su, Y.; Deng, M.; Zhu, Y.; Zhang, P.; Wu, R.; Zhao, M. Ferroptosis Activation Contributes to the Formation of Skin Lesions in Psoriasis Vulgaris. *Antioxidants (Basel).* 2023, *12*, doi:10.3390/ANTIOX12020310.
19. Zhou, Q.; Yang, L.; Li, T.; Wang, K.; Huang, X.; Shi, J.; Wang, Y. Mechanisms and Inhibitors of Ferroptosis in Psoriasis. *Front. Mol. Biosci.* 2022, *9*, doi:10.3389/FMOLB.2022.1019447.
20. Qi, D.; Peng, M. Ferroptosis-Mediated Immune Responses in Cancer. *Front. Immunol.* 2023, *14*, 1188365, doi:10.3389/FIMMU.2023.1188365.
21. Sacco, A.; Battaglia, A.M.; Botta, C.; Aversa, I.; Mancuso, S.; Costanzo, F.; Biamonte, F. Iron Metabolism in the Tumor Microenvironment— Implications for Anti-cancer Immune Response. *Cells* 2021, *10*, doi:10.3390/cells10020303.
22. Zheng, Y.; Yan, F.; He, S.; Luo, L. Targeting Ferroptosis in Autoimmune Diseases: Mechanisms and Therapeutic Prospects. *Autoimmun. Rev.* 2024, *23*, 103640, doi:10.1016/J.AUTREV.2024.103640.
23. Wu, N.; Hu, Q.; Fu, Z.; Tong, X.; Gao, L.; Tan, L.; Yan, S.; Wang, D.; Zeng, J.; Lu, J.; et al. Pilot Study of the Role of Ferroptosis in Abnormal Biological Behaviour of Keratinocytes in Psoriasis Vulgaris. *Arch. Dermatol. Res.* 2024, *316*, doi:10.1007/S00403-024-03345-X.
24. Reznik, A.S.; Vats, K.; Singh, K.; Mizes, A.; Jaklitsch, E.; Bayır, H.; Kagan, V.E.; Bunimovich, Y.L. Emerging Roles of Ferroptosis in Skin Pathophysiology. *Journal of Investigative Dermatology* 2025, *145*, 2701–2718, doi:10.1016/j.jid.2025.06.1289.
25. Shou, Y.; Yang, L.; Yang, Y.; Xu, J. Inhibition of Keratinocyte Ferroptosis Suppresses Psoriatic Inflammation. *Cell Death Dis.* 2021, *12*, doi:10.1038/S41419-021-04284-5.
26. Battaglia, A.M.; Chirillo, R.; Aversa, I.; Sacco, A.; Costanzo, F.; Biamonte, F. Ferroptosis and Cancer: Mitochondria Meet the "Iron Maiden" Cell Death. *Cells* 2020, *9*, doi:10.3390/cells9061505.

27. Antonelli, A.; Battaglia, A.M.; Sacco, A.; Petriaggi, L.; Giorgio, E.; Barone, S.; Biamonte, F.; Giudice, A. Ferroptosis and Oral Squamous Cell Carcinoma: Connecting the Dots to Move Forward. *Frontiers in oral health* 2024, *5*, doi:10.3389/FROH.2024.1461022.
28. Battaglia, A.M.; Sacco, A.; Perrotta, I.D.; Faniello, M.C.; Scalise, M.; Torella, D.; Levi, S.; Costanzo, F.; Biamonte, F. Iron Administration Overcomes Resistance to Erastin-Mediated Ferroptosis in Ovarian Cancer Cells. *Front. Oncol.* 2022, *12*, doi:10.3389/fonc.2022.868351.
29. Battaglia, A.M.; Sacco, A.; Giorgio, E.; Petriaggi, L.; Elzanowska, J.; Cruz, A.R.; Rocha, L.; Pereira, C.E.; Strano Moraes, M.C.; Palazzo, L.; et al. Expulsion of Iron-Rich Ferritin via CD63-Mediated Exosome Drives Ferroptosis Resistance in Ovarian Cancer Cells. *Front. Cell Dev. Biol.* 2025, *13*, 1532097, doi:10.3389/FCELL.2025.1532097/BIBTEX.
30. Dixon, S.J.; Stockwell, B.R. The Hallmarks of Ferroptosis. *https://doi.org/10.1146/annurev-cancerbio-030518-055844* 2019, *3*, 35–54, doi:10.1146/ANNUREV-CANCERBIO-030518-055844.
31. Dixon, S.J.; Lemberg, K.M.; Lamprecht, M.R.; Skouta, R.; Zaitsev, E.M.; Gleason, C.E.; Patel, D.N.; Bauer, A.J.; Cantley, A.M.; Yang, W.S.; et al. Ferroptosis: An Iron-Dependent Form of Nonapoptotic Cell Death. *Cell* 2012, *149*, 1060–1072, doi:10.1016/J.CELL.2012.03.042.
32. Stockwell, B.R. Ferroptosis Turns 10: Emerging Mechanisms, Physiological Functions, and Therapeutic Applications. *Cell* 2022, *185*, 2401–2421, doi:10.1016/J.CELL.2022.06.003.
33. Petriaggi, L.; Giorgio, E.; Natali, G.; Galeano, C.; Furtado, S.R.; Faniello, C.M.; Costanzo, F.S.; Biamonte, F.; Battaglia, A.M. Iron Fist in a Velvet Glove: Class IV Ferroptosis Inducers as a Novel Strategy to Target Ovarian Cancer. *Front. Biosci. (Landmark Ed).* 2025, *30*, 39675, doi:10.31083/FBL39675.
34. Biamonte, F.; Zolea, F.; Santamaria, G.; Battaglia, A.M.; Cuda, G.; Costanzo, F. Human Haematological and Epithelial Tumor-Derived Cell Lines Express Distinct Patterns of Onco-MicroRNAs. *Cell. Mol. Biol.* 2017, *63*, doi:10.14715/cmb/2017.63.11.14.
35. Zolea, F.; Biamonte, F.; Battaglia, A.M.; Faniello, M.C.; Cuda, G.; Costanzo, F. Caffeine Positively Modulates Ferritin Heavy Chain Expression in H460 Cells: Effects on Cell Proliferation. *PLoS One* 2016, *11*, doi:10.1371/journal.pone.0163078.
36. Battaglia, A.M.; Sacco, A.; Vecchio, E.; Scicchitano, S.; Petriaggi, L.; Giorgio, E.; Bulotta, S.; Levi, S.; Faniello, C.M.; Biamonte, F.; et al. Iron Affects the Sphere-Forming Ability of Ovarian Cancer Cells in Non-Adherent Culture Conditions. *Front. Cell Dev. Biol.* 2023, *11*, doi:10.3389/FCELL.2023.1272667.
37. Battaglia, A.M.; Sacco, A.; Aversa, I.; Santamaria, G.; Palmieri, C.; Botta, C.; De Stefano, R.; Bitetto, M.; Petriaggi, L.; Giorgio, E.; et al. Iron-Mediated Oxidative Stress Induces PD-L1 Expression via Activation of c-Myc in Lung Adenocarcinoma. *Front. Cell Dev. Biol.* 2023, *11*, 1208485, doi:10.3389/FCELL.2023.1208485/BIBTEX.
38. Zhong, M.; Wang, Y.; Min, J.; Wang, F. Iron Metabolism and Ferroptosis in Human Health and Disease. *BMC Biology 2025 23:1* 2025, *23*, 263-, doi:10.1186/S12915-025-02378-6.
39. Zolea, F.; Battaglia, A.M.; Chiarella, E.; Malanga, D.; De Marco, C.; Bond, H.M.; Morrone, G.; Costanzo, F.; Biamonte, F. Ferritin Heavy Subunit Silencing Blocks the Erythroid Commitment of K562 Cells via MiR-150 up-Regulation and GATA-1 Repression. *Int. J. Mol. Sci.* 2017, *18*, doi:10.3390/ijms18102167.
40. Zolea, F.; Battaglia, A.M.; Chiarella, E.; Malanga, D.; De Marco, C.; Bond, H.M.; Morrone, G.; Costanzo, F.; Biamonte, F. Ferritin Heavy Subunit Silencing Blocks the Erythroid Commitment of K562 Cells via MiR-150 up-Regulation and GATA-1 Repression. *Int. J. Mol. Sci.* 2017, *18*, doi:10.3390/IJMS18102167.
41. Sacco, A.; Battaglia, A.M.; Santamaria, G.; Buffone, C.; Barone, S.; Procopio, A.; Lavecchia, A.M.; Aversa, I.; Giorgio, E.; Petriaggi, L.; et al. SOX2 Promotes a Cancer Stem Cell-like Phenotype and Local Spreading in Oral Squamous Cell Carcinoma. *PLoS One* 2023, *18*, doi:10.1371/JOURNAL.PONE.0293475.
42. Di Sanzo, M.; Aversa, I.; Santamaria, G.; Gagliardi, M.; Panebianco, M.; Biamonte, F.; Zolea, F.; Faniello, M.C.; Cuda, G.; Costanzo, F. FTH1P3, a Novel H-Ferritin Pseudogene Transcriptionally Active, Is Ubiquitously Expressed and Regulated during Cell Differentiation. *PLoS One* 2016, *11*, e0151359, doi:10.1371/JOURNAL.PONE.0151359.

 doi:10.20944/preprints202602.1713.v1

43. Chirillo, R.; Aversa, I.; Di Vito, A.; Salatino, A.; Battaglia, A.M.; Sacco, A.; Di Sanzo, M.A.; Faniello, M.C.; Quaresima, B.; Palmieri, C.; et al. FtH-Mediated ROS Dysregulation Promotes CXCL12/CXCR4 Axis Activation and EMT-Like Trans-Differentiation in Erythroleukemia K562 Cells. *Front. Oncol.* 2020, *10*, 698, doi:10.3389/FONC.2020.00698/FULL.
44. Oliveira, D.M.; Laudanna, C.; Migliozzi, S.; Zoppoli, P.; Santamaria, G.; Grillone, K.; Elia, L.; Mignogna, C.; Biamonte, F.; Sacco, R.; et al. Identification of Different Mutational Profiles in Cancers Arising in Specific Colon Segments by next Generation Sequencing. *Oncotarget* 2018, *9*, 23960, doi:10.18632/ONCOTARGET.25251.
45. Zhang, X.; Xiang, Y.; Wang, Q.; Bai, X.; Meng, D.; Wu, J.; Sun, K.; Zhang, L.; Qiang, R.; Liu, W.; et al. Regulation of Iron Metabolism in Ferroptosis: From Mechanism Research to Clinical Translation. *J. Pharm. Anal.* 2025, *15*, 101304, doi:10.1016/J.JPHA.2025.101304.
46. Abdukarimov, N.; Kokabi, K.; Kunz, J. Ferroptosis and Iron Homeostasis: Molecular Mechanisms and Neurodegenerative Disease Implications. *Antioxidants* 2025, *14*, 527, doi:10.3390/ANTIOX14050527.
47. Pope, L.E.; Dixon, S.J. Regulation of Ferroptosis by Lipid Metabolism. *Trends Cell Biol.* 2023, *33*, 1077–1087, doi:10.1016/J.TCB.2023.05.003.
48. Sun, D.; Wang, L.; Wu, Y.; Yu, Y.; Yao, Y.; Yang, H.; Hao, C. Lipid Metabolism in Ferroptosis: Mechanistic Insights and Therapeutic Potential. *Front. Immunol.* 2025, *16*, 1545339, doi:10.3389/FIMMU.2025.1545339.
49. Weaver, K.; Skouta, R. The Selenoprotein Glutathione Peroxidase 4: From Molecular Mechanisms to Novel Therapeutic Opportunities. *Biomedicines* 2022, *10*, 891, doi:10.3390/BIOMEDICINES10040891.
50. Conrad, M.; Proneth, B. Selenium: Tracing Another Essential Element of Ferroptotic Cell Death. *Cell Chem. Biol.* 2020, *27*, 409–419, doi:10.1016/J.CHEMBIOL.2020.03.012.
51. Yang, W.S.; Stockwell, B.R. Ferroptosis: Death by Lipid Peroxidation. *Trends Cell Biol.* 2016, *26*, 165, doi:10.1016/J.TCB.2015.10.014.
52. Imai, H.; Hirao, F.; Sakamoto, T.; Sekine, K.; Mizukura, Y.; Saito, M.; Kitamoto, T.; Hayasaka, M.; Hanaoka, K.; Nakagawa, Y. Early Embryonic Lethality Caused by Targeted Disruption of the Mouse PHGPx Gene. *Biochem. Biophys. Res. Commun.* 2003, *305*, 278–286, doi:10.1016/S0006-291X(03)00734-4.
53. Brütsch, S.H.; Wang, C.C.; Li, L.; Stender, H.; Neziroglu, N.; Richter, C.; Kuhn, H.; Borchert, A. Expression of Inactive Glutathione Peroxidase 4 Leads to Embryonic Lethality, and Inactivation of the Alox15 Gene Does Not Rescue Such Knock-in Mice. *Antioxid. Redox Signal.* 2015, *22*, 281–293, doi:10.1089/ARS.2014.5967.
54. Doll, S.; Freitas, F.P.; Shah, R.; Aldrovandi, M.; da Silva, M.C.; Ingold, I.; Grocin, A.G.; Xavier da Silva, T.N.; Panzilius, E.; Scheel, C.H.; et al. FSP1 Is a Glutathione-Independent Ferroptosis Suppressor. *Nature 2019 575:7784* 2019, *575*, 693–698, doi:10.1038/s41586-019-1707-0.
55. Hadian, K. Ferroptosis Suppressor Protein 1 (FSP1) and Coenzyme Q10 Cooperatively Suppress Ferroptosis. *Biochemistry* 2020, *59*, 637–638, doi:10.1021/ACS.BIOCHEM.0C00030.
56. Dai, E.; Meng, L.; Kang, R.; Wang, X.; Tang, D. ESCRT-III–Dependent Membrane Repair Blocks Ferroptosis. *Biochem. Biophys. Res. Commun.* 2019, *522*, 415, doi:10.1016/J.BBRC.2019.11.110.
57. Kraft, V.A.N.; Bezjian, C.T.; Pfeiffer, S.; Ringelstetter, L.; Müller, C.; Zandkarimi, F.; Merl-Pham, J.; Bao, X.; Anastasov, N.; Kössl, J.; et al. GTP Cyclohydrolase 1/Tetrahydrobiopterin Counteract Ferroptosis through Lipid Remodeling. *ACS Cent. Sci.* 2020, *6*, 41–53, doi:10.1021/ACSCENTSCI.9B01063.
58. Elias, P.M.; Schmuth, M. Abnormal Skin Barrier in the Etiopathogenesis of Atopic Dermatitis. *Curr. Opin. Allergy Clin. Immunol.* 2009, *9*, 437–446, doi:10.1097/ACI.0B013E32832E7D36.
59. Gutowska-Owsiak, D.; Podobas, E.I.; Eggeling, C.; Ogg, G.S.; Bernardino de la Serna, J. Addressing Differentiation in Live Human Keratinocytes by Assessment of Membrane Packing Order. *Front. Cell Dev. Biol.* 2020, *8*, 573230, doi:10.3389/FCELL.2020.573230/BIBTEX.
60. Berdyshev, E. Skin Lipid Barrier: Structure, Function and Metabolism. *Allergy Asthma Immunol. Res.* 2024, *16*, 445–461, doi:10.4168/AAIR.2024.16.5.445.
61. Elias, P.M. Lipids and the Epidermal Permeability Barrier. *Arch. Dermatol. Res.* 1981, *270*, 95–117, doi:10.1007/BF00417155.
62. Friedmann Angeli, J.P.; Schneider, M.; Proneth, B.; Tyurina, Y.Y.; Tyurin, V.A.; Hammond, V.J.; Herbach, N.; Aichler, M.; Walch, A.; Eggenhofer, E.; et al. Inactivation of the Ferroptosis Regulator Gpx4 Triggers Acute Renal Failure in Mice. *Nat. Cell Biol.* 2014, *16*, 1180–1191, doi:10.1038/NCB3064.

 doi:10.20944/preprints202602.1713.v1

63. Choi, D.I.; Park, J.H.; Choi, J.Y.; Piao, M.S.; Suh, M.S.; Lee, J.B.; Yun, S.J.; Lee, S.C. Keratinocytes-Derived Reactive Oxygen Species Play an Active Role to Induce Type 2 Inflammation of the Skin: A Pathogenic Role of Reactive Oxygen Species at the Early Phase of Atopic Dermatitis. *Ann. Dermatol.* 2020, *33*, 26, doi:10.5021/AD.2021.33.1.26.
64. Liu, L.; Kang, X. xiao ACSL4 Is Overexpressed in Psoriasis and Enhances Inflammatory Responses by Activating Ferroptosis. *Biochem. Biophys. Res. Commun.* 2022, *623*, 1–8, doi:10.1016/J.BBRC.2022.07.041.
65. Vats, K.; Tian, H.; Singh, K.; Tyurina, Y.Y.; Sparvero, L.J.; Tyurin, V.A.; Kruglov, O.; Chang, A.; Wang, J.; Green, F.; et al. Ferroptosis of Select Skin Epithelial Cells Initiates and Maintains Chronic Systemic Immune-Mediated Psoriatic Disease. *J. Clin. Invest.* 2024, *135*, doi:10.1172/JCI183219.
66. Wu, M.N.; Zhou, D.M.; Jiang, C.Y.; Chen, W.W.; Chen, J.C.; Zou, Y.M.; Han, T.; Zhou, L.J.M. Genetic Analysis of Potential Biomarkers and Therapeutic Targets in Ferroptosis from Psoriasis. *Front. Immunol.* 2023, *13*, doi:10.3389/FIMMU.2022.1104462/PDF.
67. Liu, L.; Lian, N.; Shi, L.; Hao, Z.; Chen, K. Ferroptosis: Mechanism and Connections with Cutaneous Diseases. *Front. Cell Dev. Biol.* 2023, *10*, doi:10.3389/FCELL.2022.1079548.
68. Simmons, J.; Gallo, R.L. The Central Roles of Keratinocytes in Coordinating Skin Immunity. *Journal of Investigative Dermatology* 2024, *144*, 2377–2398, doi:10.1016/J.JID.2024.06.1280.
69. Lee, E.; Song, C.H.; Bae, S.J.; Ha, K.T.; Karki, R. Regulated Cell Death Pathways and Their Roles in Homeostasis, Infection, Inflammation, and Tumorigenesis. *Exp. Mol. Med.* 2023, *55*, 1632, doi:10.1038/S12276-023-01069-Y.
70. Freigang, S. The Regulation of Inflammation by Oxidized Phospholipids. *Eur. J. Immunol.* 2016, *46*, 1818–1825, doi:10.1002/EJI.201545676.
71. Chen, X.; Kang, R.; Kroemer, G.; Tang, D. Broadening Horizons: The Role of Ferroptosis in Cancer. *Nat. Rev. Clin. Oncol.* 2021, *18*, 280–296, doi:10.1038/S41571-020-00462-0.
72. Lowes, M.A.; Suárez-Fariñas, M.; Krueger, J.G. Immunology of Psoriasis. *Annu. Rev. Immunol.* 2014, *32*, 227, doi:10.1146/ANNUREV-IMMUNOL-032713-120225.
73. Kadl, A.; Sharma, P.R.; Chen, W.; Agrawal, R.; Meher, A.K.; Rudraiah, S.; Grubbs, N.; Sharma, R.; Leitinger, N. Oxidized Phospholipid-Induced Inflammation Is Mediated by Toll-like Receptor 2. *Free Radic. Biol. Med.* 2011, *51*, 1903, doi:10.1016/J.FREERADBIOMED.2011.08.026.
74. Chen, R.; Zou, J.; Liu, J.; Kang, R.; Tang, D. DAMPs in the Immunogenicity of Cell Death. *Mol. Cell* 2025, *85*, 3874–3889, doi:10.1016/J.MOLCEL.2025.09.007.
75. Wroński, A.; Gęgotek, A.; Skrzydlewska, E. Protein Adducts with Lipid Peroxidation Products in Patients with Psoriasis. *Redox Biol.* 2023, *63*, 102729, doi:10.1016/J.REDOX.2023.102729.
76. Wroński, A.; Wójcik, P. Impact of ROS-Dependent Lipid Metabolism on Psoriasis Pathophysiology. *International Journal of Molecular Sciences 2022, Vol. 23, Page 12137* 2022, *23*, 12137, doi:10.3390/IJMS232012137.
77. O'Donnell, V.B.; Bochkov, V. Oxidized Phospholipids in Ferroptosis, Immunity and Inflammation. *Redox Biochemistry and Chemistry* 2025, *14*, 100061, doi:10.1016/J.RBC.2025.100061.
78. Barrera, G.; Pizzimenti, S.; Daga, M.; Dianzani, C.; Arcaro, A.; Cetrangolo, G.P.; Giordano, G.; Cucci, M.A.; Graf, M.; Gentile, F. Lipid Peroxidation-Derived Aldehydes, 4-Hydroxynonenal and Malondialdehyde in Aging-Related Disorders. *Antioxidants* 2018, *7*, 102, doi:10.3390/ANTIOX7080102.
79. Li Pomi, F.; Gammeri, L.; Borgia, F.; Di Gioacchino, M.; Gangemi, S. Oxidative Stress and Skin Diseases: The Role of Lipid Peroxidation. *Antioxidants* 2025, *14*, 555, doi:10.3390/ANTIOX14050555.
80. Ioannidis, M.; Tjepkema, J.; Uitbeijerse, M.R.P.; van den Bogaart, G. Immunomodulatory Effects of 4-Hydroxynonenal. *Redox Biol.* 2025, *85*, 103719, doi:10.1016/J.REDOX.2025.103719.
81. Shen, G.; Liu, J.; Wang, Y.; Deng, Z.; Deng, F. Ferroptosis in Cancer and Inflammatory Diseases: Mechanisms and Therapeutic Implications. *MedComm (Beijing).* 2025, *6*, e70349, doi:10.1002/MCO2.70349.
82. Guo, J.; Zhang, H.; Lin, W.; Lu, L.; Su, J.; Chen, X. Signaling Pathways and Targeted Therapies for Psoriasis. *Signal Transduct. Target. Ther.* 2023, *8*, 437, doi:10.1038/S41392-023-01655-6.
83. Krümmel, B.; Plötz, T.; Jörns, A.; Lenzen, S.; Mehmeti, I. The Central Role of Glutathione Peroxidase 4 in the Regulation of Ferroptosis and Its Implications for Pro-Inflammatory Cytokine-Mediated Beta-Cell Death. *Biochim. Biophys. Acta Mol. Basis Dis.* 2021, *1867*, doi:10.1016/j.bbadis.2021.166114.

 doi:10.20944/preprints202602.1713.v1

84. Yadav, U.C.S.; Ramana, K. V. Regulation of NF-KB-Induced Inflammatory Signaling by Lipid Peroxidation-Derived Aldehydes. *Oxid. Med. Cell. Longev.* 2013, *2013*, 690545, doi:10.1155/2013/690545.
85. Yao, Y.; Chen, L.Q.; Lv, Y.B.; Tang, S.L.; Shen, W.; Sun, H.; Zhong, H.J. Skin Immune Microenvironment in Psoriasis: From Bench to Bedside. *Front. Immunol.* 2025, *16*, 1643418, doi:10.3389/FIMMU.2025.1643418/FULL.
86. Vassiliou, E.; Farias-Pereira, R. Impact of Lipid Metabolism on Macrophage Polarization: Implications for Inflammation and Tumor Immunity. *International Journal of Molecular Sciences 2023, Vol. 24, Page 12032* 2023, *24*, 12032, doi:10.3390/IJMS241512032.
87. Ni, M.; Wang, K.; Tian, Y.; Zhou, L.; Yang, X.; Ni, M. Macrophages in the Pathogenesis of Psoriasis and Anti-Psoriatic Nanotherapies. *J. Biol. Regul. Homeost. Agents* 2025, *39*, 3315, doi:10.54517/JBRHA3315.
88. Demuynck, R.; Efimova, I.; Naessens, F.; Krysko, D. V. Immunogenic Ferroptosis and Where to Find It? *J. Immunother. Cancer* 2021, *9*, e003430, doi:10.1136/JITC-2021-003430.
89. Shao, S.; Fang, H.; Dang, E.; Xue, K.; Zhang, J.; Li, B.; Qiao, H.; Cao, T.; Zhuang, Y.; Shen, S.; et al. Neutrophil Extracellular Traps Promote Inflammatory Responses in Psoriasis via Activating Epidermal TLR4/IL-36R Crosstalk. *Front. Immunol.* 2019, *10*, doi:10.3389/FIMMU.2019.00746.
90. Chiang, C.C.; Cheng, W.J.; Korinek, M.; Lin, C.Y.; Hwang, T.L. Neutrophils in Psoriasis. *Front. Immunol.* 2019, *10*, 466686, doi:10.3389/FIMMU.2019.02376/FULL.
91. Girolomoni, G.; Strohal, R.; Puig, L.; Bachelez, H.; Barker, J.; Boehncke, W.H.; Prinz, J.C. The Role of IL-23 and the IL-23/TH17 Immune Axis in the Pathogenesis and Treatment of Psoriasis. *Journal of the European Academy of Dermatology and Venereology* 2017, *31*, 1616, doi:10.1111/JDV.14433.
92. Mao, J.; Ma, X. Bioinformatics Identification of Ferroptosis-Associated Biomarkers and Therapeutic Compounds in Psoriasis. *J. Oncol.* 2022, *2022*, doi:10.1155/2022/3818216.
93. Wu, M.N.; Zhou, D.M.; Jiang, C.Y.; Chen, W.W.; Chen, J.C.; Zou, Y.M.; Han, T.; Zhou, L.J.M. Genetic Analysis of Potential Biomarkers and Therapeutic Targets in Ferroptosis from Psoriasis. *Front. Immunol.* 2023, *13*, doi:10.3389/FIMMU.2022.1104462/PDF.
94. Chen, J.; Zhan, J.; Zhou, Y. Characterization of Ferroptosis-Associated Subtypes in Psoriasis and the Potential of CHAC1 as a Diagnostic Biomarker Based on Machine Learning. *Clin. Cosmet. Investig. Dermatol.* 2025, *18*, 3277–3295, doi:10.2147/CCID.S553367.
95. Wu, X.; Sun, Y.; Wei, S.; Hu, H.; Yang, B. Identification of Potential Ferroptosis Biomarkers and Analysis of Immune Cell Infiltration in Psoriasis Using Machine Learning. *Clin. Cosmet. Investig. Dermatol.* 2024, *17*, 1281, doi:10.2147/CCID.S457958.
96. Zhou, Q.; Yang, L.; Li, T.; Wang, K.; Huang, X.; Shi, J.; Wang, Y. Mechanisms and Inhibitors of Ferroptosis in Psoriasis. *Front. Mol. Biosci.* 2022, *9*, 1019447, doi:10.3389/FMOLB.2022.1019447/FULL.
97. Zilka, O.; Shah, R.; Li, B.; Friedmann Angeli, J.P.; Griesser, M.; Conrad, M.; Pratt, D.A. On the Mechanism of Cytoprotection by Ferrostatin-1 and Liproxstatin-1 and the Role of Lipid Peroxidation in Ferroptotic Cell Death. *ACS Cent. Sci.* 2017, *3*, 232–243, doi:10.1021/ACSCENTSCI.7B00028.
98. Morini, F.; Dusatti, F.; Bonina, F.P.; Saija, A.; Ferro, M. Iron-Induced Lipid Peroxidation in Human Skin-Derived Cell Lines: Protection by a Red Orange Extract. *Alternatives to Laboratory Animals* 2000, *28*, 427–433, doi:10.1177/026119290002800310;PAGEGROUP:STRING:PUBLICATION.
99. Dobrică, E.C.; Cozma, M.A.; Găman, M.A.; Voiculescu, V.M.; Găman, A.M. The Involvement of Oxidative Stress in Psoriasis: A Systematic Review. *Antioxidants* 2022, *11*, 282, doi:10.3390/ANTIOX11020282.
100. Le, J.; Meng, Y.; Wang, Y.; Li, D.; Zeng, F.; Xiong, Y.; Chen, X.; Deng, G. Molecular and Therapeutic Landscape of Ferroptosis in Skin Diseases. *Chin. Med. J. (Engl).* 2024, *137*, 1777–1789, doi:10.1097/CM9.0000000000003164.
101. Barrea, L.; Savanelli, M.C.; Di Somma, C.; Napolitano, M.; Megna, M.; Colao, A.; Savastano, S. Vitamin D and Its Role in Psoriasis: An Overview of the Dermatologist and Nutritionist. *Rev. Endocr. Metab. Disord.* 2017, *18*, 195, doi:10.1007/S11154-017-9411-6.
102. Arbiser, J.L.; Bonner, M.Y.; Ward, N.; Elsey, J.; Rao, S. Selenium Unmasks Protective Iron Armor: A Possible Defense against Cutaneous Inflammation and Cancer. *Biochimica et Biophysica Acta (BBA)—General Subjects* 2018, *1862*, 2518–2527, doi:10.1016/J.BBAGEN.2018.05.018.

 doi:10.20944/preprints202602.1713.v1

103. Chen, C.H.; Wu, N.L.; Tsai, T.F. How Cells Die in Psoriasis? *Int. J. Mol. Sci.* 2025, *26*, 3747, doi:10.3390/IJMS26083747.
104. Jiraskova Zakostelska, Z.; Reiss, Z.; Tlaskalova-Hogenova, H.; Rob, F. Paradoxical Reactions to Anti-TNFα and Anti-IL-17 Treatment in Psoriasis Patients: Are Skin and/or Gut Microbiota Involved? *Dermatol. Ther. (Heidelb).* 2023, *13*, 911, doi:10.1007/S13555-023-00904-4.
105. Xu, H.; Lu, Y.; Zeng, Q.; Zhu, X.; Guan, W.; Liu, S. Ferroptosis of Immune Cells in Infection, Inflammation and Tumor Progression. *Biomolecules* 2025, *15*, 1464, doi:10.3390/BIOM15101464.
106. Bilski, R.; Kupczyk, D.; Woźniak, A. Oxidative Imbalance in Psoriasis with an Emphasis on Psoriatic Arthritis: Therapeutic Antioxidant Targets. *Molecules 2024, Vol. 29, Page 5460* 2024, *29*, 5460, doi:10.3390/MOLECULES29225460.
107. Zhou, Q.; Meng, Y.; Li, D.; Yao, L.; Le, J.; Liu, Y.; Sun, Y.; Zeng, F.; Chen, X.; Deng, G. Ferroptosis in Cancer: From Molecular Mechanisms to Therapeutic Strategies. *Signal Transduction and Targeted Therapy 2024 9:1* 2024, *9*, 1–30, doi:10.1038/s41392-024-01769-5.
108. Lippens, S.; Denecker, G.; Ovaer, P.; Vandenabeele, P.; Declercq, W. Death Penalty for Keratinocytes: Apoptosis versus Cornification. *Cell Death & Differentiation 2005 12:2* 2005, *12*, 1497–1508, doi:10.1038/sj.cdd.4401722.
109. Lecomte, K.; Toniolo, A.; Hoste, E. Cell Death as an Architect of Adult Skin Stem Cell Niches. *Cell Death & Differentiation 2024 31:8* 2024, *31*, 957–969, doi:10.1038/s41418-024-01297-3.
110. Radu, A.; Tit, D.M.; Endres, L.M.; Radu, A.F.; Vesa, C.M.; Bungau, S.G. Naturally Derived Bioactive Compounds as Precision Modulators of Immune and Inflammatory Mechanisms in Psoriatic Conditions. *Inflammopharmacology* 2025, *33*, 527–549, doi:10.1007/S10787-024-01602-Z.
111. Burlec, A.F.; Hăncianu, M.; Ivănescu, B.; Macovei, I.; Corciovă, A. Exploring the Therapeutic Potential of Natural Compounds in Psoriasis and Their Inclusion in Nanotechnological Systems. *Antioxidants (Basel).* 2024, *13*, doi:10.3390/ANTIOX13080912.
112. Mustafa, A.M.; Atwa, A.M.; Elgindy, A.M.; Alkabbani, M.A.; Ibrahim, K.M.; Esmail, M.M.; El-Shiekh, R.A.; Mohamed, E.M.; Kamel, K.M. Targeting Psoriatic Inflammation with Natural Compounds: Mechanistic Insights and Therapeutic Promise. *Inflammopharmacology* 2025, *33*, 3843–3870, doi:10.1007/S10787-025-01851-6.
113. Zhang, W.; Liu, Y.; Liao, Y.; Zhu, C.; Zou, Z. GPX4, Ferroptosis, and Diseases. *Biomedicine and Pharmacotherapy* 2024, *174*, doi:10.1016/j.biopha.2024.116512.
114. Yang, L.; Fang, Y.; Wang, Y.; Luo, Y.; Pan, Y.; Wu, J.; Li, Y. Ursolic Acid Induces Ferroptosis by Affecting Redox Balance and FADS2-Mediated Unsaturated Fatty Acid Synthesis in Non-Small Cell Lung Cancer. *J. Cancer* 2025, *16*, 2553–2566, doi:10.7150/JCA.105863.
115. Li, W.; Fu, H.; Fang, L.; Chai, H.; Ding, B.; Qian, S. Andrographolide Induced Ferroptosis in Multiple Myeloma Cells by Regulating the P38/Nrf2/HO-1 Pathway. *Arch. Biochem. Biophys.* 2023, *742*, doi:10.1016/j.abb.2023.109622.
116. Le, S.; Wu, X.; Dou, Y.; Song, T.; Fu, H.; Luo, H.; Zhang, F.; Cao, Y. Promising Strategies in Natural Products Treatments of Psoriasis-Update. *Front. Med. (Lausanne).* 2024, *11*, 1386783, doi:10.3389/FMED.2024.1386783/FULL.
117. Gamret, A.C.; Price, A.; Fertig, R.M.; Lev-Tov, H.; Nichols, A.J. Complementary and Alternative Medicine Therapies for Psoriasis: A Systematic Review. *JAMA Dermatol.* 2018, *154*, 1330–1337, doi:10.1001/JAMADERMATOL.2018.2972.
118. Elkhawaga, O.Y.; Ellety, M.M.; Mofty, S.O.; Ghanem, M.S.; Mohamed, A.O. Review of Natural Compounds for Potential Psoriasis Treatment. *Inflammopharmacology* 2023, *31*, 1183–1198, doi:10.1007/S10787-023-01178-0.
119. Tong, W.; Mu, X.; Xu, H.; Yin, X. Natural Products as Modulators of Ferroptosis: Therapeutic Implications and Molecular Mechanisms in Disease Treatment. *J. Nutr. Biochem.* 2026, 110259, doi:10.1016/J.JNUTBIO.2026.110259.
120. Zhang, S.; Wang, J.; Liu, L.; Sun, X.; Zhou, Y.; Chen, S.; Lu, Y.; Cai, X.; Hu, M.; Yan, G.; et al. Efficacy and Safety of Curcumin in Psoriasis: Preclinical and Clinical Evidence and Possible Mechanisms. *Front. Pharmacol.* 2022, *13*, doi:10.3389/FPHAR.2022.903160/PDF.

 doi:10.20944/preprints202602.1713.v1

121. Sarkar, D.; Pramanik, A.; Saha, J.; Das, D.; Mahanti, K.; Mahato, M.; Mondal, P.; Bhattacharyya, S. Amelioration of Imiquimod Induced Psoriasis through Reduction in IL-17A and Th17 Population by Dihydromyricetin Involves Regulation of RORγt Pathway. *Int. Immunopharmacol.* 2025, *153*, doi:10.1016/J.INTIMP.2025.114492.
122. Janda, E.; Martino, C.; Riillo, C.; Parafati, M.; Lascala, A.; Mollace, V.; Boutin, J.A. Apigenin and Luteolin Regulate Autophagy by Targeting NRH-Quinone Oxidoreductase 2 in Liver Cells. *Antioxidants (Basel).* 2021, *10*, doi:10.3390/ANTIOX10050776.
123. DaSilva, L.F.; Senan, S.; Patel, Z.M.; Reddy, A.J.; Gabbita, S.; Nussbaum, Z.; Córdova, C.M.V.; Wenteler, A.; Weber, N.; Tunjic, T.M.; et al. DNA-Diffusion: Leveraging Generative Models for Controlling Chromatin Accessibility and Gene Expression via Synthetic Regulatory Elements. *bioRxiv* 2024, doi:10.1101/2024.02.01.578352.