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Review

Redox Imbalance and the Skin: A Clinical Indicator of Hidden Systemic Risk

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ABSTRACT

Oxidative stress (OxS) is a key pathological mechanism in many dermatologic and systemic disorders. As the largest and most exposed organ, the skin mirrors systemic redox imbalance and early signs of mitochondrial dysfunction, chronic inflammation, and immune dysregulation. This review examines the interplay between oxidative stress, mitochondrial damage, and impaired autophagy, highlighting their reflection in skin diseases and systemic comorbidities. Conditions such as atopic dermatitis, psoriasis, vitiligo, and chronic urticaria share oxidative and mitochondrial alterations that contribute to inflammation, premature aging, and cardiovascular or neurodegenerative risk. In atopic dermatitis, mitochondrial hyperactivity and defective autophagy connect barrier dysfunction with systemic vascular disease. The skin thus serves as a sentinel organ for redox imbalance. Evidence suggests that single, high-dose antioxidants may be ineffective or even pro-oxidant, while multi-antioxidant approaches—including vitamin D, folate, polyphenols, selenium, zinc, and magnesium—support mitochondrial resilience and immune balance. Recognizing cutaneous oxidative stress as both a biomarker and driver of systemic disease underscores the value of integrative antioxidant strategies for preventing and managing dermatologic and age-related disorders.

Introduction

Oxidative stress (OxS) represents a critical pathological mechanism underlying various human diseases, including skin disorders. It arises from an imbalance between the generation of reactive oxygen species (ROS) and the biological system's ability to detoxify these reactive intermediates or repair the resulting damage. This damage is not random but primarily targets three major macromolecular classes: nucleic acids, proteins, and lipids (1).

ROS, such as hydroxyl radicals(•OH), readily attack DNA, causing base modifications, strand breaks, and crosslinking. Guanine, the DNA base with the lowest redox potential, is especially susceptible to oxidation, leading to the formation of 8-oxo-7,8-dihydroguanine (8-oxoG). This mutagenic lesion mispairs with adenine during replication, resulting in G→T transversions—a mutation pattern frequently observed in cancers (2).

Protein oxidation can result in fragmentation of peptide chains, partial loss of enzymatic activity, altered protein structure, and increased susceptibility to proteolytic degradation. Lipid peroxidation compromises membrane integrity and permeability, disrupts ion gradients and cellular homeostasis, and initiates apoptosis and necrosis (3). Each category of injury not only disrupts normal cellular functions but also contributes to pathological processes, including inflammation, carcinogenesis, and degenerative diseases.

The skin, being the largest and outermost organ of the body, is particularly vulnerable to oxidative insults. The objective of this report is to explore the interplay between oxidative stress and skin diseases, elucidate the molecular mechanisms involved, and evaluate potential preventive strategies, including antioxidants.

Skin mitochondria and oxidative stress

Mitochondria in skin cells play a dual role: they are essential for energy production but also serve as a significant source of ROS during electron transport. In skin tissues, mitochondrial dysfunction—often triggered by UV exposure or aging—results in excessive ROS production that damages cellular components, including mitochondrial DNA (mtDNA). This damage promotes a vicious cycle of mitochondrial decay and ROS overproduction, ultimately compromising cellular viability and tissue integrity (4).

Unlike nuclear DNA, mitochondrial DNA is not protected by histone proteins and is less efficiently repaired. ROS-induced mtDNA mutations have been implicated in dermal aging and various degenerative skin conditions. Accumulating evidence connects mitochondrial impairment with several dermatologic disorders, including cutaneous aging, hair loss, delayed wound healing, and inflammatory and autoimmune conditions such as systemic lupus erythematosus, psoriasis, atopic dermatitis, and vitiligo (4). Additionally, skin cancers associated with mutations in mitochondrial and nuclear genes regulating proliferation and apoptosis have been linked to mitochondrial dysfunction (5).

Excessive mitochondrial ROS can act as damage-associated molecular patterns (DAMPs), triggering "sterile inflammation" through pathways such as Toll-like receptor signaling (5). Chronic exposure to glucocorticoids, often used in skin disease therapy, may paradoxically aggravate oxidative stress by impairing mitochondrial function and enhancing ROS formation (6). This stress response has been associated with increased cell damage and premature senescence.

Skin autophagy and oxidative stress

Autophagy is a catabolic process that clears damaged organelles and macromolecules, playing a protective role against oxidative damage. Under oxidative stress, autophagy is upregulated to remove dysfunctional mitochondria (mitophagy), thereby preventing further ROS generation. This quality-control mechanism is crucial for maintaining mitochondrial health and skin vitality. However, chronic or excessive ROS exposure may impair autophagic flux, leading to the accumulation of damaged cellular components and inflammation (7). This impairment is observed in skin diseases such as psoriasis and atopic dermatitis, linking defective autophagy to disease pathogenesis.

Healthy skin function depends on the integrity of its barrier and immune defense. Autophagy is considered the "Guardian of the Skin Barrier" since it operates in various skin cell types, including keratinocytes and immune cells such as Langerhans cells, macrophages,

mast cells, neutrophils, NK cells, and T cells (8).

One of the critical consequences of reduced autophagy is the accumulation of senescent cells—referred to as "zombie cells"—which are metabolically active but non-dividing and resistant to apoptosis. These cells acquire a senescence-associated secretory phenotype (SASP) characterized by the secretion of inflammatory cytokines (e.g., IL-6), chemokines, growth factors, and matrix-degrading enzymes (9). This pro-inflammatory milieu contributes to tissue dysfunction and aging phenotypes. Thus, autophagy is essential for both epidermal renewal and immune surveillance.

Epigenetic effects of oxidative stress: corticosteroid resistance and allergic disease onset

OxS exerts a profound impact on the efficacy of corticosteroid therapy through altered glucocorticoid receptor (GR) isoform expression. While GR-α is the functional isoform responsible for transactivating anti-inflammatory genes via glucocorticoid response elements (GRE), OxS induces GR-β, a dominant-negative isoform that fails to bind corticosteroids and antagonizes GR-α function (10). This isoform switch contributes to steroid resistance, particularly in atopic dermatitis (11).

Furthermore, histone deacetylase-2 (HDAC2) plays a pivotal role in corticosteroid-mediated repression of pro-inflammatory gene transcription. Under oxidative stress, HDAC2 is inactivated via acetylation (12) impairing chromatin compaction and allowing open transcriptional access to pro-inflammatory genes such as thymic stromal lymphopoietin (TSLP). The net effect is an amplified inflammatory response and reduced sensitivity to corticosteroids, even in the presence of normal receptor levels. However, quercetin has been shown to impair TSLP expression, potentially counteracting this pro-inflammatory signaling pathway (13).

Recent evidence indicates that oxidative stress is not merely a byproduct of inflammation but may represent a prerequisite for the development of allergic diseases. Individuals or experimental models with an impaired ability to counteract oxidative stress—whether due to genetic, nutritional, or environmental factors—exhibit exaggerated responses to allergens. This includes overexpression of epithelial-derived cytokines or alarmins such as TSLP, which initiate and propagate Th2-driven immune responses (14). Experimental models, such as transgenic mice overexpressing TSLP in keratinocytes, demonstrate spontaneous development of eczema-like lesions, increased skin infiltration by Th2 cells, and elevated serum IgE in the absence of exogenous allergens (15). These findings underscore that oxidative stress-induced epithelial signaling alone is sufficient to trigger the atopic march, a progression from atopic dermatitis to allergic rhinitis and asthma. Moreover, oxidative stress disrupts immunometabolism and induces mitochondrial dysfunction, contributing to epigenetic alterations, especially in microRNA profiles, that further promote allergic sensitization and persistence (14). These changes act in concert to reprogram immune responses toward a pro-allergic phenotype, which cannot be counteracted by corticosteroids, as these drugs impair mitochondrial function (16, 17).

The recognition that oxidative stress undermines corticosteroid efficacy and facilitates allergy development highlights the importance of redox modulation in therapy. Antioxidants that restore HDAC2 activity and preserve GR-α function—such as quercetin, curcumin or polyphenolic compounds—have shown promise in preclinical models (13, 16) and it is biologically plausible that counteracting OxS may represent a viable strategy to prevent allergic sensitization and the onset of allergic diseases. In fact, strategies that bolster mitochondrial function or limit epithelial TSLP release may prevent allergic sensitization at its origin (13, 18).

The observation that oxidative stress impairs corticosteroid efficacy and promotes allergic disease underscores the therapeutic potential of redox modulation. Antioxidants that restore HDAC2 activity and preserve GR-α function—such as quercetin, curcumin, and other polyphenolic compounds—have shown promise in preclinical models (13, 16). Counteracting oxidative stress is therefore a biologically plausible strategy to prevent allergic sensitization and the development of allergic diseases. Moreover, approaches that enhance mitochondrial function or suppress epithelial TSLP release may help interrupt allergic sensitization at its origin.

Oxidative stress and aging: systemic and cutaneous perspectives

The free radical theory of aging, first proposed by Harman (19) and later expanded to include mitochondrial damage, posits that aging results from the accumulation of oxidative damage over time (20). Senescent cells often develop a senescence-associated secretory phenotype (SASP), releasing pro-inflammatory cytokines such as TNF-α, IL-1, IL-6, and IFN-γ, thereby contributing to inflammaging—a chronic, low-grade inflammation that accelerates aging and underlies many degenerative conditions (9). A crucial contributor to inflammaging is "macrophaging," where aged macrophages exhibit persistent activation and ROS production, overwhelming the anti-inflammatory regulatory systems, especially in elderly populations (21).

The skin, being constantly exposed to exogenous oxidative stressors such as UV radiation, pollutants, wind, and chemicals, is particularly susceptible to aging via ROS-dependent mechanisms. OxS impairs several key elements of skin architecture and function, including collagen degradation through activation of matrix metalloproteinases (MMPs), reduced collagen and elastin synthesis by fibroblasts, mitochondrial membrane damage and ATP depletion in skin cells, and increased epidermal thinning and wrinkling. ROS-mediated activation of NF-κB and MAPK pathways in keratinocytes and fibroblasts leads to overexpression of inflammatory mediators and proteolytic enzymes, compounding extracellular matrix (ECM) degradation (22). Moreover, advanced glycation end-products (AGEs), formed through nonenzymatic reactions between sugars and proteins or lipids, exacerbate skin aging (23). This process contributes to skin darkening, loss of elasticity, and links to systemic diseases such as diabetes and cataracts.

Hair aging exemplifies the visible outcomes of oxidative stress on ectodermal tissues. Major manifestations include greying (canities), associated with melanocyte apoptosis in the hair follicle bulb—likely driven by oxidative damage (24); androgenetic alopecia, linked to premature senescence of dermal papilla cells mediated by oxidative stress (25); and changes in hair fiber properties, where diameter, strength, and manageability are affected due to lipid peroxidation and matrix breakdown.

Early onset of hair aging phenomena is often observed in individuals with reduced antioxidant defenses (26), highlighting the critical protective role of endogenous redox regulation.

Oxidative stress is not merely a byproduct of aging but a driving force behind the molecular and cellular deterioration observed across tissues, with the skin being both a target and a model organ for studying redox-driven aging. Given the established role of oxidative stress in these degenerative changes, individuals showing clinical or histological signs of skin aging should be considered for intervention with a cascade of antioxidant molecules for healthy aging programming. Interventions aimed at enhancing antioxidant defenses, maintaining mitochondrial function, and modulating inflammatory signaling hold potential to slow aging and improve both skin and systemic health (13, 18).

Skin diseases and oxidative stress

Skin diseases represent a broad and heterogeneous group of conditions with increasing global prevalence, ranging from inflammatory disorders such as atopic dermatitis and psoriasis to autoimmune diseases, pigmentary disorders, premature aging, and malignancies. Despite their diversity, many skin diseases share a common pathogenic mechanism: the disruption of redox balance and the excessive generation of reactive oxygen species (ROS). When oxidative stress outweighs antioxidant capacity, it initiates a cascade of molecular events that fuel both the onset and progression of skin disorders (27).

Atopic Dermatitis: systemic oxidative stress and barrier dysfunction

Oxidative stress is a central pathogenic factor in atopic dermatitis (28). Higher urinary oxidative biomarkers correlate with SCORAD scores and disease severity (29). ROS levels are elevated both locally in the skin and systemically, leading to cellular and tissue damage. Studies reveal elevated malondialdehyde (MDA) and decreased enzymatic antioxidants (SOD, catalase, GPx) and non-enzymatic antioxidants (glutathione, vitamins A, C, and E) in AD patients' blood (30). Increased urinary markers of oxidative DNA damage such as 8-OHdG and pentosidine correlate with disease severity and risk of progression to asthma and allergic rhinitis (31). Markers of oxidative stress are elevated in the exhaled air of children with AD (32).

Such findings underscore that oxidative stress in AD is not merely local but reflects a systemic pro-oxidative state, even detectable in the respiratory tract. This supports the growing concept of atopic diseases as a multi-organ oxidative-inflammatory syndrome, where the skin-lung axis may be modulated by common redox-sensitive pathways.

Enhanced oxidative stress is observed even in non-lesional skin, suggesting a pre-activated disease state (33). Keratinocytes in atopic AD exhibit mitochondrial hyperactivity, characterized by increased fatty acid oxidation, elevated ROS production—particularly hydrogen peroxide (H_2O_2)—and enhanced mitochondrial proton leak, highlighting the pathological role of mitochondria even in non-lesional skin (33). In this study, although the antioxidative stress response was upregulated, it appeared insufficient to prevent reactive oxygen species (ROS)-mediated deleterious effects such as lipid peroxidation and DNA damage. The high production of ROS can induce autophagy, apoptosis and programmed necrosis in cells, resulting in DNA damage and skin barrier breakdown (34). In mouse models (e.g., flaky tail mice), this mitochondrial overproduction of H_2O_2 contributes to skin inflammation and barrier disruption. Targeting this dysfunction with mitochondria-specific antioxidants such as MitoQ has been shown to reduce inflammation and restore homeostasis (35). Oxidative stress contributes directly to downregulation of skin barrier proteins and to enhanced colonization by Staphylococcus aureus, which fuels inflammation and perpetuates the cycle of oxidative stress, immune activation, and barrier impairment (36).

AD skin shows reduced expression of NRF2, a master regulator of antioxidant defense and epidermal homeostasis. Proteomic analyses reveal decreased NRF2 activity, lower levels of mitochondrial proteins, and impaired detoxification responses (37). In fact, restoring NRF2 activity via NRF2-activating compounds (e.g., curcumin, quercetin, resveratrol) is emerging as a promising therapeutic strategy (38, 39). Supplementation with zinc shows beneficial effects on inflammation, pruritus, and barrier repair (40). Topical and systemic curcumin has been shown to downregulate TSLP expression, suppress STAT6 and GATA-3, normalize epidermal thickness, and inhibit the progression of the atopic march in experimental models (41).

Given the strong role of oxidative stress in AD, a multimodal antioxidant approach is warranted. This includes topical antioxidants (e.g., MitoQ, curcumin), systemic supplementation (zinc, selenium, vitamin E, vitamin D, polyphenols) (42) and bath therapy using mineral-rich salts (e.g., sodium chloride, magnesium, allantoin, urea) (43) to reduce inflammation, oxidative load and restore skin hydration. These strategies can break the cycle of oxidative damage, immune activation, and barrier dysfunction, ultimately improving patient outcomes.

Acne Vulgaris: oxidative stress as an initiating pathogenic event

Acne vulgaris is a chronic inflammatory condition of the pilosebaceous unit and is now recognized as being strongly influenced by oxidative stress (44). Recent evidence indicates that oxidative stress may represent the initiating event (45) not just a secondary phenomenon, since malfunctioning follicular walls and altered sebum composition promote local ROS production, especially superoxide (O_2^-) and hydrogen peroxide (H_2O_2). ROS activate toll-like receptor 2 (TLR2), triggering a cascade of pro-inflammatory cytokines (IL-1β, IL-8, TNF-α), thereby amplifying the inflammatory response (46).

A meta-analysis involving 14 trials and over 1,000 participants confirmed increased malondialdehyde (MDA) levels and reduced superoxide dismutase (SOD) and total antioxidant capacity (TAC) in patients compared to healthy subjects, with a clear association between MDA levels and acne severity (44). Additionally, systemic markers such as oxidized DNA, nitric oxide species, and depleted glutathione have been reported in plasma and lesion scrapings.

Besides antibiotics such as tetracycline and erythromycin, which also act by reducing H_2O_2 levels (47), antioxidant therapies using zinc, selenium, curcumin, resveratrol, and folic acid have demonstrated beneficial effects in modulating redox imbalance and improving metabolic parameters, especially in individuals with acne linked to metabolic syndrome (44). While isotretinoin remains the gold standard, it paradoxically increases oxidative stress, often requiring antioxidant supplementation to mitigate systemic side effects (48).

Psoriasis: mitochondrial oxidative stress and chronic immune activation

Extensive data link oxidative stress with both the onset and severity of psoriasis. A 2019 meta-analysis revealed that patients with psoriasis had lower total antioxidant status (TAS), higher total oxidant status (TOS), increased levels of MDA, and decreased catalase activity compared to controls (49). Psoriatic lesions show elevated mitochondrial ROS (mtROS) production and mitochondrial ROS are essential for the development of psoriatic inflammation (50). In the serum of these patients, mitochondrial DNA (mtDNA) is found in oxidized form, reflecting systemic oxidative stress. These changes activate inflammatory cascades via dendritic cell stimulation, MAPK phosphorylation, and NF-κB signaling (51).

In mouse models, mitoquinone (MitoQ), a mitochondria-targeted antioxidant, was effective in reducing psoriatic inflammation (47). Psoriasis patients exhibit oxidative and epigenetic damage to blood DNA, particularly 8-hydroxy-2′-deoxyguanosine, indicating widespread nuclear damage (52). Shortened telomeres in T cells ($CD8^+CD28^+$) suggest chronic immune stimulation and increased turnover, consistent with accelerated immune aging in both patients with psoriasis and atopic dermatitis (53).

Antioxidants such as curcumin (including Meriva and nanocurcumin formulations) improve psoriasis severity index scores and modulate lipid profiles when combined with retinoids (e.g., acitretin) (54, 55). Curcumin also reduces serum IL-22, a cytokine linked to psoriasis pathogenesis (56). Topical or oral vitamin D analogues (e.g., calcipotriol) also function indirectly by inhibiting phosphorylase kinase, which is redox-sensitive and linked to lesion resolution (50).

Chronic Spontaneous Urticaria: a critical pathogenic driver

Emerging evidence highlights OxS as a critical and underrecognized contributor to chronic spontaneous urticaria (CSU) persistence, severity, and treatment resistance (57). Multiple studies have demonstrated that patients with CSU exhibit significantly higher systemic oxidative stress compared to healthy controls (58, 59). This is characterized by increased markers of lipid peroxidation, such as elevated malondialdehyde (MDA) levels in serum and platelets, alongside reduced antioxidant enzyme activity—notably superoxide dismutase (SOD) and glutathione peroxidase (GPx) (60). Additionally, patients show lower total antioxidant status (TAS) and elevated total oxidant status (TOS) in plasma, resulting in a significantly higher oxidative stress index (OSI) (58-60).

Importantly, there is a positive correlation between TOS/OSI and the urticaria activity score (UAS7), suggesting that oxidative stress intensity directly relates to disease activity ($\rho = 0.381$ and $\rho = 0.337$, respectively; $p < 0.01$) (59). Children with CSU also demonstrate elevated nitrosative stress, with significantly increased serum nitrite and total nitric oxide (NOx) metabolites that positively correlate with UAS7 scores. Nitric oxide (NO), as a reactive nitrogen species, functions not only as a vasodilator but also enhances vascular permeability, further aggravating dermal edema and wheal formation (59).

Advanced oxidative stress markers, including advanced glycation end products (AGEs) and advanced oxidation protein products (AOPPs), are significantly elevated in CSU patients (55). These markers reflect oxidative modification of circulating and tissue proteins, particularly albumin, and are linked with chronic inflammation and immune dysregulation. Notably, these markers remain uninfluenced by autologous serum/plasma test positivity, suggesting they reflect a fundamental metabolic disturbance in CSU.

Activated platelets from CSU patients demonstrate a particularly interesting pathophysiological profile. They contain significantly elevated MDA levels, show decreased SOD and GPx activity, and release increased levels of pro-inflammatory cytokines, including IL-6 and high-sensitivity CRP (59). This evidence suggests that platelets function as active sources of reactive oxygen species (ROS) and inflammatory mediators, contributing to the prothrombotic and inflammatory state characteristic of CSU (61).

Gene expression profiling from lesional skin of CSU patients reveals upregulation of oxidative stress-related genes and increased expression of vascularization markers such as CYR61. The normalization of these gene expression signatures following omalizumab treatment, which corresponds with clinical improvement, provides compelling evidence for the therapeutic relevance of targeting oxidative pathways (62).

These findings collectively demonstrate that oxidative stress operates not only systemically but also manifests locally in skin lesions, providing a molecular basis for the persistent cutaneous manifestations observed in CSU. Therefore, oxidative stress emerges as a major

pathogenic driver in chronic spontaneous urticaria, influencing disease activity, inflammation, vascular permeability, and treatment responsiveness.

Given the central involvement of reactive oxygen species (ROS) and reactive nitrogen species (RNS), antioxidant-based therapies represent a promising therapeutic avenue. These may include nutritional supplementation, targeted pharmacological agents, or immune modulation strategies such as omalizumab, all of which may offer significant benefits in CSU management. This perspective becomes particularly relevant considering that nearly half of patients with CSU do not respond adequately to antihistamines, highlighting the need for alternative therapeutic strategies (63). Future therapeutic approaches should therefore consider redox modulation as an integral component of personalized treatment strategies in CSU

Vitiligo: mitochondrial oxidative stress and melanocyte dysfunction

Vitiligo is a complex skin disorder characterized by melanocyte dysfunction and death, leading to depigmented patches. A central mechanism in its pathogenesis is oxidative stress, particularly mitochondria-derived ROS overproduction (64).

Mitochondrial dysfunction in vitiligo is marked by altered electron transport chain (ETC) activity, increased proton leak, and reduced ATP synthesis, especially in peri-lesional skin. The accumulation of hydrogen peroxide (H_2O_2) and impaired antioxidant defenses induce melanocyte apoptosis via the TRPM2 channel, which mediates Ca^{2+}-dependent mitochondrial cell death (65, 66). Morphological changes in mitochondria, including cristae abnormalities, are evident alongside elevated mitochondrial ROS levels that can reach up to 257% higher in peri-lesional melanocytes compared to healthy controls (66).

Meta-analyses confirm increased malondialdehyde (MDA) and lipid peroxidation in blood and erythrocytes of vitiligo patients, highlighting a systemic oxidative phenotype (67). These data strongly indicate that oxidative stress acts as both an initiator and amplifier of vitiligo pathology, directly impairing melanocyte function and survival while driving immune-mediated secondary damage.

Systemic Lupus Erythematosus: oxidative stress and autoimmune amplification

Systemic Lupus Erythematosus (SLE) is a multisystem autoimmune disease with common skin involvement and a well-established oxidative pathophysiological profile (68). Mitochondria in lupus patients exhibit excessive ROS production, dysfunctional antioxidant enzymes, and mitochondrial DNA (mtDNA) oxidation (69). Oxidized mtDNA is released into the cytosol, where it activates the cGAS-STING pathway, inducing type I interferon-stimulated genes (ISGs) and amplifying autoimmunity. Chronic oxidative phosphorylation dysfunction in immune cells drives sustained inflammation, autoantibody production, and tissue damage. Nrf2, a key antioxidant transcription factor, is underactive in SLE, and Nrf2-activating compounds are emerging as novel therapeutic strategies, particularly for lupus nephritis (70).

Melanoma: the double-edged role of oxidative stress

Melanoma arises from melanocytes, which naturally maintain high ROS levels due to melanin synthesis (71). This redox activity represents both a protective and pathogenic factor in melanocyte biology. Melanin synthesis, particularly pheomelanin production, generates substantial ROS and can promote DNA damage and carcinogenesis, especially under UV exposure (72). OxS leads to global DNA hypomethylation, genomic instability, and oncogene activation in melanocytes (73). Melanoma progression is associated with increased lipid peroxidation, as evidenced by elevated malondialdehyde (MDA) levels in serum, confirming systemic oxidative imbalance that correlates with tumor stage (74).

Nrf2 plays a particularly complex dual role in melanoma pathogenesis: it functions protectively in early melanocyte homeostasis and UV defense, but becomes tumor-promoting in established melanoma, where it helps cancer cells maintain redox balance, resist therapy, and facilitate metastasis (75, 76). This paradoxical role highlights the importance of context-dependent redox signaling in cancer biology.

Therapeutic approaches targeting this oxidative vulnerability show promise. Agents like naringenin, derived from citrus fruits, demonstrate potential in selectively inducing ROS-mediated apoptosis in melanoma

cells (77). In melanoma, oxidative stress represents a double-edged sword—promoting initial transformation and progression while simultaneously providing exploitable vulnerabilities for therapeutic targeting through pro-oxidant drugs and redox modulation strategies.

Wound Healing: balancing beneficial and harmful ROS effects

ROS play a biphasic role in wound healing, proving essential at low concentrations yet deleterious when present in excess (78). During acute wound repair, ROS provide beneficial functions including antimicrobial activity, cell signaling facilitation, angiogenesis promotion, and matrix remodeling support.

In contrast, chronic wounds such as diabetic foot ulcers are characterized by persistent oxidative stress, mitochondrial dysfunction, and failure of redox homeostasis (79). This oxidative imbalance disrupts all phases of healing, from initial inflammation through final tissue remodeling. ROS overproduction damages endothelial cells, fibroblasts, and keratinocytes, promoting tissue breakdown rather than facilitating repair processes.

Therapeutic interventions targeting oxidative stress have shown clinical promise (80). Nutraceuticals like curcumin improve wound healing outcomes by reducing systemic oxidative markers such as MDA and CRP, improving endothelial function and flow-mediated dilation, and modulating insulin resistance and inflammatory cytokine profiles (81).

These findings demonstrate that while controlled ROS generation is vital for successful acute wound healing, excessive oxidative stress serves as a major driver of chronic non-healing wounds. Antioxidant therapies, including curcumin supplementation, represent effective adjunctive treatments to promote tissue regeneration and restore normal healing processes.

Skin Infectious Diseases: the dual role of oxidative stress in host defense

Oxidative stress (OxS) plays a dual and context-dependent role in skin infectious diseases. On one hand, reactive oxygen species (ROS) are critical for host defense, enabling the immune system to eliminate pathogens effectively. On the other hand, uncontrolled ROS production can cause collateral damage to host tissues, aggravate inflammation, and impair healing processes (27). Skin, serving as the primary barrier against environmental insults, represents a critical site where this delicate balance is frequently challenged.

ROS in Innate Immune Response and Pathogen Control

During infection, neutrophils, macrophages, and keratinocytes produce ROS via NADPH oxidase and mitochondrial pathways as part of the innate immune response. These ROS serve multiple protective functions: eliminating invading bacteria, viruses, and fungi; regulating inflammatory responses; and activating signaling pathways that stimulate antimicrobial peptide production and cytokine release. However, excessive ROS production can lead to tissue damage, prolonged infection, and delayed resolution by damaging DNA, proteins, and lipids in skin cells, disrupting skin barrier function, and inducing apoptosis or necrosis of keratinocytes (82).

Bacterial Infections and Oxidative Imbalance

Staphylococcus aureus infections exemplify this dual role of oxidative stress. S. aureus activates Toll-like receptors (TLRs) on keratinocytes, triggering ROS production that participates in pathogen elimination. However, S. aureus superantigens and toxins can amplify ROS formation beyond protective levels, causing epidermal damage and promoting chronic inflammation (83). Biofilm formation further exacerbates oxidative imbalance by shielding bacteria from host defenses while sustaining prolonged inflammatory responses (84).

Viral Infections and Redox Dysregulation

Viral pathogens such as herpes simplex virus (HSV) induce significant oxidative stress during replication. ROS are generated in both infected keratinocytes and responding immune cells, and this oxidative stress contributes to viral reactivation, skin lesion formation, and impaired antiviral immunity (85). In these clinical contexts, antioxidant interventions can reduce viral load and symptom severity by modulating redox-sensitive signaling pathways (86).

Fungal and Parasitic Infections

Pathogens including Candida albicans and dermatophytes are similarly influenced by host ROS responses, which have been shown to induce biofilm formation (87). While ROS help contain fungal spread initially, chronic fungal infections can lead to excessive ROS accumulation and tissue damage. In cutaneous leishmaniasis, oxidative stress demonstrates a particularly complex dual role: beneficial through parasite-killing mechanisms, yet harmful by contributing to tissue ulceration and delayed healing processes (88).

Therapeutic Implications and Future Directions

A deeper understanding of redox biology in skin infections offers significant opportunities to develop adjunctive therapies that not only combat infection effectively but also preserve skin integrity and accelerate recovery. Such approaches could optimize the protective functions of ROS while minimizing their detrimental effects on host tissues.

Skin diseases as a “canary in the mine”: a sentinel for oxidative and inflammatory dysregulation

1. The skin as a sentinel organ

The skin, being the largest and most exposed organ of the human body, is uniquely positioned to reflect internal physiological disturbances, including those related to climatic changes and environmental pollution (89). Just as a canary in a coal mine warns of invisible toxic gases, skin diseases often precede or co-occur with deeper systemic disorders, acting as an early and visible alert for underlying OxS and chronic low-grade inflammation (90).

2. Early dermatological signs of systemic dysfunction

i) Skin Aging as a Mortality Predictor

Skin aging and wrinkles can be considered mortality predictors with significant clinical implications. A longitudinal study in French workers demonstrated that forehead wrinkles were significantly associated with cardiovascular mortality, independent of age or classical risk factors. Subjects with the deepest wrinkles had a 6-fold higher risk of death compared to those without wrinkles (91). These findings suggest that cutaneous changes—such as collagen degradation and oxidative damage—can mirror vascular and metabolic aging processes throughout the body.

ii) Hair Changes as Cardiometabolic Warnings

Hair graying and baldness should be considered important cardiometabolic warning signs. Hair graying is linked to melanocyte apoptosis caused by ROS, making it a visible marker of oxidative tissue injury. Androgenetic alopecia correlates with cardiovascular risk, including hypertension and coronary artery disease, as evidenced by data from the Framingham Heart Study (92).

3. Cutaneous diseases and systemic inflammation

i) Atopic Dermatitis, Systemic Inflammation, and Degenerative Comorbidities

Atopic dermatitis (AD) is associated not only with atopic conditions but also with a heightened risk of cardiovascular disease (93), mental illness (94) and autoimmune disorders (95). Mechanistically, this association is driven by mitochondrial oxidative dysfunction, endothelial activation, and platelet hyperactivity, forming a nexus of systemic inflammation and vascular risk (93). A comprehensive UK study involving 3.6 million people demonstrated increased hazard ratios for stroke, myocardial infarction, and heart failure in individuals

with AD (96). Moreover, recent evidence suggests that adults with atopic dermatitis may also have a higher susceptibility to age-related macular degeneration (97). Both conditions share features of impaired autophagy and oxidative stress–driven barrier dysfunction, leading to chronic inflammation and tissue degeneration (8). This mechanistic overlap supports the view of AD as a systemic disorder extending beyond the skin, with redox imbalance and defective cellular clearance processes contributing to multiple age-related pathologies.

ii) Psoriasis and Systemic Immune Activation.

Psoriasis is characterized by systemic immune activation, oxidative DNA damage, and vascular stiffening (98, 99). It demonstrates strong associations with metabolic syndrome, autoimmune conditions, and premature aging in relation to endothelial dysfunction (100). The disease reflects ongoing mitochondrial stress and inflammaging processes, even in younger patients. Epidemiological studies have shown that the incidence of cognitive impairment, including dementia and Alzheimer's disease, is higher in subjects with certain inflammatory skin disorders, including psoriasis and chronic eczematous dermatitis (101). Because of the pathogenic role of epidermal dysfunction in ageing-associated cutaneous inflammation, improvements in epidermal function could be an alternative approach for mitigation of the ageing-associated decline in cognitive function.

iii) Vitiligo and Systemic Complications.

Vitiligo, traditionally viewed as a localized skin depigmentation disorder, is now recognized as being associated with sensorineural hearing loss (102), cardiovascular disease (103) and metabolic syndrome (104)—all conditions with a foundation in oxidative stress and systemic immune imbalance.

iv) Chronic spontaneous urticaria (CSU) and autoimmunity.

CSU is increasingly recognized to co-occur with various autoimmune conditions. Among these, autoimmune thyroid diseases, particularly Hashimoto's thyroiditis and hypothyroidism, have been prominently associated with CSU even in the absence of overt thyroid disease symptoms (105). This comorbidity underscores the importance of screening CSU patients for thyroid function and autoantibody levels, particularly in cases of treatment resistance or persistent urticaria.

v) Oxidative Stress and Metabolic Syndrome as Shared Pathogenic Mechanisms in Acne Vulgaris.

Recent evidence highlights a significant link between acne vulgaris and metabolic syndrome (106), a cluster of conditions including obesity, insulin resistance, hypertension, and dyslipidemia. This association suggests shared pathophysiological mechanisms primarily involving oxidative stress and systemic inflammation qui c'era 106 errore (106) (45).

4. Health programming implications

Given the pathogenic role of epidermal dysfunction in aging-associated cutaneous inflammation, improving epidermal function may represent a complementary strategy for mitigating the progression of aging-related non-communicable diseases (101). However, skin health should not be addressed in isolation. Given the wealth of data linking cutaneous changes to systemic pathology, dermatological symptoms should be viewed as windows into internal health rather than isolated cosmetic concerns. In this context, good care of the skin should be implemented alongside strategies aimed at managing oxidative stress. Physicians should adopt a 'redox-aware' perspective, whereby visible skin alterations prompt a comprehensive evaluation of oxidative load, metabolic function, and inflammatory status.
Evidence from a study in obese children indicates that vitamin D, folic acid, curcumin, resveratrol, zinc, selenium and magnesium supplementation improve endothelial dysfunction. Based on these findings, it is plausible that these antioxidants may also contribute to improved skin conditions and reduced cardiometabolic risk (107). Furthermore, incorporating redox and inflammatory screening into dermatologic evaluations may offer powerful opportunities for early intervention, preventive care, and health optimization strategies.
The different skin-related conditions and their associated systemic risk events are summarized in Table I.

Table I. *Skin diseases and their associated systemic consequences.*

Skin Disease / Condition	Associated Systemic Consequences	Mechanisms / Notes
Skin Aging (Wrinkles)	Cardiovascular mortality	Forehead wrinkles linked to 6x increased risk of death; reflect vascular and metabolic aging via collagen degradation and OxS.
Hair Graying & Baldness	Cardiometabolic risk (hypertension, coronary artery disease)	ROS-induced melanocyte apoptosis; androgenetic alopecia linked to CVD risk.
Atopic Dermatitis (AD)	Cardiovascular disease, mental illness (including dementia) and autoimmune disorders	Driven by mitochondrial oxidative dysfunction, endothelial activation, and platelet hyperactivity.
Psoriasis	Metabolic syndrome, autoimmune diseases, premature vascular aging, cognitive impairment	Systemic immune activation, oxidative DNA damage, vascular stiffening, inflammaging, and mitochondrial stress.
Vitiligo	Sensorineural hearing loss, cardiovascular disease, metabolic syndrome	Associated with oxidative stress and systemic immune imbalance.
Chronic Spontaneous Urticaria (CSU)	Autoimmune thyroid disorders (especially Hashimoto's thyroiditis and hypothyroidism)	High co-occurrence even without overt thyroid symptoms; immune dysregulation mechanism.
Acne Vulgaris	Metabolic syndrome (obesity, insulin resistance, hypertension, dyslipidemia)	Shared mechanisms involve chronic inflammation and oxidative stress.

Multicomponent antioxidant strategies: beyond single-molecule interventions

The limitations of monotherapy

Large clinical trials using high-dose vitamin C or E—the so-called "non-selective antioxidant therapies"—have failed to show significant benefit in major diseases such as cardiovascular disease or chronic inflammatory conditions (108, 109). This failure reflects a critical issue: OxS is not a single-pathway disturbance, and therefore, its mitigation cannot rely on a single antioxidant compound.

Monotherapies often lack pleiotropic effects, meaning they fail to address multiple mechanisms of action simultaneously. High-dose single antioxidants can even become pro-oxidant under certain metabolic conditions. Trials such as EPIC-Norfolk highlight that dietary source of antioxidants from fruits and vegetables are more beneficial than isolated supplement forms (110). The advantages of multi-component supplementation are exemplified by what occurs naturally with a diet rich in fruits and vegetables. Just as in nature there is never an isolated substance - when we eat an apple, we don't just consume quercetin, but a harmonious ensemble of nutrients that enhance each other - this principle should guide antioxidant supplementation with multiple molecules with different and synergic effects as shown in Table II (111). Micronutrient deficiencies do not occur in isolation (112) and an approach optimizing multiple micronutrients may have significant short- and even long-term benefits (113).

Table II. *Biological effects of different nutritional components.*

Effect/Substances	Folic acid	Vitamin C	Vitamin D	Vitamin E	Magnesium	Selenium	Zinc	Phytochemicals
Antiviral activity			✓		✓	✓	✓	✓
Immune modulation	✓	✓	✓	✓	✓	✓	✓	✓
Anti-inflammatory	✓	✓	✓	✓	✓	✓	✓	✓
Auto immunity prevention		?	✓	?	?	✓	✓	✓
Antioxidant effect	✓	✓	✓	✓	✓	✓	✓	✓
Anti-thrombotic effect	✓		✓	✓	✓	✓		✓
Endothelial protective	✓	✓	✓	✓	✓	✓	✓	✓
Cytoprotective & organ damage prevention	✓		✓	✓	✓	✓		✓
Antiarrhythmic effect			✓		✓	?		✓
Antidepression effect	✓		✓		?	?	✓	✓
Microbiome	✓		✓	✓		?	?	✓

Based on the comparative analysis of micronutrient functions, Vitamin D and phytochemicals (particularly polyphenols) emerge as the only compounds demonstrating activity across all evaluated domains. Notably, a combined supplementation strategy involving also vitamin E, selenium, magnesium, and zinc appears to cover nearly all functional targets when considered together.

The case for multimodal antioxidant therapy

Oxidative stress is intimately linked to a network of biological processes, including inflammation, autoimmunity, endothelial dysfunction, platelet activation, and mitochondrial damage. Therefore, a successful antioxidant approach should address all these dimensions simultaneously. This concept is supported by data from both experimental and clinical studies, which demonstrate that combinations of micronutrients and phytochemicals are significantly more effective than individual agents (114-123).

The following compounds demonstrate antioxidant, anti-inflammatory, immune-regulatory, and vascular-protective effects, as detailed in Table III.

Table III. *Micronutrients with Documented Multilevel Effects.*

Molecule	Documented Actions
Curcumin	Antioxidant, anti-inflammatory, anti-IL-1β/IL-6, endothelial protection
Resveratrol	ROS scavenger, mitochondrial support, platelet aggregation inhibitor
Zinc	Supports immune function, antioxidant enzyme cofactor (e.g., SOD), antiviral
Magnesium	Modulates oxidative metabolism, smooth muscle tone, endothelial function
Selenium	Integral for GPx activity, immune support, redox homeostasis
Vitamin D	Immune regulation, inflammation control, telomere stabilization
Folic Acid	Methylation supports endothelial health, reduces homocysteine
Vitamin E	Lipid membrane antioxidant, suppresses MDA generation
Quercetin	Flavonoid with anti-inflammatory and mast cell stabilizing effects
Melatonin	Antioxidant, anti-tumor, circadian regulator
Eucalyptus Oil	Topical antioxidant, antimicrobial, insect repellent

Each of these compounds addresses different facets of oxidative damage and immune dysfunction.

Clinical and experimental evidence supporting combination therapy

Studies in elderly populations demonstrate that multivitamin and multimineral supplementation improves immune responses, reduces infection risk, and lowers systemic inflammation (124-126). The OBELIX study provided compelling evidence that a formulation including curcumin, resveratrol, zinc, selenium, magnesium, vitamin D, and folic acid significantly improved endothelial function in obese pediatric patients over six months (107). Supplementation was associated with improved hyperemic response and endothelial function.

Broader health implications

Multicomponent antioxidant strategies are not only beneficial for dermatological health (127) but are also increasingly recognized for their roles in preventing autoimmune progression, modulating platelet activity, slowing telomere attrition, and supporting healthy aging processes (128).

Effective antioxidants must not only neutralize ROS but also block inflammatory cytokine cascades (e.g., IL-6, TNF-α, IL-17A), protect endothelial and mitochondrial integrity, and modulate immune tolerance to prevent overactivation (129, 130). This comprehensive approach addresses the multifaceted nature of oxidative stress and its systemic consequences.

High-dose supplementation with single antioxidants such as vitamin E or β-carotene has been associated with paradoxical pro-oxidant effects, sometimes increasing oxidative stress and all-cause mortality rather than reducing it. This phenomenon, described by Miller et al. (131) and Halliwell (132), arises because reactive oxygen species (ROS) are not solely deleterious; they play essential roles in redox signaling, immune defense, and metabolic adaptation. Excessive quenching of ROS can therefore disrupt physiological signaling and redox balance.

Several antioxidants can switch from antioxidant to pro-oxidant activity under specific conditions—for instance, vitamin E in the absence of recycling cofactors or vitamin C in the presence of transition metals—thus propagating rather than preventing lipid oxidation. Furthermore, biological compartmentalization of oxidative processes limits the efficacy of single compounds. Oxidative reactions occur heterogeneously within cells, as different organelles and microenvironments produce and neutralize ROS distinctly. Each antioxidant has a preferred site of action depending on its solubility, molecular size, charge, and redox potential—for example, polyphenols act in the cytosol while vitamin E protects lipid membranes. By supporting glutathione peroxidase, superoxide dismutase, and other redox enzymes, selenium, zinc, and magnesium help maintain mitochondrial integrity, limit ROS accumulation, and sustain efficient oxidative phosphorylation (133).

Conversely, multi-antioxidant supplementation that includes vitamin D, folic acid, polyphenols, selenium, and trace elements provides broader protection through complementary mechanisms. Folic acid supports redox equilibrium by reducing homocysteine accumulation and enhancing glutathione regeneration, while vitamin

D modulates Nrf2-dependent antioxidant enzymes and suppresses NF-κB–mediated inflammation. This integrated approach promotes a balanced oxidative–inflammatory response and minimizes the risk of pro-oxidant conversion observed with isolated antioxidants at high doses (134).

Conclusions

The evidence reviewed underscores oxidative stress as a central pathogenic mechanism in a broad spectrum of skin disorders, including chronic spontaneous urticaria, atopic dermatitis, melanoma, and impaired wound healing. Beyond its dermatological manifestations, the skin's role as a sentinel organ positions it as a valuable indicator of systemic redox and inflammatory imbalance, offering an accessible window for early intervention.

Addressing oxidative stress in skin diseases requires more than symptomatic relief—it calls for a comprehensive strategy to restore redox homeostasis. Approaches involving antioxidant therapy, nutraceuticals, and mitochondrial support not only improve clinical symptoms but may also alter disease trajectories. Single-molecule interventions are inadequate in the face of complex redox dysregulation; instead, a layered, multi-targeted approach—integrating antioxidants, anti-inflammatories, mitochondrial protectors, and immunomodulators—is essential to achieve sustained clinical benefit. This paradigm aligns with the multifaceted biology of oxidative stress and its shared contribution to dermatological, metabolic, cardiovascular, and neurodegenerative conditions.

Notably, recent longitudinal multi-omics studies reveal that biological aging follows a nonlinear path, with inflection points around 44 and 60 years marking critical shifts in mitochondrial, immune, and metabolic function (135). These critical transitions correspond to shifts in major biological processes, with the first crest (~44 years) associated with perturbations in cardiovascular function, lipid and alcohol metabolism, and mitochondrial homeostasis, and the second (~60 years) linked to dysregulation in immune responses and carbohydrate metabolism. These findings advocate flexible, age-adapted interventions that reinforce mitochondrial resilience and immune-metabolic stability.

Moreover, with evidence suggesting that nearly half of dementia cases could be prevented through optimal vascular health maintenance in later life, redox management emerges as a powerful, system-wide tool (136). It holds promise not only for skin health but also for delaying or preventing cognitive decline and mitigating the burden of cardiovascular and metabolic diseases. As redox biology continues to evolve, personalized, integrative antioxidant strategies represent a frontier with wide-reaching clinical implications—supporting not just dermatological outcomes but also contributing to the broader pursuit of healthy aging and chronic disease prevention. In this context, skin diseases may serve as a "canary in the mine," offering early signals that guide the implementation of optimal, comprehensive antioxidant treatment strategies.

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