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Review Article

Hydrogen peroxide and antioxidant defence in vitiligo: mechanistic evidence, measurement challenges and therapeutic implications

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ABSTRACT

Vitiligo is an acquired depigmenting disorder involving the loss or dysfunction of epidermal melanocytes. Oxidative stress has been investigated as a contributor to melanocyte injury and as a link between cellular stress and immune activation. Hydrogen peroxide has received particular attention because altered peroxide handling may reflect an imbalance between oxidant generation and antioxidant defence. This narrative review examines evidence concerning hydrogen peroxide, catalase, superoxide dismutase, glutathione peroxidase, and lipid peroxidation in vitiligo. It also considers antioxidant-response signalling, autophagy, emerging ferroptosis research, and communication between stressed epidermal cells and the immune system. Early studies reported reduced epidermal catalase activity and increased hydrogen peroxide, whereas subsequent investigations produced conflicting findings. Antioxidant enzyme activities vary across tissue compartments and disease states, highlighting the limitations of a uniform enzyme-deficiency model. Experimental studies support peroxide-associated cellular injury, but they do not establish the initiating cause of clinical disease. Measurement differences, specimen handling, assay interference, and anatomical-site variation further complicate interpretation. Clinical trials of peroxide-removing and antioxidant interventions have yielded mixed results. Oxidative imbalance remains a plausible component of vitiligo pathogenesis, but standardized longitudinal studies and controlled clinical investigations are needed to establish causation, biomarker utility, and treatment relevance.

Keywords: Vitiligo, Hydrogen peroxide, Catalase, Antioxidant enzymes, Lipid peroxidation, Nrf2, Autophagy, Ferroptosis

INTRODUCTION

Vitiligo is characterized by depigmented lesions associated with loss or dysfunction of epidermal melanocytes. Its biological basis involves interacting cellular and immune processes. Oxidative stress has attracted sustained attention because changes in oxidant generation, antioxidant defence, and cellular stress responses could influence melanocyte susceptibility.

Early investigations reported reduced catalase (CAT) activity in involved and uninvolved epidermis and increased susceptibility of cultured vitiligo melanocytes to peroxidative injury.[1,2] Subsequent work described epidermal hydrogen peroxide (H_2O_2) accumulation and proposed that impaired peroxide clearance contributes to cellular dysfunction.[3] These observations provided a biochemical framework for investigating antioxidant enzymes and peroxide-removing interventions.

However, tissue studies have reported different patterns of superoxide dismutase (SOD) and glutathione peroxidase (GSH-Px) activity, and later Raman spectroscopy measurements did not consistently reproduce epidermal H_2O_2 elevation.[4–6] The important question is therefore not simply whether oxidative abnormalities occur, but what the measurements establish about their location, timing, and contribution to disease.

This review examines the evidence for altered peroxide handling in vitiligo, its relationship to lipid peroxidation and cellular stress responses and the limitations affecting translation into biomarkers and treatment. Also, this review emphasizes the distinction between measured oxidative abnormalities, evidence of causal cellular injury, and clinical treatment benefit, with particular attention to why findings differ across sampling and analytical approaches.

REVIEW APPROACH

This focused narrative review draws on selected PubMed-indexed human studies, experimental investigations, clinical trials and methodological publications. Targeted searches addressed vitiligo, hydrogen peroxide, catalase, superoxide dismutase, glutathione peroxidase, lipid peroxidation, nuclear factor erythroid 2-related factor 2, autophagy, ferroptosis, and antioxidant treatment. Publications were selected for their relevance to the proposed mechanism, conflicting observations, analytical interpretation, or clinical translation.

The synthesis was qualitative. No original patient measurements or laboratory results are presented. Relevant publications were identified through targeted PubMed searches conducted on January 2026 to July 2026, using combinations of “vitiligo,” “hydrogen peroxide,” “catalase,” “antioxidant enzymes,” “lipid peroxidation,” “Nrf2,” “autophagy,” and “ferroptosis.” No publication-year restriction was applied. Additional methodological and clinical studies were selected for their relevance to the review. This was a narrative review; no systematic screening / exhaustive screening, formal risk-of-bias assessment, or meta-analysis was performed.

HYDROGEN PEROXIDE AND ANTIOXIDANT ENZYME BALANCE

SOD converts superoxide into H_2O_2, while CAT and GSH-Px participate in peroxide removal. These activities form an interconnected system: a change in one enzyme cannot reliably describe overall redox balance.

Increased SOD activity may represent adaptation to superoxide exposure. If peroxide-removing capacity is insufficient, increased SOD activity can coexist with oxidative injury. Conversely, reduced CAT activity does not prove that H_2O_2 is elevated, because peroxide production, other clearance pathways, and enzyme localization also influence exposure.

Studies in vitiligo illustrate this complexity. Sravani and colleagues reported increased SOD activity in lesional and non-lesional skin compared with controls, alongside reduced CAT activity in the skin assessed for that enzyme.[4] Dammak and colleagues reported increased SOD, GSH-Px, and malondialdehyde (MDA) in active vitiligo tissue, with decreased CAT.[5] These findings do not support assuming that every antioxidant enzyme is uniformly deficient.

CATALASE DEFICIENCY: FINDINGS AND INTERPRETATION

Schallreuter and colleagues found lower CAT activity in suction-blister epidermis from involved and uninvolved vitiligo skin compared with phototype-matched controls.[1] Maresca and colleagues subsequently reported reduced CAT activity and increased susceptibility to cumene hydroperoxide in cultured melanocytes from apparently unaffected vitiligo skin.[2]

These observations support investigating altered peroxide defence beyond visibly depigmented lesions. They do not establish that CAT deficiency necessarily precedes melanocyte injury. Lower measured activity could reflect differences in expression, enzyme function, oxidative exposure, or the composition of the sampled material.

Genetic investigations provide another perspective. Mansuri and colleagues examined CAT variants, expression, enzyme activity, and lipid peroxidation, reporting findings linking CAT variation with altered biochemical responses in their study population.[6,7] This indicates that regulation of CAT may differ among individuals; it does not establish a universal genetic explanation for vitiligo.

CAT activity, protein abundance, and messenger RNA expression should therefore be distinguished. Evidence concerning one cannot automatically establish the others.

CONFLICTING EVIDENCE FOR EPIDERMAL HYDROGEN PEROXIDE

Earlier studies reported epidermal H_2O_2 accumulation using in vivo spectroscopy and experimental approaches.[3] These findings encouraged a model in which peroxide exposure contributes to melanocyte dysfunction.

However, Zailaie’s Raman spectroscopy study did not identify a consistent elevation of epidermal H_2O_2 across its non-segmental vitiligo groups.[6] Differences in treatment exposure and skin phototype were relevant to the study’s comparisons. This finding challenges a universal peroxide-accumulation model without excluding other oxidative abnormalities.

Possible explanations for disagreement include differences in disease activity, anatomical site, specimen preparation, and analytical technique. These are plausible contributors

rather than established explanations. Measurements normalized to extracted protein also cannot be directly equated with concentrations inferred from intact-skin spectroscopy.

The defensible interpretation is that H_2O_2 accumulation has been reported in particular settings and requires confirmation in each defined population and measurement system.

LIPID PEROXIDATION AND MELANOCYTE INJURY

Lipid peroxidation is a possible downstream consequence of an altered oxidative environment. Increased MDA-related measurements have been reported in vitiligo tissue, particularly in active disease.[5] Nevertheless, a tissue-level measurement cannot establish which cell type sustained the injury or identify the responsible oxidant.

Analytical specificity is also important. The thiobarbituric acid reactive substances (TBARS) assay detects a broader reaction than MDA alone. Unless the analyte is specifically separated or identified, results should be described as TBARS or MDA equivalents.[8] Sample handling and storage can affect interpretation.

A correlation between H_2O_2 and TBARS would support an association between the measured variables. It would not demonstrate that H_2O_2 directly caused lipid peroxidation in melanocytes.

NRF2 SIGNALING AND CELLULAR STRESS TOLERANCE

Individual enzyme measurements capture only part of cellular antioxidant defence. Nuclear factor erythroid 2-related factor 2 (Nrf2) regulates adaptive responses through antioxidant response elements (AREs).

Jian and colleagues reported impaired Nrf2 activation in vitiligo melanocytes exposed to H_2O_2, including reduced nuclear translocation and transcriptional activity. Decreased heme oxygenase-1 expression accompanied increased susceptibility to oxidative injury.[9] These findings support a model involving impaired adaptation to stress rather than an isolated CAT abnormality.

Experimental restoration of signaling can help establish a pathway's role within a cell model. However, it does not demonstrate that targeting the pathway will produce safe, sustained repigmentation in patients.

AUTOPHAGY AND OXIDATIVE SUSCEPTIBILITY

Autophagy provides another mechanism through which cells respond to stress. He and colleagues found that normal melanocytes increased autophagic responses following H_2O_2 exposure, whereas vitiligo melanocytes showed dysregulated autophagy and greater susceptibility to injury. Manipulation of the Nrf2–p62 pathway reduced injury in their experimental system.[10]

These observations suggest that removal or processing of damaged cellular components may influence oxidative tolerance. They also demonstrate why autophagy findings must be interpreted dynamically: accumulation of autophagic structures alone cannot establish effective completion of the process.

FERROPTOSIS: AN EMERGING MECHANISM

Ferroptosis is a candidate mechanism connecting iron-dependent lipid peroxidation with cell death. Recent melanocyte research has examined this pathway under peroxide exposure.

Li and colleagues reported that tanshinone IIA reduced H_2O_2-associated ferroptosis-related changes and activated Nrf2 signaling in cultured melanocytes. An Nrf2 inhibitor reversed the reported protective effect.[11] These findings support further mechanistic investigation; they do not establish clinical efficacy or prove that ferroptosis is the predominant mode of melanocyte death in vitiligo.

Higher MDA, reactive oxygen species, or iron measurements alone cannot establish ferroptosis. Interpretation requires convergent evidence of lipid-peroxidation-dependent death and suitable intervention controls. Total GSH-Px activity should also not be treated as a specific measurement of glutathione peroxidase.[4]

OXIDATIVE STRESS AND IMMUNE ACTIVATION

Oxidative injury and immune mechanisms may reinforce one another. Li and colleagues demonstrated that stressed keratinocytes increased C-X-C motif chemokine ligand 16 (CXCL16) expression through unfolded-protein-response pathways. CXCL16 promoted migration of CXCR6-positive CD8-positive T cells from patients with vitiligo.[12]

Cui and colleagues examined high-mobility group box 1 (HMGB1) release from oxidatively stressed melanocytes and its effects on neighboring cells, identifying a potential route connecting cellular injury with inflammatory signaling.[13]

More recently, Kang and colleagues linked transient receptor potential melastatin 2 (TRPM2)-dependent calcium signaling, impaired keratinocyte autophagy, and increased CXCL16 secretion under oxidative stress.[14]

Together, these experiments support investigating oxidative stress within an epidermal–immune network. They do not establish that reduced CAT initiates every subsequent immune event.

MEASUREMENT CHALLENGES

The biological compartment represented by each sampling approach differs (Table 1).

Assay interference is another concern. Votyakova and Reynolds demonstrated that NADH and reduced-glutathione auto-oxidation can affect the Amplex Red assay.[15] Recovery controls, suitable blanks, validated dilution ranges, and standardized handling are therefore important.

Enzyme activity assays require compatible extraction conditions. Chemicals used to preserve one analyte may interfere with another assay. Protein normalization improves comparability but does not remove extraction bias or differences in cell composition.

Table 1: Interpretation of sampling approaches in vitiligo oxidative-stress research.

Specimen or approach	Main information obtained	Important limitation
Isolated epidermis	Measurements from epidermal cells collectively	Not melanocyte-specific
Whole-skin biopsy	Combined epidermal and dermal measurements	Tissue composition influences values
Tape strips	Superficial stratum-corneum measurements	Do not directly represent the melanocyte compartment
Blood	Systemic oxidative measurements	Cannot substitute for local skin measurements
Cultured cells	Responses to controlled exposures	Limited representation of clinical disease
Intact-skin spectroscopy	Spectral assessment without tissue extraction	Requires method-specific validation and calibration

Therapeutic evidence

Mechanistic plausibility and clinical benefit are separate questions. Catalase present during experimental H_2O_2 exposure may attenuate injury by reducing exposure. Demonstrating reversal requires treatment after injury develops, while functional recovery requires outcomes beyond cellular morphology.

Clinical peroxide-removing studies have produced mixed results. Bakis-Petsoglou and colleagues found no significant incremental benefit from pseudocatalase cream added to narrowband ultraviolet B compared with placebo plus the same phototherapy.[16] A pilot trial of a pseudocatalase/SOD preparation also reported no significant therapeutic effect under its study conditions.[17]

In contrast, Dell'Anna and colleagues reported improved outcomes with an oral antioxidant combination used alongside narrowband ultraviolet B.[18] Because the intervention contained multiple components and was combined with phototherapy, its findings cannot be attributed specifically to CAT restoration or generalized to every antioxidant preparation.

These differences support evaluating each formulation and treatment setting separately.

Research priorities

Future studies should determine whether oxidative changes precede disease activity or follow established injury. Repeated measurements from carefully defined sites could help address this sequence.

Mechanistic studies should combine peroxide measurements, enzyme activity and expression, specific lipid peroxidation assessment, and functional cellular outcomes. Clinical investigations should record anatomical site, phototype, treatment exposure, and disease activity consistently.

Candidate biomarkers need evidence of reproducibility, association with clinically meaningful outcomes, and added value beyond existing assessments. A biochemical response to treatment should not automatically be interpreted as disease control or repigmentation.

Limitations

This narrative review examines selected publications rather than an exhaustive evidence set. Formal risk-of-bias assessment and quantitative pooling were not performed. Some studies were assessed through indexed abstracts and bibliographic records, limiting evaluation of detailed laboratory procedures. Heterogeneity in specimens, assays, and clinical populations further restricts comparison.

CONCLUSION

Oxidative imbalance is a plausible component of vitiligo biology, supported by observations involving CAT activity, peroxide susceptibility, lipid peroxidation, and altered cellular stress responses. However, epidermal H_2O_2 elevation is not consistently demonstrated, and antioxidant

enzyme patterns vary across specimens and disease states. Nrf2 signaling, autophagy, and oxidative–immune communication provides a broader framework than a single enzyme-deficiency model. Ferroptosis is an emerging area requiring further validation.

Clinical antioxidant and pseudocatalase studies have yielded mixed findings. Standardized sampling, validated assays, longitudinal observations, and controlled trials are needed to determine whether oxidative measurements can guide clinical decisions and whether modifying these pathways produces sustained patient benefit.

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