REVIEW ARTICLE

Oxidative Stress and Potential Antioxidant Therapies in Vitiligo: A Narrative Review

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Abstract

Vitiligo is a chronic skin disorder characterised by the loss of melanocytes and subsequent skin depigmentation. Although many theories have been proposed in the literature, none alone explains the pathogenesis of vitiligo. Oxidative stress has been identified as a potential factor in the pathogenesis of vitiligo. A growing body of evidence suggests that antioxidant therapies may offer a promising approach to managing this condition. This review summarises the potential mechanisms of oxidative stress and the types of melanocyte death in vitiligo. We also provide a brief overview of the most commonly studied antioxidants. Melanocytes in vitiligo are thought to be damaged by an accumulation of reactive oxygen species to destroy the structural and functional integrity of their DNA, lipids, and proteins. Various causes, including exogenous and endogenous stress factors, an imbalance between prooxidants and antioxidants, disruption of antioxidant pathways, and gene polymorphisms, lead to the overproduction of reactive oxygen species. Although necroptosis, pyroptosis, ferroptosis, and oxeiptosis are newer types of cell death that may contribute to the pathophysiology of vitiligo, apoptosis remains the most studied cell death mechanism in vitiligo. According to studies, vitamin E helps to treat lipid peroxidation of the skin caused by psoralen ultra-violet A treatment. In addition, *Polypodium leucotomos* increased the efficacy of psoralen ultra-violet A or narrow-band ultraviolet B therapy. Our review provides valuable insights into the potential role of oxidative stress in pathogenesis and antioxidant-based supporting therapies in treating vitiligo, offering a promising avenue for further research and the development of effective treatment strategies.

1 Introduction

Vitiligo is an acquired chronic depigmentation disorder of the skin affecting about 0.5–2% of the population worldwide. It is characterised by demarcated white patches resulting from the selective loss of epidermal melanocytes [1]. Although vitiligo can appear at any age, it most frequently affects young people aged between 10 and 30 years [2]. Treatment options for vitiligo vary and range from topical and oral drugs and phototherapy to cellular and tissue grafts [3]. Understanding etiopathogenesis is crucial for finding new treatment modalities. Various hypotheses have been developed to explain the pathogenesis of vitiligo. These include genetic, oxidative stress, autoimmune, autoinflammatory, neural, apoptotic, molecular adhesion disorder and multifactorial mechanisms [1]. None of the hypotheses proposed so far explains the pathogenesis of vitiligo entirely. Numerous studies in recent years have shown that oxidative stress hypersensitivity plays a significant role in determining melanocyte degeneration, leading to the development of the disease [4]. Oxidative stress and defects in metabolic pathways can promote dysregulation of immune responses in vitiligo [5]. Redox disequilibrium can cause melanocyte death by activating cytotoxic T cells and other death modalities such as apoptosis, necroptosis, and necrosis or oxeiptosis [6]. Because of their properties of neutralising reactive oxygen species, supplementation with antioxidants could be a potential treatment support option [7]. Unfortunately, there is limited evidence of antioxidant efficacy [8]. Therefore, in this review, we provide an overview of the mechanisms of vitiligo-associated oxidative stress and the most commonly studied antioxidants, describe the proposed mechanisms of action, and discuss the underlying evidence for their use or ineffectiveness.

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2 Oxidative Stress

Oxidative and nitrosative stress are thought to play an important role in the development of vitiligo [9]. Oxidative stress refers to the excessive production of highly active molecules such as reactive oxygen species (ROS) in the body [2]. Melanocytes are thought to be damaged by an accumulation of ROS by destroying the structural and functional integrity of their DNA, lipids and proteins [10]. Exogenous and endogenous stimuli both play a role in excessive ROS production. Considering the external stressor, environmental triggers, including ultraviolet radiation, cytotoxic chemicals, trauma, pregnancy, stress, and immunisation, can contribute to the overproduction of ROS [11, 12]. However, when endogenous stimuli are considered, excessive ROS may also stem from melanogenesis. Melanin production is accompanied by active production of ROS and melanin itself absorbs ultraviolet light, which causes oxidative stress. The conversion of DOPA to dopaquinone and dopaquinone to dopachrome results in the formation of ROS during the melanin synthesis process. Hence, melanocytes are one of the different types of cutaneous cells that contain massive amounts of ROS [13]. It is worth noting that the energy-intensive aspect of melanogenesis suggests a high demand for adenosine triphosphate. In mitochondria, ROS are self-produced in the biosynthesis of adenosine triphosphate, another example of endogenous stimuli of excessive ROS production. Because of their control over oxidative stress-related ageing and apoptosis, mitochondria are considered a dominant source of ROS [14]. In a normal physiological state, the small amount of ROS

produced by the body is converted into non-toxic substances by the antioxidant system so that it does no harm. However, when ROS production increases in pathological conditions, it creates an imbalance between prooxidants and antioxidants in the skin and the blood [3]. Patients with vitiligo have been found to have not only significantly increased average levels of hydrogen peroxide (H_2O_2) in their skin lesions, but also significantly lower measured activities of catalase, superoxide dismutase, glutathione peroxidase and glutathione S-transferase than in the control group, as well as significantly increased levels of malondialdehyde [9, 15, 16]. Compared with the segmental vitiligo group, these changes in prooxidants and antioxidants were particularly pronounced in non-segmental vitiligo. However, no significant correlation with the duration of vitiligo was found [15].

Oxidative stress can lead to vitiligo through various mechanism (Fig. 1). First, it disrupts the process of melanin synthesis by inducing the release of high mobility group box 1 (HMGB1) protein, thus downregulating the melanin biosynthesis-related proteins: melanocyte-inducing transcription factor, tyrosinase, tyrosinase-related protein-1, tyrosinase-related protein-2, RAB27A and fascin actin-bundling protein 1 [17, 18]. Furthermore, the excessive accumulation of ROS not only disrupts the process of melanin synthesis, but also destabilises, synthesises and disrupts the circulation of lipids in melanocytes, resulting in damage to the mitochondrial electron transport chain and increased ROS production, creating a vicious cycle and destroying melanocytes [19]. Oxidative stress is a critical factor in inducing the release of chemokines from keratinocytes that direct CD8+ T cells and lead to migration into skin tissue, causing melanocyte death [20]. In addition, cytokines produced by skin-invading T cells can further amplify the immune response [21]. Remarkably high levels of proinflammatory interleukins are found in perilesional vitiligo skin and in the peripheral bloodstream [22]. The most prominent interleukins (ILs) are IL-15, C-X-C motif ligand 16 (CXCL16), CXCL9, IL -17 and IL-1b [19, 20, 22–24]. Most of those interleukins potentiate the activation and expression of cytotoxic proteins in CD8+ T cells [22]. As for interleukin, IL-17 and IL-1b act by inhibiting cell-specific melanosomal proteins and activating T helper-17 cells, which increase cell damage by causing mitochondrial dysfunction [19]. Inhibition of the chemotactic axis could be a promising therapeutic option [20, 22].

Nuclear factor E2-related factor 2 (Nrf2), activated by ROS, protects against oxidative stress and chemically induced cell damage. The Kelch-like ECH-associated protein 1 (KEAP1) regulates Nrf2 activity. The KEAP1-Nrf2 complex breaks down when the cell is exposed to oxidative stress, and the released Nrf2 is then transported into the nucleus and binds to antioxidant response elements [25, 26]. Jian et al. found that induction of haem oxygenase-1 through

activation of the Nrf2-ARE pathway protected melanocytes from H_2O-induced toxicity and that upregulation of Nrf2 expression reduced H_2O_2-induced apoptosis of human melanocytes [27]. It suggests that the KEAP1/Nrf2/ARE pathway may be one of the most important signalling pathways in protecting cells from oxidative stress. Furthermore, abnormalities in the Nrf2-p62 pathway also impair autophagy in vitiligo melanocytes under oxidative stress [28, 29]. The role of Nrf2 gene polymorphisms in the susceptibility of patients to vitiligo and in altering the clinical presentation of the disease is also suspected [30].

Sirtuins (SIRTs) are a protein family with versatile functions, such as metabolic control, epigenetic modification and lifespan extension [31]. It has been observed that the expression and deacetylase activity of SIRT3 are attenuated in vitiligo melanocytes. Oxidative stress impairs SIRT3 activity and transcription by regulating protein carbonylation and transcriptional function of peroxisome proliferator-activated receptor-γ coactivator-1α, leading to mitochondrial dysfunction and activation of the mitochondrial apoptotic pathway via optic atrophy 1 to induce cell death of vitiligo melanocytes [32].

A genetic predisposition to oxidative stress and immune-mediated destruction of melanocytes may influence the development of vitiligo. Several human leukocyte antigen (HLA) alleles associated with an increased risk of vitiligo can be distinguished between different nations and ethnic groups [33]. Human leukocyte antigen alleles encode histocompatibility glycoproteins that enable the initiation of a specific immune response through the presentation of antigens to T cells and have been identified as risk factors for other skin diseases such as psoriasis [34]. Hayran et al. showed that serum total antioxidant capacity is significantly lower in patients without the HLA-DRB1*01 allele. The HLA-DRB1*01 allele was more common in the control group and in patients with vitiligo with high serum total antioxidant capacity levels, suggesting a protective role of this allele in vitiligo [33].

3 Forms of Melanocyte Death Associated with Oxidative Stress

Cell death may occur in multiple forms in response to different stressors, particularly oxidative stress [35], which is also firmly implicated in several pathways leading to vitiligo melanocyte loss. Apoptosis is the mechanism of cell death that has been most studied in vitiligo. However, other types of cell death, such as typical necrosis and autophagy, also appear to be implicated in the death of melanocytes in patients with vitiligo. The pathogenesis of vitiligo may also be influenced by the emerging processes of regulated cell death known as ferroptosis, necroptosis and pyroptosis [25]. Cells can die through regulated cell death or accidental cell death [35]. Spontaneous attacks and damage beyond possible control mechanisms can trigger accidental cell death, such as necrosis. Regulated cell death apoptosis, in contrast, has different biochemical, functional and immunological effects and is carried out by a group of identified effector molecules (apoptosis, necroptosis, pyroptosis, oxeiptosis, ferroptosis, parthanatos) [36]. Several diseases, including cancer, neurodegenerative diseases, autoimmune diseases, infectious diseases and vitiligo, are caused by a loss of control over single or combined modes of cell death. In recent years, understanding of the aetiology of the disease has improved with a number of studies investigating the molecular mechanism behind the loss of melanocytes in vitiligo [37].

**Fig. 1** Impact of oxidative stress on the development of vitiligo
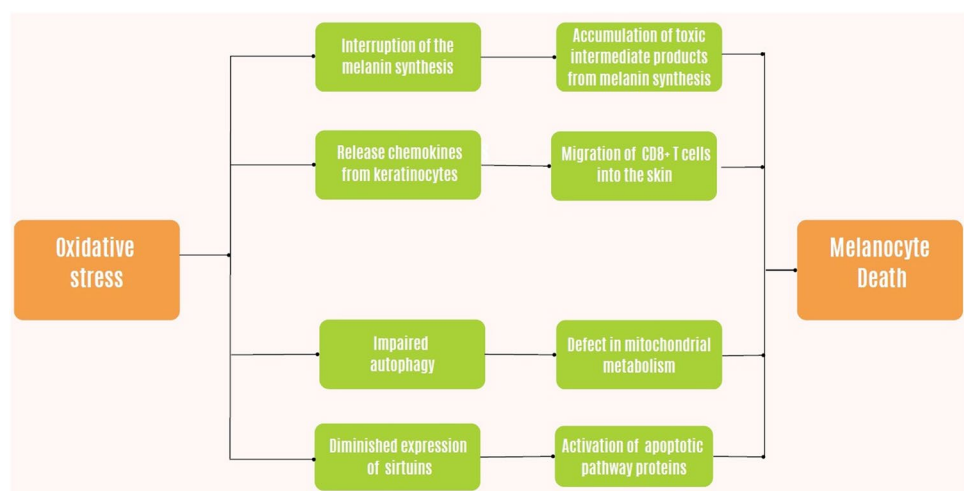
3.1 Apoptosis

Apoptosis is the primary mechanism by which ROS destroys melanocytes in vitiligo [38]. Apoptosis occurs in all multi-cellular organisms and is the best studied form of programmed cell death. Several molecular mechanisms are involved in the induction of apoptosis in melanocytes in vitiligo. Nevertheless, we can mainly divide them into the extrinsic and intrinsic apoptosis signalling pathways regulated by activated caspases and molecular systems such as Bcl-2/Bax and Fas/Fas ligand [39, 40]. The mitochondrial signalling pathway of intrinsic apoptosis is particularly relevant to the pathogenesis of vitiligo (Fig. 2) [41]. Among the members of the caspase family, caspase-3 is a crucial modulator of apoptosis in mammalian cells [42]. The Bcl-2 family, in contrast, includes Bcl-2, which can protect cells from various apoptotic triggers, and Bax, an apoptosis agonist that acts through heterodimerisation with Bcl-2 [43]. It has been shown that perilesional melanocytes have a lower ratio of Bcl-2/Bax than control melanocytes, suggesting that melanocytes from patients with vitiligo are more susceptible to apoptosis activation due to altered Bcl-2 and Bax expression and that the balance between pro-apoptotic and anti-apoptotic proteins in vitiligo melanocytes is shifted towards apoptosis [44].

In this pathway, oxidative stress can trigger the release of cytochrome c from mitochondria into the cytosol. Cytochrome c binds to apoptotic protease activation factor-1, a cytosolic protein that forms an oligomeric apoptosome complex with procaspase-9. The apoptosome complex activates caspase-9, which cleaves and activates downstream effector caspases such as caspase-3 and caspase-7. The activated effector caspases then cleave various cellular substrates, leading to apoptosis.

The endoplasmic reticulum (ER) is essential for the synthesis, folding and transport of proteins. Any disruption of the normal function of the ER, especially oxidative stress, can lead to ER stress, which is characterised by an accumulation of misfolded or unfolded proteins in the ER lumen. Endoplasmic reticulum stress triggers a cellular response known as the unfolded protein response (UPR), which aims to restore ER homeostasis. However, suppose the stress is prolonged or severe. In this case, the UPR can activate apoptotic signalling pathways that lead to cell death [45, 46]. Homocysteine has been shown to cause vitiligo-related death of melanocytes by triggering ER stress and UPR activation in a ROS-dependent manner [47]. Moreover, the ROS-induced increase in the activity of CXCL16, a chemokine essential for the migration of cytotoxic T cells in vitiligo, is also caused by UPR activation [23]. In addition to intrinsic apoptosis, oxidative stress may also contribute to extrinsic apoptosis in vitiligo. The extrinsic pathway is triggered by the binding of a death ligand such as tumour
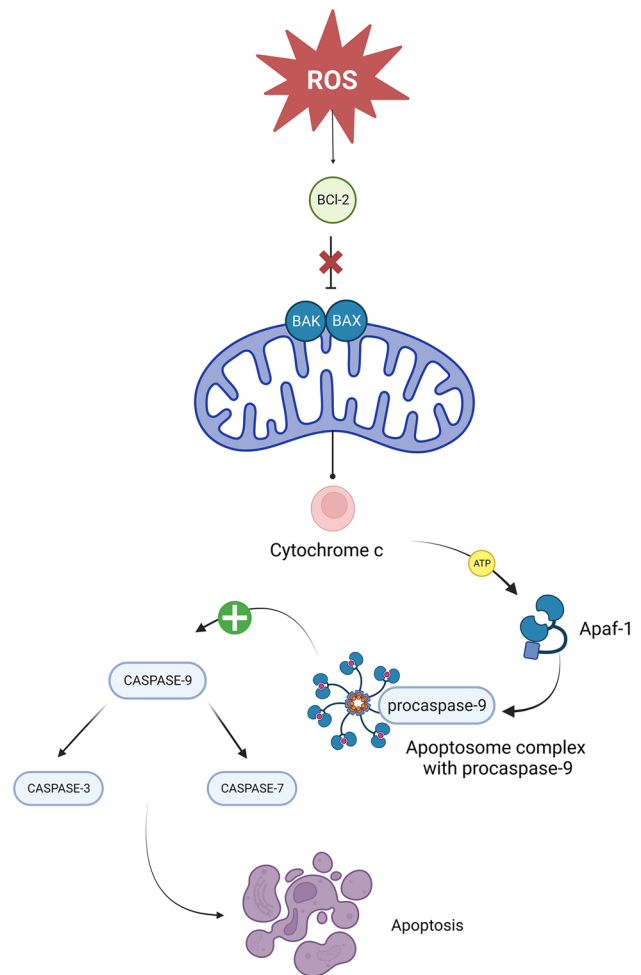
Fig. 2 Schematic mitochondrial control of apoptosis. *ROS* reactive oxygen species

necrosis factor (TNF) or Fas ligand to the corresponding death receptors such as TNF receptor 1 and Fas receptor, respectively [48]. Furthermore, cytokines such as TNF-α and interferon-gamma have been shown to induce extrinsic apoptosis in melanocytes in addition to ROS. These cytokines are produced by activated T cells that invade the skin in vitiligo [49, 50]. It was shown that keratinocytes can influence melanocyte function and survival through several mechanisms and are involved in a vitiligo potential pathomechanism. In some cases, keratinocytes can promote melanocyte loss. Keratinocytes release cytokines to attract autoreactive T cells. They interfere with signal transduction in melanocytes, leading to the death of these cells and acting as a mediator of the damaging effects of oxidative stress [22]. Caspase-3-mediated death of melanocytes can also be triggered by ROS-induced secretion of adenosine triphosphate from keratinocytes, which can also induce nearby keratinocytes to produce CXCL9 to chemically attract CD8+ T cells [24]. One of these microRNAs (miRNAs), miR-25, has been

shown to have important functions in keratinocytes. MiR-25 is overexpressed in both keratinocytes and melanocytes in response to oxidative stress, which decreases the activity of antioxidant enzymes and impairs melanosome transport, leading to redox imbalance [51]. Furthermore, oxidative stress activates the release of HMGB1 signal transduction in keratinocytes by decreasing the level of melanogenetic molecules (including gp100) and inducing apoptosis. In addition to inducing apoptosis, the transfer of HMGB1 from the melanocyte nucleus to the cytosol under oxidative stress can also suppress Nrf2 expression [52, 53].

3.2 Pyroptosis

In contrast to apoptosis, pyroptosis is an inflammatory form of programmed cell death that often occurs during infection with intracellular pathogens [54]. Activation of gasdermin D and the caspase-1/4/5/11 series distinguishes pyroptosis from other forms of death. However, the main regulator of pyroptosis is caspase 1, which is activated by the inflammasome, a large supramolecular complex. The activated caspases then cleave gasdermin, form pores in the cell membrane, and lead to cell lysis and secretion of IL-1β [55, 56]. An essential element of the NLRP1 inflammasome that activates IL-1 is the protein pyrin domain-containing protein 1 [57, 58]. It has been suggested that the inflammasome and IL-1β are involved in melanocyte loss, as staining for these markers was highly positive in the perilesional skin of patients with active vitiligo [59]. Pyroptosis was discovered to be involved in cell death via granzyme A, which cleaves gasdermin B. These findings support the hypothesis that pyroptosis may be involved in melanocyte death associated with ROS in vitiligo [12, 60].

3.3 Necroptosis

Necroptosis is a programmed cell death response to a specific environmental signal, morphologically resembling necrosis. It differs from the processes of apoptosis and autophagy in its particular mechanism of action and physiological significance [61]. Receptor-interacting proteins (RIPK) 1 and RIPK3 are crucial components of this pathway. The mixed lineage kinase-like domain, identified as a critical mediator in necroptosis, is then activated by RIPK3 [62]. Numerous stimulants, including activation of death receptors (such as Fas), Toll-like receptors (e.g. TLR3 and TLR4) and adhesion receptors, can lead to necroptosis [63]. Studies have shown that ROS is involved in necroptosis, particularly mitochondrial ROS, which promotes the autophosphorylation of RIP1 necessary for the inscription of RIP3 into necrosomes, and also ROS, which is dependent on RIP3, promotes necroptosis [64]. Necroptosis has been shown to be strongly associated with vitiligo, as melanocytes

from perilesional skin affected by vitiligo were significant for necroptosis markers, such as phosphorylated RIP3 and a phosphorylated mixed-lineage kinase-like domain. Some studies found that mitochondrial ROS production mediated by RIP1 contributes to the development of a necrosome in melanocytes. The RIP1 pathway was also shown to contribute specifically to the promotion of oxidative stress-induced necroptosis, which leads to melanocyte death. This means that melanocytes exposed to oxidative stress may undergo necroptosis when the RIP1 pathway is activated [37, 65].

3.4 Ferroptosis

Ferroptosis is a form of regulated cell death characterised by the accumulation of iron and lipid peroxides in cells [66]. It is driven by iron-dependent phospholipid peroxidation and regulated by several cellular metabolic events, including redox homeostasis, iron handling, mitochondrial activity, and metabolism of amino acids, lipids and sugars [67]. Although ferroptosis has been extensively studied in many diseases [68–70]. It is still unclear whether ferroptosis contributes to melanocytes loss in vitiligo. Oxidative stress is one of the main factors that trigger ferroptosis, as shown by the significantly increased levels of LIP-ROS and ROS [71]. Melanocytes in the skin have more accessible iron than keratinocytes. The level of Fe^{2+} in melanocytes increases in response to external oxidative stimulation. This significantly increases the sensitivity of melanocytes to ferroptosis [72]. Ferroptosis triggers can be divided into those that act through the cystine/glutamate antiporter system, such as erastin, and those that act by inhibiting the activity of glutathione peroxidase, such as Ras Selective Lethal 3 [73, 74]. Some studies have shown that glutathione peroxidase is decreased in the serum and skin of patients with vitiligo, although the role of glutathione peroxidase 4 in vitiligo has not been fully elucidated [75]. Yang et al. found that Ras Selective Lethal 3 can induce ferroptosis in primary melanocytes, as reflected by suppressed cell growth, mitochondrial dysfunction, increased ROS production and iron ion accumulation [76]. According to studies by Wu et al., the level of ferroptosis markers, especially erastin, changed dramatically in the epidermis of patients with vitiligo. In in vitro conditions, erastin increased iron overload, oxidative stress and lipid peroxide production in human epidermal melanocytes [77]. This provides new evidence that ferroptosis may occur during the vitiligo process.

3.5 Oxeiptosis

In 2018, Holze et al. discovered that high concentrations of ozone (O_3) or H_2O can trigger an apoptosis-like death

process called oxeiptosis [78]. Oxeiptosis is a caspase-independent cell death that is triggered by oxidative stress and acts in the elimination of pathogens. Oxeiptosis is mediated by KEAP1, phosphoglycerate mutase family member 5, and apoptosis-inducing factor mitochondrion-associated 1 under oxidative stress [6]. The reduction of KEAP1 and phosphoglycerate mutase family member 5 demonstrated that the KEAP1-phosphoglycerate mutase family member 5-apoptosis-inducing factor mitochondrion-associated 1 signalling pathway is responsible for the death of melanocytes initiated by oxidative stress [6]. In the perilesional skin of patients with vitiligo, Chen et al. demonstrated oxeiptosis in melanocytes exposed to ROS [12]. However, it is still unclear how melanocyte apoptosis is involved in the aetiology of vitiligo [37]. Mitochondria may play a crucial role in controlling oxeiptosis, as they are an important source of ROS and a component of the oxeiptosis locus. However, this relationship needs further investigation [79].

4 Potential Therapeutic Approaches to Reduce Oxidative Stress

An antioxidant is a compound that considerably lessens or stops the harmful effects of free radicals on human tissue. Antioxidants can be categorised based on their structure, solubility and the kinetics of the processes in which they are involved [80]. The skin is endowed with natural antioxidants because it is exposed to numerous environmental factors. Vitamin E, catalase, superoxide dismutases and glutathione peroxidases are present in the viable layer of the epidermis. Glutathione, vitamin C, uric acid, alpha-tocopherol, squalene and coenzyme Q10 are present in the stratum corneum of human skin [81]. Antioxidant-based supporting treatment has been proposed as a therapy to prevent photo-ageing of the skin [82, 83], skin cancers [84] and autoimmune diseases of the skin [85]. To date, numerous drugs containing antioxidant-like substances have been investigated to either support or replace standard treatments for vitiligo (Table 1). Insufficient knowledge of antioxidants has been reported as a significant predictor of a lower frequency of antioxidant use by dermatologists in China [7].

4.1 Vitamin C

Vitamin C eliminates oxidative stress by oxidising ascorbate to monodehydroascorbate and dehydroascorbate. It is also a cofactor for the enzymatic activity of prolyl hydroxylase in collagen synthesis. Vitamin C and its derivatives inhibit tyrosinase activity and melanin content in a dose-dependent manner [86]. In a study with 30 patients with vitiligo,

significantly lower vitamin C levels were found in patients with vitiligo [87]. In Madagascar, a combination of a cream containing clobetasol propionate 0.05%, oral vitamins C and B_{12} and microtrauma suppression proved to be an effective therapy. Response to treatment was better in young people, in lesions younger than 1 year, and when vitiligo was localised to the face and neck [88].

4.2 Vitamin E

Vitamin E is a photoprotective antioxidant that absorbs certain wavelengths and protects against lipid peroxidation [89]. A meta-analysis by Liu et al. showed low plasma and tissue vitamin E levels in patients with vitiligo [90]. Studies suggest that the combination of vitamin E with psoralen and ultraviolet A (PUVA) phototherapy may prevent oxidative disorders resulting from PUVA therapy, but did not improve clinical improvement of vitiligo lesions [91]. However, the combination of narrow-band ultraviolet B (NB-UVB) with oral supplementation of vitamin E may increase the efficacy of therapy [92–94].

4.3 Selenium

Selenium is considered as an important trace element in the modulation of oxidative stress [95]. The main role of selenium is attributed to its presence in glutathione peroxidase, which protects cells from the damaging effects of free radicals. A meta-analysis by Iv et al. examined ten studies of changes in selenium levels in patients with vitiligo. Ultimately, it was found that patients with vitiligo had similar selenium levels to healthy controls. Another subgroup analysis showed that patients with vitiligo had lower selenium levels in skin and hair compared with controls, but no difference in serum levels [96]. Another study found that the total selenium levels of patients with vitiligo and healthy controls were similar. Subsequently, a subgroup analysis showed that selenium levels were lower in patients with vitiligo than in Asian controls, while there was no significant difference between Caucasians and healthy controls [95]. By comparison, other studies have shown an increase in serum selenium levels in patients with vitiligo compared with the control group [97].

4.4 Zinc

Zinc can protect melanocytes through its anti-apoptotic and antioxidant effects. It may also regulate melanin production by the release of the α-melanocyte stimulating hormone and the precipitation of zinc-α2-glycoprotein in

Table 1 An overview of research on the effectiveness of vitiligo therapies with antioxidants

Antioxidant component	Patients number	Interventions	Formulation and dose of antioxidant	Duration of treatment	Main significant finding in repigmentation	Author, year
ALA	39	Betamethasone injections 3 times at 1-month interval and NB-UVB twice or three times a week ± ALA	Oral 300 mg; once daily	6 months	In the treatment group, over 40% patients achieved more than 50% improvement by 3-month therapy. This percentage increased to 90% at 6 months. No difference was seen at 6 months between treatment and placebo groups	Li et al., 2016
ALA, vitamin C, vitamin E, polyunsaturated fatty acids and cysteine mono-hydrate	28	NB-UVB twice weekly ± antioxidants	Oral tablet containing α-lipoic acid (50 mg), vitamin C (50 mg), vitamin E (20 mg), polyunsaturated fatty acids (12%), and cysteine mono-hydrate (50 mg); twice daily	8 months	Antioxidants increased the effect of NB-UVB treatment, with 47% of the patients obtaining > 75% repigmentation vs 18% in the placebo group	Dell'Anna et al., 2007
C/DSO	23	0.05% Betametha-sone on one lesion + C/DSO on second similar lesion. Sun exposure was advised for a 15-minute period	Cream; twice daily	10 months	Percentage of skin repigmentation increased to 18.5 ± 93.14% with betamethasone and to 12.4 ± 59% with C/DSO, but no statistical difference was found	Sanclemente et al., 2008
	19	NB-UVB three times a week + gel containing C/DSO from the plant *Cucumis melo*	Gel; twice daily	6 months	More than 50% of overall repigmentation was noticed in 57.9% of patients. Of these, 15.79% of patients showed more than 75% (excellent) repigmentation. The best response was achieved in the lesions located on the face and neck	Kostović et al., 2007
Coenzyme Q10	24	Co-enzyme Q10 or placebo	Gel; 75 mg; twice daily	8 weeks	No significant difference in VASI between the co-enzyme Q10 group and the placebo group after 4 weeks while a significant decrease in VASI after 8 weeks was found	Hameed et al., 2013
GB	47	GB monotherapy or placebo.	Oral 40 mg; three times per day	6 months	75% or greater repigmentation was seen in 10 patients in the GB group	Parsad et al., 2003
	11	GB monotherapy	Oral 60 mg; twice daily	12 weeks	Total VASI score improved by 0.5 from 5 to 4.5. The mean percent improvement in the VASI score was 15%	Szczurko et al., 2011
GP-SOD	50	NB-UVB twice weekly ± GP-SOD	Oral; 1 g per day for 12 weeks and 0.5 per day for next 12 weeks	24 weeks	A greater improvement in VES was observed in the GP-SOD group (19.85%) compared with the placebo group. The difference in the repigmentation rate between GP-SOD and placebo groups was not statistically significant	Fontas et al., 2021

Table 1 (continued)

Antioxidant component	Patients number	Interventions	Formulation and dose of antioxidant	Duration of treatment	Main significant finding in repigmentation	Author, year
PL	44	NB-UVB twice weekly ± PL	Oral 480 mg, twice daily	6 months	PL combined with NB-UVB improved repigmentation as well as increased the response rate compared with patients treated with NB-UVB alone (47.8% vs 22%)	Pacifico et al., 2021
	19	PUVA ± PL	Oral 720 mg; once daily	12 weeks	The percentage of subjects with a skin repigmentation > 50% was significantly higher in the PUVA + PL group than in the PUVA + placebo arm	Reyes et al., 2006
	49	NB-UVB twice weekly ± PL	Oral 250 mg; three times daily	25–26 weeks	The PL group shows a trend towards more repigmentation compared with the placebo group in all four body area categories (head and neck, trunk, extremities, hands and feet). Most prominent in the head and neck area where differences were nearly statistically significant	Middelkamp-Hup et al., 2007
Pseudocatalase	33	UVB exposure twice a week + pseudo-catalase + calcium chloride	Cream; twice daily	Mean duration 15.3 months	Complete repigmentation on the face and dorsum of the hands appeared in 90% of the group. No improvement with lesions on fingers and feet	Schallreuter et al., 1995
	26	NB-UVB twice a week + pseudo-catalase	Mousse; twice daily	24 weeks	Patients did not improve during the study, although 10 of the 26 patients did show at least some improvement of either the hands or face	Patel et al., 2002
	32	NB-UVB three times weekly ± pseudocatalase cream	Cream; twice daily	24 weeks or earlier if complete repig-mentation occurred	No statistically significant improvement in the percent-age area affected in the pseudocatalase cream group when compared with pla-cebo. However, a statistically significant improvement was found within each group by week 12, which was main-tained throughout the study	Bakis-Petsoglou et al., 2009
	59	Climatotherapy at the Dead Sea ± pseudocatalase cream PC-KUS	Cream; twice daily	21 days	Placebo cream/Dead Sea climatotherapy and climato-therapy in monotherapy had significantly less follicular repigmentation in the face (no patients with > 50% follicular/confluent repig-mentation) compared with the patient group treated with pseudocatalase PC-KUS in combination with climato-therapy (76.92% patients with > 50% follicular/conflu-ent repigmentation on the face)	Schallreuter et al., 2002

Table 1 (continued)

Antioxidant component	Patients number	Interventions	Formulation and dose of antioxidant	Duration of treatment	Main significant finding in repigmentation	Author, year
	71	NB-UVB + topical pseudocatalase PC-KUS on the entire body	Cream; twice daily	12 months	More than 75% repigmentation was achieved in 66 of 71 patients on the face and neck, 48 of 61 on the trunk and 40 of 55 on the extremities; however, repigmentation on the hands and feet was disappointing	Schallreuter et al., 2008
PSD	23	Topical gel of PSD on one lesion + placebo on second similar shaped lesion	Gel; twice daily	6 months	Insignificant repigmentation of vitiligous lesions treated with PSD. There were no significant changes in the lesion area and perifollicular pigmentation in each group	Naini et al., 2012
	49	Tacrolimus 0.1% ointment ± PSD	Ointment; twice daily	9 months	The percentage of pigmentation in 9 months for the monotherapy group was 60 and 62.4% for the group with PSD. There was no significant difference according to repigmentation percentages between the two groups	Alshiyab et al., 2020
Superoxide dismutase, copper, zinc, vitamin B_{12} and calcium panthotenate	30	308 nm excimer light therapy twice a week ± topical application of antioxidants on target lesions	Gel; once daily	3 months	Repigmentation above 75% was obtained in 22% of lesions from the antioxidant-treated group and 0% of the monotherapy laser-treated group lesions. In the treatment of UV-sensitive lesions, the group receiving antioxidants showed statistically better efficacy than the monotherapy laser group	Soliman et al., 2016
Vitamin A, vitamin E, vitamin C and zinc	80	Antioxidants or placebo	Oral tablet containing vitamin A (25,000 IU), vitamin E (400 IU), vitamin C (1000 mg), and zinc (40 mg); once daily	2 months	The onset of repigmentation was noted significantly earlier among the antioxidant group as compared with the placebo group	Kumar et al., 2019
Vitamin C and vitamin B_{12}	308	Clobetasol propionate cream 0.05% + vitamin C and vitamin B_{12}	Oral vitamin C (500 mg) and oral vitamin B_{12} (100 mg); once daily	80 days	> 76% area depigmented was noted in 65.7% aged less than 14 years and in 31.5% of patients aged between 25 and 49 years, 3 months after the initiation of treatment. Repigmentation was significant for lesions in the cephalic area	Sendrasoa et al., 2019
Vitamin E	20	NB-UVB three times a week ± vitamin E	Oral 400 IU; once daily	6 months	72.7 % in the treatment group and 55.6 % of the control group patients achieved excellent repigmentation	Elgoweini et al., 2009
	30	PUVA three times weekly ± vitamin E	Oral 900 IU; once daily	6 months	No significant difference in the clinical improvement between the two group of patients	Akyol et al., 2002

Table 1 (continued)

Antioxidant component	Patients number	Interventions	Formulation and dose of antioxidant	Duration of treatment	Main significant finding in repigmentation	Author, year
Vitamin E and vitamin A	46	NB-UVB three times a week ± vitamins A + E	Oral retinol (5000 IU) and tocopherol (400 mg); once daily	4 months	The greatest improvement in skin lesion repigmentation was observed in patients treated with a combination therapy, with a reduction in VASI of 6.95 ± 4.69	Nowowiejska et al., 2023
Vitamin E, beta-carotene, vitamin C, selenium, copper, zinc and manganese	30	PUVA ± antoxidants	Oral tablet containing vitamin E (25 mg), beta-carotene (30% dispersion 10 mg), vitamin C (100 mg), selenium (75 mcg), copper (1 mg), zinc (27.5mg), manganese (1.5 mg); once daily	3 months	In both groups, some of the lesions showed a decrease in area. No statistically significant difference was found between the two groups	Jayanth et al., 2002
Vitamin E, PE and carotenoids	130	Comparable topical therapy and/or phototherapy ± antioxidants	Oral tablet containing PE (100 mg), vitamin E (4.7 mg) and carotenoids (10 mg); three times per day	6 months	Patients who received antioxidants had significant mild repigmentation in the head and neck region and on the trunk, a higher not significant repigmentation for each body site. The number of patients who presented with no repigmentation in the head/neck, trunk, upper, and lower limbs was significantly higher in the control group	Colucci et al., 2015
Zinc	35	Topical corticosteroid twice daily ± oral zinc sulfate	Oral 220 mg; twice daily in teenager and adults and 10 mg/kg of a capsule or syrup for children	4 months	The mean of responses in the corticosteroid group and the zinc sulfate-corticosteroid combination group were 21.43 and 24.7%, respectively, but there was no statistically significant difference between them	Yaghoobi et al., 2011

ALA alpha-lipoic acid, *C/DSO* catalase/dismutase superoxide, *GB* ginkgo biloba, *GP-SOD* gliadin-protected superoxide dismutase, *NB-UVB* narrow-band ultraviolet, *PE* Phyllanthus emblica, *PL* Polypodium leucotomos, *PSD* pseudocatalase/superoxide dismutase, *PUVA* psoralen ultraviolet A, *VASI* Vitiligo Area Scoring Index, *VES* Vitiligo Extent Score

tissues. Zinc is also one of the non-specific elements that contribute to the regulation of cell-mediated immunity and the control of gene expression [98]. A prospective study by Zaki et al. found a negative correlation between serum zinc levels and the severity and extent of vitiligo [99]. An analysis of three articles comparing serum zinc levels in patients with vitiligo and controls found that higher serum zinc levels may reduce the risk of vitiligo [97]. The average serum zinc level was significantly decreased in patients with vitiligo. In contrast, the levels of cytokines involved in the control of melanocyte proliferation and differentiation and the inhibition of melanogenesis, IL-17, IL-4 and IL-6, were significantly increased in the vitiligo group compared with the control group. Serum zinc levels correlated significantly negatively with IL-6, IL-4

and IL-17 [98]. A combination of oral zinc and a topical corticosteroid was also found to be more effective in repigmentation than the topical corticosteroid alone [100].

4.5 Copper

Copper (Cu) plays two main roles: it promotes melanogenesis and provides physiological protection against oxidative stress by participating in the destruction of free radicals through the formation of superoxide dismutase, which catalyses the dismutation of reactive oxygen species to oxygen (O_2) or H_2O_2. Together with zinc, they catalyse the rearrangement of dopachrome to 5,6-dihydroxyindole-2-carboxylic acid in the final phase of eumelanin formation in melanogenesis [101, 102]. In a study of a Chinese population,

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serum Cu levels were significantly lower in patients with vitiligo than in healthy controls [103]. In Iranian patients, mean serum Cu and zinc levels were also significantly lower in patients with lower segmental and non-segmental vitiligo than in the control group [104]. By comparison, in the study by Wacewicz et al., serum Cu levels did not differ significantly between patients with vitiligo and control subjects [102]. A case-control study of 100 patients with vitiligo from India showed increased Cu levels compared with healthy individuals [105].

4.6 Ginkgo Biloba

Ginkgo biloba (GB) is a traditional Chinese herb. Ginkgo biloba extract protects melanocytes from oxidative damage by inhibiting H_2O_2-induced apoptosis and suppresses the autoimmune response to melanocytes by reducing the release of heat shock protein 70 [106]. In another study, GB's protective effect on melanocytes was shown to be dependent on activation of the Nrf-ARE pathway and downstream antioxidant genes, including NQO-1, SOD2 and haem oxygenase-1 [107]. Ginkgo biloba also has anti-inflammatory properties, reducing cyclooxygenase activity and decreasing IL-8 and vascular endothelial growth factor release in response to TNF-α [108]. A double-blind, placebo-controlled, clinical trial in 47 patients with vitiligo showed that the administration of GB 40 mg three times daily could halt disease progression and cause repigmentation of most perifacial vitiligo lesions [108]. Another prospective non-randomised study showed that a GB 60-mg dose twice daily can reduce disease severity in patients with vitiligo [109]. Although there was no evidence of severe side effects in the above studies, GB may be associated with the risk of clotting disorders or interactions with other medications. Therefore, the risks of taking GB may outweigh the known benefits of this supplement [110].

4.7 Catalase

Catalase is a haem-containing enzyme that catalyses the decomposition of H_2O_2 into water and molecular oxygen. During the enzymatic process leading to the dissociation of H_2O_2, catalase is first oxidised to a hypervalent iron intermediate known as compound I and then reduced back to its resting state by a second H_2O_2 molecule. Catalases are classified into three types based on their structure and sequence: monofunctional catalase or conventional catalase, catalase peroxidase and pseudocatalase or manganese catalase [111]. High concentrations of H_2O_2 in the epidermis are toxic to melanocytes because they inhibit tyrosinase and deactivate catalase. Some studies have shown a reduction in the catalase level compared with normal healthy controls [112, 113] In other studies, the catalase activity of erythrocytes from

patients with vitiligo was not significantly different from that of healthy individuals [114, 115]. However, clinical trials showed that topical pseudocatalase/superoxide dismutase gel was ineffective in treating vitiligo [116, 117]. Similarly, a study combining pseudocatalase cream with NB-UVB did not appear to provide benefit for NB-UVB therapy [118]. The efficacy of pseudocatalase foam applied twice daily with NB-UVB twice weekly for 24 weeks has also not been proven [119], but in a study combining pseudocatalase cream twice daily with UVB irradiation and calcium chloride, complete repigmentation occurred on the face and dorsum of the hands in 90% of patients [120]. In the study with topical pseudocatalase cream (PC-KUS) with NB-UVB, repigmentation of more than 75% on the face and neck was achieved in 66 of 71 patients [121]. A faster onset of repigmentation was also achieved with a combination of pseudocatalase cream (PC-KUS), a Dead Sea bath and sun exposure over a treatment period of 21 days [122].

4.8 Superoxide Dismutase

Superoxide dismutase (SOD) is a metalloenzyme and performs the first step in the breakdown of the superoxide radical (O_2^-) to H_2O_2 and O_2. Some studies have shown significantly lower activity of SOD in patients with generalised and localised vitiligo [15, 87, 113]. Opposing studies show higher levels of SOD, such as Dell'Anna et al. [93] or the meta-analysis by Shi et al. [123] and a study by Sravani et al. [112], which found a significant increase in the levels of SOD in the skin of people with vitiligo. However, there was no significant difference between the SOD levels in lesioned and normal skin in patients with vitiligo.

4.9 Alpha-Lipoic Acid

In its reduced dihydrolipoate form, alpha-lipoic acid (ALA) reacts with ROS and reactive nitrogen species and protects cell membranes by interfering with the vitamin C and E pathways [124]. Alpha-lipoic acid is found in small amounts in foods such as spinach and broccoli and is also synthesised in the liver [125]. In clinical trials, ALA has been tested in combination with other antioxidants such as vitamins C and E and polyunsaturated fatty acids in conjunction with NB-UVB phototherapy. Treatment with mixed antioxidants, in addition to NB-UVB, significantly improved the efficacy of phototherapy, with 47% of participants achieving > 75% repigmentation, compared with 18% in the control group [93]. Combination therapy with oral ALA, betamethasone injection and NB-UVB has also been shown to be beneficial in non-segmental progressive vitiligo [126]. It is known that ALA can accelerate the initial repigmentation response. However, combination therapy of ALA alone with NB-UVB

has not shown any additional benefit in the treatment of non-segmental stable vitiligo [127].

4.10 Coenzyme Q10

Coenzyme Q10 (CoQ10) is a vitamin-like ubiquitous compound that is an electron transfer agent in the mitochondrial respiratory chain. It plays an important role in the metabolism of fatty acids, pyrimidines, and lysosomes and mediates the expression of several genes, including those involved in inflammation [128]. Although CoQ10 is widely recommended as a systemic antioxidant, topical application of creams containing CoQ10 may induce facial vitiligo in susceptible individuals. Coenzyme Q10-mediated reduction of ROS by activated PC-KUS leads to cessation of depigmentation and repigmentation [129]. In contrast, researchers in a randomised, single-blind, placebo-controlled trial in Iraq found a significant reduction in the Vitiligo Area Scoring Index after 8 weeks of topical gel application with CoQ10 [130].

4.11 Phyllanthus emblica

Phyllanthus emblica has a high antioxidant capacity owing to its high content of polyphenolic compounds and vitamin C. The fruit extract can be used as an antioxidant and can inhibit lipid peroxidation and scavenge free radicals such as superoxide anions, hydrogen radicals, hydrogen peroxide and nitric oxide radicals [131, 132]. One study investigated the effect of oral intake of fruit extracts in combination with vitamin E and carotenoids on repigmentation in patients with vitiligo after phototherapy [133]. A significantly higher repigmentation rate was observed when supplementing with a mixture of antioxidants. In combination with two or three servings of fresh *P. emblica* per day, the recommended daily amount of vitamin C can be achieved.

4.12 *Polypodium leucotomos*

Polypodium leucotomos (PL) is a fern species native to Central America. It was first studied in Honduras as a treatment for psoriasis [134]. *Polypodium leucotomos* primarily prevents lipid peroxidation and membrane damage in fibroblasts and keratinocytes. In addition, PLE inhibits the oxidation of glutathione and acts as a direct ROS absorber against superoxide anion, hydroxyl, oxygen and oxygen peroxide. It can stimulate IL-10 production and promote a shift in the cytokine profile from type 1 to type 2 T cells [135]. Middelkamp-Hup et al. compared the use of PL in combination with NB-UVB therapy in a double-blind, placebo-controlled, clinical trial [136]. The authors showed that patients taking the supplement had significantly more repigmentation in the head and neck area compared with the placebo. No significant differences were found in other body regions. In a study by Reyes et al. the researchers investigated the effect of adding PL to PUVA therapy. It was found that subjects receiving PUVA and PL had a higher proportion of patients with repigmentation of 50% or more [137]. A study by Pacifico et al. suggests that treatment with NB-UVB phototherapy in combination with PL increases the extent of repigmentation and thus shortens the repigmentation time in patients with diffuse vitiligo at lower cumulative doses [138].

5 Conclusions

Oxidative stress is an important factor in the destruction of melanocytes. Melanocytes are particularly susceptible to oxidative stress because they are involved in melanin formation, which produces ROS as a by-product. While apoptosis is widely recognised as the primary form of melanocyte death in vitiligo, other forms of cell death such as oxeiptosis and ferroptosis have also been considered, primarily because of their close association with oxidative stress. In-depth studies of the intricate relationships between oxidative stress and various forms of cell death in vitiligo are expected to provide crucial insights into the mechanisms underlying melanocyte loss. A comprehensive understanding of the mechanisms underlying the different types of cell death observed in vitiligo is a crucial first step in developing therapeutic strategies. Such studies may shed light on the underlying causes of melanocyte destruction and pave the way for interventions that prevent melanocyte degeneration and allow for long-lasting repigmentation, an important therapeutic target in vitiligo treatment. The use of antioxidants in the treatment of vitiligo may seem attractive because of their antioxidant-protective properties against oxidative stress. A literature review revealed that more research on such subjects is needed. In most cases, antioxidants taken as monotherapy fail to produce significant improvement in skin repigmentation. To achieve satisfactory results, they should be used in conjunction with standard pharmacology or phototherapy.

Declarations

Conflict of interest Aleksandra Białczyk, Adam Wełniak, Barbara Kamińska and Rafał Czajkowski have no conflicts of interest that are directly relevant to the content of this article.

Ethics approval This article does not contain any studies with human participants or animals.

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