Review

Antioxidant Agents for Treatment and Prevention of Patients with Atopic Dermatitis

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Antioxidant Agents for Treatment and Prevention of Patients with Atopic Dermatitis

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Abstract: Atopic dermatitis (AD) is a chronic inflammatory skin disease characterized by itching, impaired epidermal barrier function and unbalanced inflammatory response. The pathophysiology involves immune dysregulation, with a predominance of T-helper 2 cells. AD is triggered by many known and unknown factors, including oxidative stress. Reactive oxygen species (ROS) contribute to AD pathogenesis by causing cellular damage and inflammation. Moreover, increased oxidative stress in AD leads to hyperactivation of the MAP kinase pathway, extracellular signal-regulated kinase (ERK) and p38, with DNA damage and subsequent skin barrier dysfunction. This narrative review provides a comprehensive overview of the role of natural antioxidant compounds, highlighting their potential therapeutic value in AD management. They include vitamin D, vitamin E, pyridoxine (vitamin B6), Vitamin C, carotenoids and melatonin, in AD. Despite some studies have shown an association between vitamin D, vitamin E, vitamin C and carotenoids levels and AD course, conflicting results exist. Pyridoxine supplementation has shown mixed results, and melatonin has demonstrated antioxidant and anti-inflammatory properties in AD; in fact, melatonin treatment resulted in a decrease in symptoms in patients with AD, although no significant correlation with changes in sleep latency was reported. In addition, iron and zinc (Zn) supplementation can also improve AD symptoms. Further research is needed to elucidate the optimal use of these natural antioxidants in AD treatment.

Keywords: atopic dermatitis; antioxidant agents; oxidative stress; reactive oxygen species

1. Introduction

Atopic dermatitis (AD), also known as atopic eczema, is a chronic and recurrent inflammatory skin disease with a multifactorial etiology. It is characterized by itching and has a typical distribution of lesion based on age [1]. The prevalence of AD varies between populations, ranging from 10-20% in childhood to 2-8% in adulthood [2,3].

About one-fifth of AD cases are classified as mild to severe according to different clinical scales such as the Investigator Global Evaluation (IGA), Eczema Area and Severity Index (EASI), Three Item Severity score (TIS), and SCORing Atopic Dermatitis (SCORAD) scales [4].

AD commonly develops before the age of five, with a slightly higher incidence in females. Approximately 50% of individuals diagnosed with AD during childhood continues to experience persistent symptoms beyond infancy. Early onset of AD, within the first six months of life, is associated with more severe disease[1,5].

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AD is associated with various comorbidities, both allergic and nonallergic, indicating its systemic nature, particularly bacterial and fungal infections, neuropsychiatric conditions, autoimmune disorders, hematologic malignancies, and metabolic diseases[6–11].

The pathophysiology of AD is complex and involves a combination of genetic predisposition and impaired epidermal barrier function, along with unbalanced inflammatory response to environmental factors [1,12].

Genetic factors play a significant role in AD, with several genes encoding epidermal structural proteins and elements of the immune system being implicated. Barrier dysfunction in AD patients can be attributed to reduced expression of the filaggrin gene, ceramide deficiency and excessive manifestation of epidermal proteases [12–14].

The exact primary cause of skin inflammation in AD is not yet fully understood. However, skin scratching can trigger the immune system activation and the release of pro-inflammatory cytokines by keratinocytes [15].

Environmental factors, such as infections, pollutants, smoke and detergents, can disrupt the epidermal barrier and trigger an inflammatory response by generating reactive oxygen species (ROS) [16–19]. These species play a significant role in AD pathophysiology; however, the role of antioxidant agents in preventing or controlling oxidative stress in patients with AD is not fully understood [18,20].

This narrative review aims to describe of the role of oxidative stress in AD pathophysiology, and to provide a comprehensive overview of key natural antioxidant compounds in patients with AD.

2. Materials and Methods

A search was conducted on Pubmed using "atopic dermatitis, antioxidant agents, oxidative stress, reactive oxygen species and antioxidant agents, askeywords. Only English language studies were included in the narrative review. The purpose is to summarize the latest evidence produced regarding the efficacy of exogenous antioxidants in patients with AD.

3. Oxidative stress in atopic dermatitis

ROS, including singlet oxygen (-O2), superoxide anion (●O2-), hydroxyl radical (●HO) and hydrogen peroxide (H2O2), can cause cellular damage and have been implicated in various diseases such as psoriasis, cancer, ageing, atherosclerosis [18,21–23]. Elevated levels of total immunoglobulin E (IgE) and pro-inflammatory cytokines like interleukin (IL)-4, IL-13 and IL-17 can increase ROS production, which further contributes to pathophysiology of AD [18,24].

Increased oxidative stress in AD leads to the hyperactivation of the MAP kinase pathway, namely extracellular signal-regulated kinase (ERK) and p38, with DNA damage and subsequent skin barrier dysfunction (Figure 1) [18,25,26].

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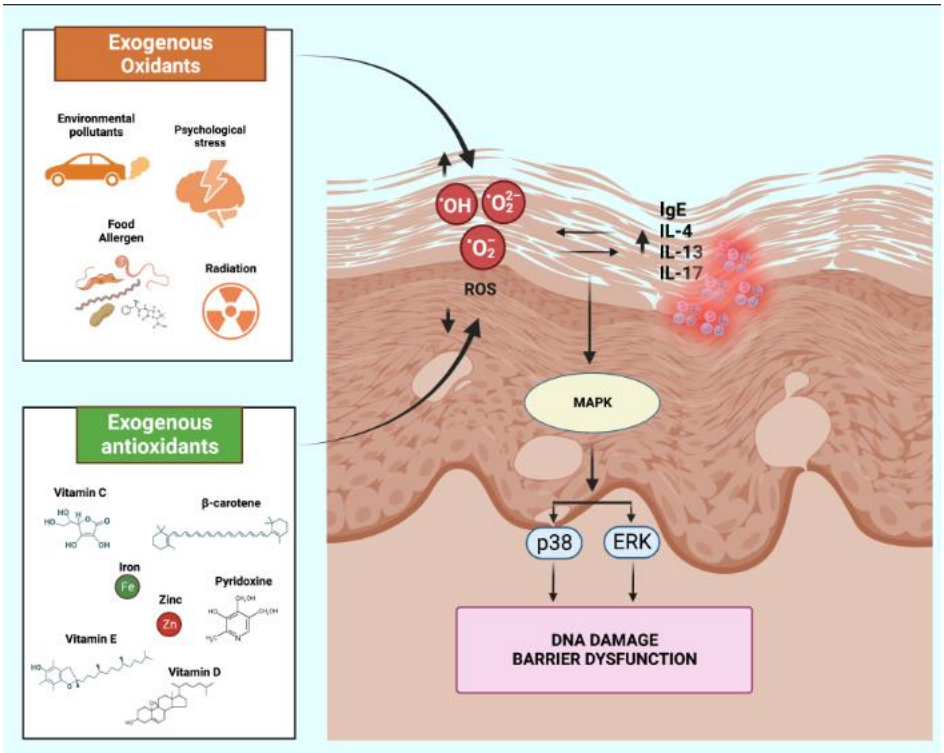

The AD inflammatory response involves both adaptive and non-adaptive immunity and occurs in two-steps [1,27]. In the acute phase, the allergens cross the immune barrier and stimulate a T-helper 2 response. Mast cells (MCs) are stimulated and degranulate, releasing histamine, IL-6, IL-8, prostaglandin D2 and tumor necrosis factor-alpha (TNF)-a together with interleukin-23 (IL-23) and IL-31 and other cytokines [27]. Additionally, keratinocytes and Langerhans cells (LCs), release cytokines such as IL-10, IL-12, IL-18, IL-23, IL-17 and IL-22 and thymic stromal lymphopoietin (TSLP), leading to an enhanced Th2-type inflammatory response [24,27,28].

The transition to the chronic inflammatory phase is triggered by the production of IL-12 and IL-18 by inflammatory epidermal dendritic cells (IDEC) or eosinophils, resulting in the activation of Th1 cells. Th1 cell-released interferon-gamma induces keratinocyte apoptosis, while IL-22 promotes skin changes and thickening in chronic AD. Chronic skin lesions in AD are associated with increased release of IL-5 and IL-12 and decreased levels of IL-4 and IL-13 [27].

Angiogenesis, the process of forming new blood vessels, contributes to the pathophysiology of AD similarly to other diseases such as psoriasis and melanoma [29–31]. Keratinocytes and mast cells have been shown to be an important source of vascular endothelial growth factor (VEGF) expression in AD; in fact, VEGF levels are elevated in the serum and skin of patients with AD compared with healthy controls [29,31].

The human body has an antioxidant defense system to counteract oxidative insults, including enzymes like superoxide dismutase (SOD), glutathione peroxidase (GPx), carnitine-acetyl transferase (CAT) and glutathione reductase (GR), as well as like vitamin C, vitamin E and glutathione (GSH).

Since the skin is continuously exposed to exogenous oxidative insults, a high antioxidant capacity is required [18]. The epidermis, particularly the stratum corneum, has a higher antioxidant capacity compared to the dermis, as it represents the body's main protective barrier [18].

In particular, the activities of SOD and CAT gradually decrease toward the skin surface. CAT activity has been shown to decrease when the skin is more exposed to sunlight. In contrast, SOD activity is not affected by chronic sun exposure [32,33]. This effect has been attributed to ultraviolet A (UVA) exposure, whereas ultraviolet B (UVB) does not seem to have this effect. However, the skin regained normal CAT activity within 4 weeks after exposure [32].

Oxidative stress and lipid peroxidation contribute to the progression of inflammation in AD, as well as psoriasis, resulting in decreased antioxidant enzyme activities and levels of non-enzymatic antioxidants [34,35].

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Recent studies have provided evidence of impaired functioning of high-density lipoprotein (HDL) in individuals with AD, which is accompanied by reduced levels and activity of the enzyme paraoxonase 1 (PON1) [36,37].

Moreover, an elevated ratio of serum myeloperoxidase (MPO) to PON1 levels has emerged as a potential marker indicating dysfunctional HDL in AD patients. Additional research has demonstrated alterations in HDL function in patients with AD, characterized by an increase in eosinophil effector responses induced by agonists when compared with the HDL level of control patients [38–42].

While the precise role of ROS in the pathophysiology of AD has yet to be fully elucidated, numerous studies have shown that treatment with antioxidant compounds can yield improvements in AD patients, by maintaining ROS levels within appropriate physiological limits.

4. Vitamin D

Vitamin D is a fat-soluble vitamin which plays a crucial role in calcium-phosphorus metabolism, bone disorders, immune system regulation and inflammation [43]. Indeed, vitamin D has been shown to upregulate the expression of various antioxidants, such as SOD, thioredoxin reductase (TrxRs), and glucose-6-phosphate dehydrogenase (G6PD). This gene overexpression mediated by vitamin D has been observed in prostate cells, where it has demonstrated a protective effect against cell death induced by H2O2 [26].

In the skin, vitamin D regulates the production of antimicrobial peptides such as cathelicidin and human beta-defensin (HBD) by skin keratinocytes and monocytes but its antioxidant activity in skin cells needs to be fully elucidated. These peptides help prevent skin infections and participate in the synthesis of filaggrin, an important component of the skin barrier. [43,44].

Vitamin D suppresses the maturation of dendritic cells and the proliferation of Th1 lymphocytes by reducing the secretion of Th1 cytokines. It also plays a role in modulating the secretion of Th17 cytokines and IL-2 by regulatory T cells (Treg) [43].

The body's requirement for vitamin D can be met through sun exposure and dietary sources such as fish, egg yolk, and dairy products.

In vitro studies and clinical trials have demonstrated the role of vitamin D in AD, although the findings are not jet entirely conclusive [45].

An inverse relationship between 25-OH-D3 levels and AD onset and severity emerged. In fact, a randomized controlled trial (RCT) including 60 patients showed a reduction in SCORAD and TIS in the group treated with 1600 IU of vitamin D for 60 days, compared to the control group [46]. (Table 1).

In another trial, 65 patients were randomized to receive standard therapy (topical corticosteroids, emollients) with 5000 IU/day of vitamin D or placebo, for three months. The achievement of serum levels of 25-OH vitamin D of 20 ng/ml or more, in combination with standard therapy, was demonstrated to be sufficient to reduce SCORAD in patients with AD [47].

A study by Peroni et al. investigated the correlation between reduced serum vitamin D levels and the severity of AD in 37 pediatric patients, aged between 8 months and 12 years. Levels of 25-OH vitamin D, determined by the chemiluminescence method, were significantly higher in patients with mild disease compared those with moderate or severe disease [48]

Lastly, in an RCT where patients with AD and healthy subjects received 4000 IU of oral vitamin D3 daily for 3 weeks, a significant increase in cathelicidin levels was observed in AD patients [49].

However, other studies have shown conflicting results. A randomized study by Javanbakht et al showed no significant association between serum 25-OH vitamin D3 levels and SCORAD [50].

The association between 25-OH vitamin D3 supplementation and increased levels of cathelicidin and HBD has also been questioned. In a double-blind study, 30 AD patients, 30 non-atopic subjects and 16 patients with psoriasis were randomized to receive cholecalciferol 4000 IU or placebo for 21 days. The study measured levels of 25-OH vitamin D, cathelicidin, HBD, IL13 and the Eczema Area and Severity Index (EASI) were measured. After 21 days, serum levels of 25-OH vitamin D had increased, but there were no significant changes in skin levels of cathelicidin, HBD, IL-13 or the EASI

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score. Low levels of 25-OH vitamin D correlated with increased Fitzpatrick skin type and body mass index (BMI), but not with AD severity [51].

Another study involving 97 pediatric patients aged between 1 and 18 years showed no significant correlation between plasma 25-OH vitamin D concentration and SCORAD (p=.99) [52]. However, these studies are limitated by the inability to control for sun exposure, dietary vitamin D intake, basic therapy for AD, and the lack of longitudinal follow-up.

It is also important to analyze basaline levels of 25-OH-vitamin D3 in the different patients being studied because differences in vitamin D levels at baseline may confound the results of the trials. In fact, only the studies by Amestejani et al. and Hata et al. measured vitamin D levels at baseline [44,52].

5. Vitamin E

Vitamin E is an essential nutrient with antioxidant properties and includes both tocopherol (TP) and tocotrienol (T3), which differ in their aliphatic tails [53]. It serves as crucial antioxidant barrier in human skin and is implicated in suppressing inflammation and promoting keratinocyte differentiation, suggesting a potential therapeutic role in atopic dermatitis (AD). Vitamin E-rich foods include oils, margarines, oily fruits, and cereal germs [54].

Preclinical studies provided insights into the role of Vitamin E in AD: it seems to reduce transepidermal water loss (TEWL), which is associated with AD pathogenesis, and to induce the expression of the transgluaminase-1 gene, involved in terminal differentiation of keratinocytes and in the formation of the stratum corneum [55–57].

In mouse models, alpha-TP injected at a dose of 200 mg/kg demonstrated a reduction in AD development due to its antioxidant and anti-inflammatory properties. Similar results were observed in studies conducted with alpha-TP supplementation in dogs with AD [58,59].

Case-control studies highlighted an inverse association between vitamin E and AD. In a paediatric study of involving 180 children with AD and 242 healthy controls, vitamin E levels were found to be inversely associated with AD prevalence. Similar findings were reported in studies conducted with Japanese students and Korean children, where higher dietary intake of vitamin E or higher serum alpha-TP levels were associated with improved AD symptoms and lower serum total IgE levels [20,60–62].

Supplementation with vitamin E and/or vitamin D has also shown to improve the clinical manifestations of AD, as indicated by reduced SCORAD scores in a study by Javanbakht et al [63]. However, it is worth noting that a study by Nwaru et al. in 2013 did not find a significant correlation between serum vitamin E levels and AD at 1 year [64].

6. Vitamin C

Vitamin C, also known as ascorbic acid, is an essential micronutrient with pleiotropic functions. It acts as a potent antioxidant and serves as a cofactor for a family of regulatory enzymes. Since humans cannot synthesize vitamin C, it must be obtained exclusively through the diet, primarily from fruits and vegetables [65].

In the context of AD, the abnormal immune response leads to elevated levels of cytokines such as IL-2, resulting in increased production of ROS and lipid peroxidation [66]. As an antioxidant, vitamin C plays a crucial role in protecting against this harmful mechanism by accepting protons (H+). Moreover, vitamin C promotes keratinocyte differentiation and enhances the production of interstitial material, in order to maintain the normal function of the skin barrier [65]. The antioxidant role of vitamin C may explain the observed low plasma levels of vitamin C in adults with AD. Additionally, vitamin C levels in the dermis of patients with AD are significantly lower compared to those of healthy individuals [66].

In a study involving 17 patients with AD, 82.4% of them had plasma vitamin C levels below 25 μmol/L, while only 3 patients had levels within the normal range (25-80 μmol/L). Notably, two patients with severe AD exhibited particularly low vitamin C levels of 8.24 and 12.30 μmol/L. These findings suggest a correlation between the progressive worsening of moderate-severe AD and

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vitamin C decreased levels. However, despite its adjuvant therapeutic role in many inflammatory skin diseases, vitamin C may also potentially induce symmetric AD [65,67,68].

To better evaluate this correlation and explore the potential therapeutic role of vitamin C, further data and large-scale analyses of vitamin C levels in skin biopsies from patients with moderate and severe AD are needed [68].

7. Pyridoxine

Pyridoxine, also known as vitamin B6, is an essential water-soluble vitamin involved as cofactor in different metabolic pathways [69]. These pathways include catalyze transamination, decarboxylation and protein synthesis, as well as amino acid metabolism, carbohydrate metabolism, nucleic acid transcription, glucocorticoid receptor regulation and neurotransmitter synthesis [70,71].

Food sources rich in pyridoxine include white meat, fish, spinach, potatoes, and legumes. In a double-blind study involving 20 patients with AD the administration of 1.5 mg/kg per day of pyridoxine hydrochloride resulted in improvement of disease in 6 out of 10 patients, while only one patient in the placebo group experienced improvement [72].

However, a similar study with 48 patients, where 19 received 50 mg/day of pyridoxine hydrochloride and 22 received placebo, did not show significant differences between the two groups [70].

8. Melatonin

Melatonin is an indolamine hormone primarily produced by the pineal gland, although it can also be synthesized by other tissues such as the thymus, respiratory epithelium and bone marrow [73].

It is a potent endogenous antioxidant and exhibits strong anti-inflammatory properties, as demonstrated by both in vivo and in vitro studies [74–76].

Melatonin stimulates key antioxidant enzymes like SOD, GPx and GR, protecting cells from lipid peroxidation and neutralizing harmful radicals. In addition to its antioxidative and anti-inflammatory effects, melatonin plays a crucial role in various physiological processes, including the regulation of circadian rhythm.

Melatonin receptors, specifically MT1 and MT2 receptors, are expressed in the skin[77].

In AD, melatonin is hypothesized to preserve skin integrity and maintain a functional skin barrier through its antioxidant properties, which include reducing lipid peroxidation and exerting anti-apoptotic effects [78,79].

Patients with AD often exhibit reduced production of interferon (IFN)-gamma, leading to decreased melatonin production. This, in turn, results in sleep deprivation and additional stress for patients with AD [80,81].

Preclinical data also suggest that melatonin, as well as its precursor 1-tryptophan, can reduce IgE and IL-4 levels, preventing the development of AD [82]. Moreover, melatonin appears to hinder the activation, degranulation, and infiltration of mast cells, which are involved in skin damage [74].

Munoz-Hoyos et al. showed that during AD onset phase, patients had reduced circulating levels of melatonin and beta-endorphin, despite higher nocturnal levels of both hormones. They hypothesized that the physiological peak of melatonin produced at night may compensate for the decreased melatonin production by extra-pineal tissues during the daytime, which occurs during AD onset episodes [83].

A preclinical study in mice demonstrated that melatonin treatment can improve edema and skin dryness, leading to an overall enhancement in clinical scores [84]

Additionally, a randomized trial including 73 children aged between 1 and 18, with at least 5% skin involvement by AD, compared melatonin (3 mg/day) with placebo, both administered for a 4-week period, with a 2-week washout period. Following melatonin treatment, the SCORAD index decreased by 9.1 points compared to placebo (from 49.1 to 40.2). Moreover, the latency period for sleep was reduced by 21.4 minutes after melatonin treatment compared to placebo. However, it

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should be noted that the improvement in SCORAD did not exhibit a significant correlation with changes in sleep latency[85] .

In contrast, a study on 30 patients with AD aged 6 to 12 years and 30 healthy individuals evaluated serum levels of melatonin, SOD, and GPx and showed that melatonin levels were higher in AD group compared to the control group. However, it should be noted that the levels of GPx and SOD were also higher in AD cases, although the observed difference was not statistically significant [86].

9. Carotenoids

Carotenoids are powerful antioxidant compounds involved in ROS scavenging and in protection of skin barrier integrity.

The total carotenoid content serves as a reliable indicator of the overall antioxidant status of the body. The skin predominantly contains α-, γ-, β-carotene lutein, zeaxanthin, lycopene, and their isomers as the main forms of carotenoids [87,88].

Unlike vitamins A, C, and E, the human body cannot synthesize carotenoids on its own. Therefore, dietary intake is essential to fulfill the body's carotenoid requirements. After digestion and a complex metabolic process, carotenoids are absorbed and exert their beneficial effects. Excess carotenoids can be stored in fatty tissue, the liver, and other organs [89,90].

Fruits and vegetables are the primary dietary sources of carotenoids, responsible for the red, orange, and yellow colors found in nature [91,92]. They can also be found in certain animals such as fish and crustaceans, although to a lesser extent [91].

Carotenoids are also utilized in dermatological and cosmetic products. as active ingredients for skin application [90].

The biological functions of carotenoids are closely related to their chemical structure. Most carotenoid molecules have a characteristic skeleton of 40 hydrocarbons with a system of conjugated double bonds. This structure is crucial for light absorption in photosynthetic organisms and photoprotection ROS generated by sunlight [91,93].

In vitro and in vivo tests have revealed the effects of carotenoids on patients with AD.

[94]. It has been conducted a study on HR-1 hairless mice with AD symptoms induced by a low zinc (Zn)/ magnesium (Mg) diet (HR-AD diet) and it has been investigated the effects of orally administered β-carotene. The results showed that β-carotene improved skin symptoms by reducing inflammation and enhancing skin barrier function. It also suppressed the expression of inflammatory factors and matrix metalloproteinases (MMPs) while increasing the expression of filaggrin protein.

Another study on oxazolone-induced AD in hairless mice supported these findings and suggested that β-carotene alleviates skin inflammation. It showed a reduction in the expression of inflammatory factors and MMP-9 activity, as well as an increase in filaggrin expression [95,96].

Several studies highlighted the role of vitamin A deficiency in the pathophysiology of atopic dermatitis, especially in early childhood.

Timely vitamin A supplementation during pregnancy and childhood could prevent the onset or exacerbation of AD [97,98].

A study by Ruhl et al. reported significantly lower serum vitamin A concentrations in infants with AD. Specifically, lower concentrations of lycopene and non-vitamin A carotenoids were observed in atopic infants, suggesting that lycopene may provide protection against atopy [99].

Regarding the intake of antioxidant nutrients and their protective effect against AD, it has been found that β-carotene can reduce the risk of AD. Children with a higher intake of β-carotene have a lower risk of developing atopic dermatitis (OR=0.69, p=0.0166) [20].

Maternal consumption of vegetables during pregnancy has also been associated with a lower likelihood of eczema and asthma [100]. A prospective study by Inoue et al. on a cohort of 267 infants with a family history of allergy found that certain levels of carotenoids, such as lutein and lycopene, were associated with a reduced likelihood of developing atopic dermatitis at one year of age ($p<0.001$) [101].

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10. Zinc

Zinc (Zn) is an essential micronutrient with catalytic, structural, and regulatory functions [102]. It plays a central role in maintenance of skin integrity by promoting keratinocyte differentiation, regulating the immune system, and suppressing the production of inflammatory cytokines [103–107].

Although the precise relationship between Zn deficiency and AD is not fully understood, Zn deficiency appears to contribute to the pathogenesis of this disease.

The effects of Zn deficiency primarily manifest in the skin and have been studied in mouse models subjected to a Zn-deficient diet. These models exhibit typical features of AD, including skin dryness, itching, increased transepidermal water loss and elevated serum IgE levels [94].

Furthermore, genetic Zn deficiency can lead to a skin condition called acrodermatitis enteropathica, which shares a similar clinical presentation with AD [108].

Few data about the association between Zn levels/deficiency and AD, as well as Zn supplementation in AD, are available.

A study conducted by David et al. measured serum Zn concentrations in 65 children with AD and 79 control individuals. The results showed that the mean serum Zn concentration in the AD group (11.4±2 micromol/L) was significantly lower than in the control group (13.7±2.3 micromol/L) ($p<0.0001$). However, there was no correlation between serum Zn concentration and eczema severity or height/weight percentile [109]. While serum Zn accounts for only about 1% of total body Zn, intracellular Zn levels, such as erythrocyte Zn, provide a better indicator of overall Zn status in the body [110].

Similarly, a study involving 67 patients with AD and 49 healthy controls found that mean erythrocyte Zn levels were significantly lower in AD group compared to healthy controls (34.4 mg/g vs. 40.4 mg/g hemoglobin; $p < 0.001$). Additionally, SCORAD and EZ showed a strong negative correlation ($p < 0.001$). Interestingly, despite significant differences in EZ levels, no significant differences in serum Zn levels were observed between the two groups [111]

Oral Zn supplementation for AD is controversial. A study involving 50 children with AD found that supplementation with Zn sulfate did not lead to clinical improvement in disease severity or a reduction in the need for topical or oral medications [112].

However, in contrast, Kim et al. demonstrated that oral Zn supplementation may have beneficial effects in AD patients. In their study, hair Zn levels were measured in 58 children with AD and 43 controls and compared with lEASI, TEWL, and visual analogue scales for pruritus and sleep disturbance. After supplementation, a significant increase in hair Zn levels ($p<0.001$), EASI scores ($p=0.044$), TEWL ($p=0.015$), and visual analogue scale for pruritus ($p<0.001$) was observed in the supplementation group. Therefore, oral Zn supplementation may be beneficial for patients with AD, particularly for those with low hair Zn levels [113].

11. Iron

Iron is a cofactor for proteins and enzymes involved in energy metabolism, respiration, cell cycle and DNA synthesis. Additionally, it plays a critical role in immunity, as iron deficiency can impair T cel responses, promote Th2 cell survival, facilitate antibody class switching, and stimulate mast cell degranulation [114–116].

Indeed, severe cases of iron deficiency anemia have been associated with elevated levels of the Th2-related cytokine IL-4 [117]. Similarly, in a study assessing the immune status of children living in a malaria-endemic area of Africa, iron deficiency was found to be associated with high levels of IL-4 mRNA expression [118].

Consequently, iron deficiency in humans creates a Th2 predominant immune environment that contributes to the development of atopic diseases. Furthermore, an epidemiological study of children in the USA showed that pediatric atopic subjects were more likely to suffer from iron deficiency anemia than children without allergies and atopic diseases. Iron deficiency anemia is more prevalent in atopic children, and the likelihood of microcytic anemia increases with the presence of multiple atopic diseases [118].

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Similar findings were observed in a study conducted in Korea, which revealed a significantly higher odds ratio (OR) for iron deficiency in patients with atopic dermatitis (OR: 1.42; p>0.001), suggesting the involvement of iron itself in the etiology of atopic disease [119].

Moreover, a case-control study investigated the association between antioxidant intake and the risk of atopic dermatitis in young children [120]. The study included 180 children with atopy and 242 control children, and it indicated a negative association between dietary iron intake and atopic dermatitis (adjusted OR: 0.39, P<0.001). Additionally, iron intake from supplements was associated with a lower likelihood of atopic dermatitis (adjusted OR: 0.51; p<0.001) [20].

Considering the growing interest in prenatal environmental exposure and AD development, an Italian study explored the association between iron and folic acid intake during pregnancy and the risk of AD in the first 6 years of life. The study found that children whose mothers took both iron and folic acid had a reduced risk of developing AD (OR=0.22, P=0.02), suggesting a protective effect of prenatal antioxidant supplementation [121,122].

Table 1. Correlation between exogenous antioxidants and AD. **Keys**: AD: atopic dermatitis; OD: Odds Ratio; patients: pts; year:y; week: wk.

Authors and year	Study design	Evidence
	Vitamin D	
Amestejani et al. 2012 [39]	60 pts with AD Randomized, double-blind, placebo-controlled: vitamin D group (n=30) and placebo group (n=30) treated for 60 days	The Vitamin D group showed significant improvement in patients with AD in terms of SCORAD and TIS (P<0.05). No improvement in the placebo group (P<0.05).
Sanchez-Armendariz et al. 2018 [40]	65 pts with AD Randomized, double-blind, placebo-controlled: Vitamin D3 group (n=33) at dose 5000 IU/day or placebo along with baseline therapy (n=32)	Achieving serum levels of 25(OH)D > 20 ng/mL in conjunction with standard therapy is sufficient to achieve a reduction in severity (SCORAD) in pts with AD.
Hata et al. 2008 [42]	28 pts (14 with AD and 14 controls) A single center controlled: received 4000 IU of oral vitamin D3 daily for 3 wk	In patients with AD significant increase in cathelicidin expression, from a median of 3.53 relative copy units (RCU) before supplementation to a median of 23.91 RCU after supplementation (P < 0.01).
Javanbakht et al. 2009 [43]	45 pts with AD Randomized double-blind, placebo controlled: Group P (n = 11): placebo vitamin E and D; Group D (n = 12): 1600 IU vitamin D3 and vitamin E placebo; Group E (n = 11): 600 IU synthetic all-rac-α-tocopherol plus vitamin D placebo; Group DE (n = 11), 1600 IU vitamin D3 plus 600 IU synthetic all-rac-α-tocopherol. Four groups and treated for 60 days	Positive correlation between SCORAD and intensity, objective, subjective and extension (p < 0.001), on the other hand negative association between plasma α-tocopherol and SCORAD, intensity, objective, and extension (p = 0.02).
Hata et al. 2013 [44]	30 pts with AD, 30 non-atopic subjects, and 16 pts with psoriasis A multi-center, placebo-controlled, double-blind study: received	At baseline, 20% of AD subjects had serum 25OHD levels below 20 ng/mL and low serum 25OHD levels correlated with increased Fitzpatrick

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	cholecalciferol 4000 IU or placebo for 21 days	Skin Type and elevated BMI, but not AD severity. At day 21 increased serum Vit D levels, but there were no significant changes in skin cathelicidin, HBD-3, IL-13 or EASI scores.
Peroni et al. 2011 [41]	37 children with AD aged between 8 months and 12 y. Observational study: correlation between Vit D levels and severity	Mean ± SD serum levels of 25(OH)D were significantly higher ($P < 0.05$) in pts with mild disease (36.9 ± 15.7 ng/mL) compared to those with moderate (27.5 ± 8.3 ng/mL) or severe AD (20.5 ± 5.9 ng/mL).
Chiu et al. 2013 [45]	97 pts with AD aged between 1 to 18 years of age. Observational study	Vitamin D deficiency (25-hydroxyvitamin D <20 ng/mL) was present in 37 subjects (39%), insufficiency (25-hydroxyvitamin D 21-29 ng/mL) in 33 (35%), and sufficiency (25-hydroxyvitamin D ≥30 ng/mL) in 24 (26%).The correlation between 25-hydroxyvitamin D concentration and SCORAD was not significant ($r = -0.001$; $P = .99$).
Vitamin E		
S-Y Oh et al. 2010 [17]	180 children with AD and 242 healthy controls Observational study	Vitamin E levels were found to be inversely associated with AD prevalence
Okuda et al. 2010 [53]	396 Japanese pts with AD aged 10-13 years Observational study	Inverse correlation between serum alpha-tocopherol levels and AD prevalence. (OR)s for the third and fourth quartiles of serum α-tocopherol with AD were 0.33 (95% IC: 0.15–0.73) and 0.36 (0.14–0.89), respectively, and the trend was negatively significant (Ptrend=0.048).
Lee et al. 2012 [54]	119 Korean children aged 0-24 months. Cross-sectional study	Serum vitamin E levels showed a significantly inverse association with serum total IgE and all specific IgE levels ($P < 0.05$).
Tsoureli-Nikita et al. 2002 [55]	96 pts with AD aged 10-60 years Observational study	In pts with improving AD in the vitamin E group, there was a 62% decrease in serum IgE levels from baseline while in the placebo group the difference was 34.4%.
Pyridoxine		
Koller et al. 1987 [65]	20 pts with AD A double-blin: patients received 1.5 mg/kg per day.	Improvement in 6 of the 10 pts treated with pyridoxine, only 1 of the placebo-treated pts experienced improvement.
Mabin et al. 1995 [63]	48 pts with AD, of whom 19 received 50 mg/day of pyridoxine hydrochloride and 22 received placebo. Double-blind, placebo-controlled	There were no significant differences between the two groups.

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Vitamin C		
Shin et al 2016 [61]	17 pts with AD. Observational study	82.4% of them had plasma vitamin C levels below 25 μmol/L, while only 3 pts had levels within the normal range (25-80 μmol/L).
Melatonin		
Yung-Sen Chang et al. 2016 [78]	73 pts with at least 5% skin involvement by AD, aged 1-18 y. Melatonin was administered at a dosage of 3 mg/day or placebo for 4 wk with a washout of 2 wk.	After melatonin treatment, SCORAD was reduced by 9.1 compared with placebo, from 49.1 to 40.2. In addition, the sleep latency interval was reduced by 21.4 minutes after melatonin treatment compared with placebo, but SCORAD improvement was not significantly correlated with change in sleep latency.
Devadasan et al. 2020 [79]	30 AD pts aged 6 to 12 years and 30 healthy patients. Observational study: evaluated serum levels of melatonin, peroxide dismutase, and glutathione reductase.	Melatonin levels were higher in AD subjects than in controls. In contrast, levels of glutathione peroxidase and superoxide dismutase were higher in cases than in controls, but the difference was not statistically significant.
Lycopene		
Inoue et al. 2023 [94]	263 mothers and their children, 40 with AD and 263 non-AD, in 1 y of age Observational study.	Maternal blood lutein level (OR, 0.002; p = .002), and infant blood lycopene level at 1 y (OR, 0.01; p = .007) were significantly related to AD at 1 year of age.
Ruhl et al. 2010 [92]	122 children, 41 with AD and 81 non-AD Observational study	Lower concentrations of lycopene and non-vitamin A carotenoids were observed in atopic infants, suggesting that lycopene may provide protection against atopy
Beta-carotene		
Gromadzinska et al. 2018 [90]	252 mother-child pairs Observational study	No statistically significant associations between β-carotene, vitam A and the risk AD in children up to 2 y of age.
S-Y Oh et al. 2010 [17]	422 children, 180 with AD and 242 with non-AD Observational study	Reduced AD risk for the highest quintile of b-carotene (OR 0.69, p< 0.0166)
Miyake et al., 2010 [93]	763 mother-child pairs Observational study	b-carotene during pregnancy was significantly associated with a reduced risk of eczema in the offspring between the highest and lowest quartile (OR: 0,41, p<0,01)
Zinc		
David et al. 1984 [102]	65 children with atopic eczema and 79 controls Observational study	Mean serum zinc of the patients with AD, (11.4±2.0 micromol/l) was significantly lower than that of the controls (13.7±2.3 micromol/l, P<oooo1). There was no correlation between serum Zn concentration and

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		eczema severity or height/weight percentile
Karabacak et al., 2016 [104]	67 pts with AD and 49 controls Observational study	Erythrocyte zinc levels were significantly lower in AD patients than in the control group ($p < 0.001$), serum zinc levels did not differ between the groups ($p = 0.148$). In the AD patient group, there was a negative correlation between the SCORAD score and erythrocyte zinc levels ($r = –0.791$; $p < 0.001$).
Ewing et al, 1991 [105]	50 children with AD aged 1-16 years Interventional study	No significant improvement in disease severity after eight-week zinc sulfate supplementation
Kim et al, 2014 [106]	58 AD pts, 43 controls Interventional study	Mean zinc level was significantly reduced in AD pts (113.1 μg/g vs. 130.9 μg/g, p=0.012) at baseline. After 8 wk of supplement, hair zinc level increased significantly (p<0.001) and EASI scores, TEWL, and visual analogue scales for pruritus improved (p=0.044, 0.015 and <0,001 respectively)
	Iron	
Drury et al. 2015 [113]	207.007 young children Case-control study	Children with AD had higher odds of microcytic anemia (p<0.009)
Rhew et al. 2020 [112]	1,468,033 patients Interventional study	Higher prevalence of iron deficiency anemia in patients with atopic dermatitis (OR: 1,40, p<0,001)
S-Y Oh et al. 2010 [17]	422 children, 180 with AD and 242 with non-AD Interventional study	Reduced AD risk for the highest quintile of iron (OR: 0.39, p< 0.01), and after iron supplementation is not associated with AD risk (OR=0,51, p=0,18)
Fortes et al. 2018 [114]	395 mother-child pairs Interventional study	Mothers use of both iron and folic acid supplementation is correlated to a decreased risk of developing AD [OR=0.22; p=0.02]

12. Conclusion

In conclusion, the onset and pathophysiology of AD are characterized by oxidative stress and inflammation. Early preclinical and clinical evidence suggests a possible role of antioxidant agents as adjuvant therapy of AD patients and in the prevention of AD.

It is important to take a multidisciplinary approach with nutritionists and dermatologists to ensure optimal and safe use of exogenous antioxidants in patients with AD.

However, further prospective studies with larger sample sizes are needed to evaluate the activity and efficacy of antioxidant compounds.

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