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Oxidative stress as a therapeutic target in atopic dermatitis: A systematic review

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ABSTRACT

Atopic dermatitis (AD) is a chronic, non-infectious disease that most often begins in childhood. It is characterized by itchy erythematous lesions located mainly on the flexural surfaces, as well as dry skin and lichenification. The pathogenesis of atopic dermatitis consists of immunological, genetic, and environmental aspects that start the dysfunction of the epidermal barrier and promote dysregulation of the immune response. This entire process leads to chronic inflammation, and it is related to oxidative stress. Studies confirm that bioactive compounds, plant extracts, and hydrogels have important antioxidant and anti-inflammatory properties. Moreover, they are able to control reactive oxygen species (ROS) production due to antioxidant therapies, which may become a promising strategy for treating AD. The introduction of such therapeutic strategies could help improve the quality of life for patients with atopic dermatitis and reduce the symptoms associated with this chronic skin disease. This piece aims to explore the aspect of oxidative stress in the pathogenesis of atopic dermatitis and to evaluate the efficacy of various antioxidant therapies with a focus on their therapeutic potential.

Keywords: atopic dermatitis, oxidative stress, oxidative stress in atopic dermatitis, ROS, reactive oxidative stress.

1. INTRODUCTION

Atopic dermatitis (AD) is a constant and persistent disease that typically develops in early childhood (Sroka-Tomaszewska & Trzeciak, 2021; Criado et al., 2024). Its clinical representation combines itchy erythematous lesions often located on the flexural surfaces. The main symptoms are scratching and dry skin, which result in skin damage and lichenification (Sroka-Tomaszewska & Trzeciak, 2021; Frazier & Bhardwaj, 2020).

Various immunological, genetic, and environmental aspects were disclosed as contributing to AD development. These induce immunological dysregulation and epidermal barrier dysfunction. A deteriorated epidermal barrier has been shown to

intensify the skin's permeability to allergens and irritants. These factors lead to consistent inflammation (Criado et al., 2024). Th2 cells produce a tremendous amount of cytokines, including IL-4, IL-5, IL-13, IL-31, IL-33, and thymic stromal lymphopoietin (TSLP), which enhance the chronic inflammatory response (Otsuka et al., 2017; Brough et al., 2020). The above processes lead to the production of reactive oxygen species (ROS), which, when accumulating, outnumber the defense capabilities of the antioxidant system (AOS), thus leading to oxidative stress (OS) (Bertino et al., 2020).

Hydrogen peroxide (H_2O_2), superoxide anion (O^{2-}), peroxide (O_2^{2-}), hydroxyl radical (OH), hydroxyl ion (OH^-), singlet oxygen (O_2), and reactive nitrogen species (RNS) take part in oxidative stress. Under natural conditions, the primary producer of ROS is mitochondrial respiration. Only 10% of ROS production is due to the action of other enzymes present in the body (Teleanu et al., 2022; Baek & Lee, 2016). Oxidative stress negatively affects lipids, proteins, DNA, and carbohydrates, leading to their damage. Damage accumulates, disrupting cell proliferation and leading to cell degradation (Bertino et al., 2020; Turcov et al., 2023).

Oxidative stress has been identified as a key factor in the pathogenesis of AD. This article aims to provide a comprehensive overview of casual treatment methods centred on antioxidant activity.

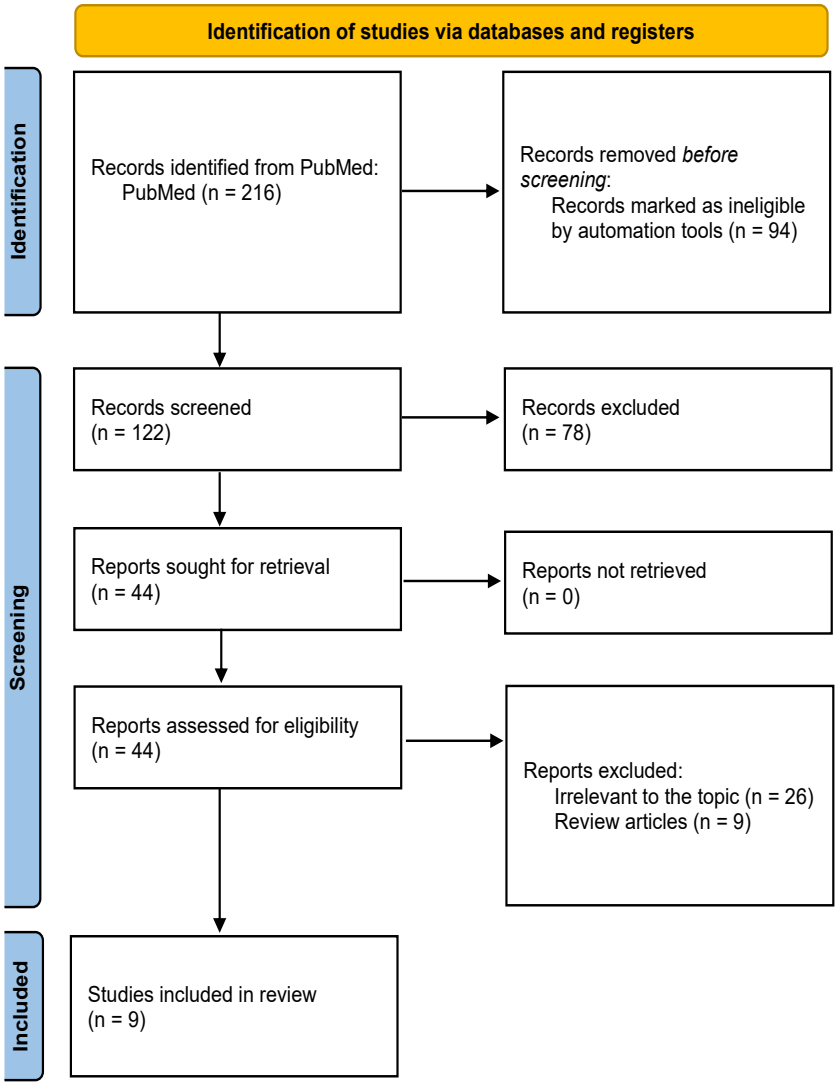

Figure 1: PRISMA flow diagram.

2. REVIEW METHODS

The PubMed database was vital in the literature review. Articles from 2020 to 2025 were searched using the phrase "antioxidant therapy in atopic dermatitis". A total of 216 articles were identified. The inclusion criteria were English-language, free full-text publications. After applying the requirements, 122 works remained. Titles and abstracts were screened first. A total of 78 articles were excluded.

Then, full-text publications were assessed. Of the 44 articles that were included, 26 were found to be irrelevant to the topic under discussion, and 9 were review articles that also did not meet the criteria. Finally, nine articles were included in this review (Figure 1).

3. RESULTS & DISCUSSION

Quercetin

This substance belongs to the group of polyphenolic flavonoids. It is commonly observed in fruits and vegetables, such as capers, which possess a large quantity of quercetin - 180.7 mg/100g and in rocket 66.1 mg/100g. And in smaller amounts in juniper berries 46.6 mg/100g, and elderberries 26.7 mg/100g (Aghababaei & Hadidi, 2023).

Beken et al., (2020) evaluated the effects of quercetin on inflammation, oxidative stress, and wound healing. Researchers cultured immortalized human HaCaT keratinocytes in the culture medium with inflammation-inducing cytokines and thymic stromal lymphopoietin (TSLP), TNF-α, IL-4, and IL-13, which were designed to cause atopic dermatitis.

Initially, apoptosis, indicators of death, and cell cycle phase were observed via flow cytometry. The lack of effect of quercetin on cell viability and cell cycle progression was proven. On the other hand, increased expression of anti-inflammatory cytokine (IL-10) mRNA was confirmed, and decreased expression of pro-inflammatory cytokines IL-1β, IL-6, and IL-8, thus confirming the regulatory effect of quercetin on inflammatory mediators. The cell migration assay also demonstrated more effective closure of the wound gap, supporting its wound-healing-promoting properties.

Exposure of HaCaT cells decreased the expression of natural antioxidants, including superoxide dismutase 1 (SOD1), superoxide dismutase 2 (SOD2), catalase (CAT), and glutathione peroxidase (GPx). However, after administration of quercetin, induction of the expression of these enzymes was observed, thus demonstrating its antioxidant effect (Beken et al., 2020).

Apigenin

This substance belongs to the flavonoid group, and large amounts are found naturally in barley sprouts. They used RAW264 cells (mouse macrophages) for the study and proved that apigenin significantly inhibited NO production, as well as contained the expression of IL-1β, IL-6, iNOS, and COX-2, proving their anti-inflammatory and antioxidant effects (Park et al., 2020).

***Erigeron annuus* (EAE)**

It is a herb observed all across North America, Europe, Asia, and Russia, which contains nearly 170 bioactive substances, including flavonoids, coumarins, and sterols (Rana et al., 2023). They used the measurement of intracellular activities of malondialdehyde (MDA), which is the end product of lipid peroxidation, and superoxide dismutase (SOD), which is the primary catalyst of superoxides, to test antioxidant activity. Cells were treated with H_2O_2, and ROS production was measured using a fluorescent probe.

EAE effectively reduced MDA levels and increased SOD activity, demonstrating its ability to protect against oxidative damage. In addition, the use of fluorescence analysis revealed that EAE is capable of reducing the production of free radicals in cells as well as neutralising them (Jeong et al., 2024).

EAE extract has been proven to exert its effects through the Nrf2/HO^{-1} signaling pathway. Nrf2, as a regulator of the cellular response to oxidative stress, is released from the complex and, upon reaching the cell nucleus, is transcribed, initiating the activation of antioxidant enzymes. Nrf2 binds to heme oxidase-1 (HO^{-1}), which demonstrates antioxidant activity. This suggests that activation by this method increases the expression of antioxidant enzymes and reduces inflammation (Jeong et al., 2024; Zhang et al., 2021).

Aristotelia chilensis

Aristotelia chilensis is native to southern Chile. These berries, called maqui fruits, contain a significant volume of bioactive substances which are found in the seeds. This includes coumarins, flavonoids, monounsaturated (MUFA), anthocyanins, polyunsaturated (PUFA) fatty acids, and delphinidin (García-Milla et al., 2024).

In addition, *Aristotelia chilensis* water extract demonstrated anti-inflammatory effects in the RAW 264.7 (cells of a mouse macrophage cell line) cell model, inhibiting nitric oxide (NO) production in a dose-dependent manner, and proving by microscopic examination to reduce the thickness and weight of mouse erythema and serum levels. However, it increased IFN-γ level, which could result in the inhibition of enhanced Th2 response that is typical of AD (Moon & Kim, 2020).

Resveratrol

It is a polyphenolic compound that occurs naturally in many plant products, such as grapes, peanuts, and tea (Galiniak et al., 2019). Shin et al., (2020) used particulate matter (PM) to induce an inflammatory response in human epidermal keratinocytes. The effects of resveratrol and its molecular mechanisms were studied then.

Using the fluorescent dye 2′,7′-dichlorodihydrofluorescein diacetate (DCF-DA), initially high levels of ROS were visualized by confocal microscopy, where they decreased after resveratrol treatment, proving the antioxidant effect. In addition, resveratrol was shown to reduce aromatic hydrocarbon receptor (AhR) expression, demonstrating its ability to block signaling pathways associated with ROS generation.

Furthermore, resveratrol has been proven capable of effectively inhibiting PM-induced expression of cyclooxygenase-2 (COX-2) and prostaglandin E2 (PGE2), and reducing levels of pro-inflammatory cytokines such as MMP-1, MMP-9, and IL-8, which are key mediators of inflammatory processes (Shin et al., 2020).

***Hibiscus cannabinus* L.**

Hibiscus cannabinus L. is also known as Kenaf. Its leaves and seeds have been proven to contain high amounts of phenols and flavonoids (Adnan et al., 2020). Han et al., (2024) evaluated the outcome of *Hibiscus cannabinus* L. flower alcohol extract (HCFE) on human keratinocytes (HaCaT) cells.

The study confirmed the presence of bioactive compounds such as anthocyanins (1.53 ± 0.031 mg per 100mg HCFE dry weight) and myricetin (2.43 ± 0.06 mg per 1g HCFE dry weight), which significantly reduced the production of reactive oxygen species (ROS). It has been demonstrated that the antioxidant effect of HCFE at 100 μg/ml was equivalent to that of ascorbic acid. This suggests that the extract can effectively counteract oxidative stress.

In addition, the extract decreased the gene expression of inflammatory cytokines (IL-1β, IL-4, IL-6, IL-8, IL-13) and chemokines (CXCL10, CCL5, CCL17, CCL22, MCP-1) in HaCaT cells, thus demonstrating the anti-inflammatory effect of HCFE by reducing the intracellular activation of NF-κB and MAPK pathways. In addition, HCFE inhibited the activation of the NLRP3 inflammasome and restored the levels of filaggrin and involucrin, inducing the restoration of the skin barrier damaged by Diesel Particulate Matter (DPM) (Han et al., 2024).

In addition, the oral therapy could be varied in the future with compounds and plants mentioned in previous studies. Moreover, researchers attempted to develop a topical treatment focused on the main issues of atopic dermatitis (AD), which is the chronic skin inflammation associated with itching and irritation due to scratching, leading to dysregulation of the epidermal barrier. The studies used hydrogel compresses containing compounds able to capture free radicals. They were then enriched with other substances, which were expected to act synergistically, enhancing the therapeutic effect (Jia et al., 2023; Qiu et al., 2023).

HCPF hydrogel

Jia et al., (2023) developed a hybrid adhesive hydrogel (HCPF) based on boronate ester with polydopamine nanoparticles (PDA NP) that capture reactive oxygen species (ROS), and liposomes containing a focal adhesion kinase inhibitor (FAKi-lipo) to inhibit FAK phosphorylation.

Authors demonstrated that increased FAK phosphorylation in both the skin of patients with atopic dermatitis and in a mouse model is significantly associated with inflammation exacerbated by scratching, suggesting that FAK is a central mediator of mechano-immune signaling in AD. This means that scratching triggers the production of ROS, which correlates with the severity of local inflammatory reactions.

In vivo experiments showed that the hydrogel can effectively alleviate oxidative stress, suppress inflammation induced by mechanical irritation, and improve the epidermal barrier by maintaining the integrity of intercellular junctions. Additionally, it was shown that the hydrogel component – carboxymethyl chitosan – has antibacterial features, reduces the risk of colonization and infection of damaged skin by Staphylococcus aureus.

Zn-MOF hydrogel (Gel@ZIF-8)

Qiu et al., (2023) developed a polyvinyl alcohol (PVA)-based hydrogel with reactive oxygen species (ROS) combing capacity, which was afterwards reinforced with metal-organic framework nanomaterials, which release zinc ions (Zn-MOF), ensuring antibacterial properties.

In vivo studies in mice demonstrated that AD induced by 1-chloro-2,4-dinitrobenzene (DNCB). DNCB was significantly alleviated after the topical application of the Gel@ZIF-8 hydrogel. It reduced epidermal hyperplasia, serum IgE levels, and mast cell infiltration. Removed free radicals, mitigating oxidative damage, while the Zn-MOF restored skin homeostasis through protective antibacterial action.

CeNP hydrogel

Kim et al., (2022) developed an alginate hydrogel that provides a constant aqueous environment with cerium oxide nanoparticles (CeNPs), responsible for scavenging free oxygen radicals. To evaluate the biocompatibility and cytoprotective features of hydrogels, in vitro experiments were conducted. The studies were managed under oxidative stress induced by DNCB and hydrogen peroxide (H_2O_2). The results demonstrated elevated cell viability of human dermal fibroblasts (HDFs) and a 45% reduction in ROS levels in human keratinocytes, demonstrating antioxidant properties.

In vivo experiments were conducted on mice. Inflammation was induced by H_2O_2 on the mouse skin, and then CeNP hydrogel was applied to the affected area. The results prove a substantial reduction in wound size and faster wound healing. Histological analyses revealed that the epidermal thickness was significantly reduced, indicating effective tissue regeneration. In addition, levels of oxidative stress markers, such as 8-hydroxy-2-deoxyguanosine (8-OHdG), were reduced by approximately 44%, which also indicates the reduction of oxidative damage.

Moreover, reducing IgE levels, Th2-type inflammatory cytokines, and mast cell infiltration, which regulates the immune response, has been proven which lead to a reduction of skin inflammation (Kim et al., 2022).

The present surveys on oxidative stress and the related overproduction of reactive oxygen species indicate that bioactive compounds exhibit potent antioxidant and anti-inflammatory properties. Previously mentioned substances include quercetin, apigenin, resveratrol, and plants like Erigeron annuus, *Aristotelia chilensis*, and Hibiscus cannabinus L (Table 1). These features could have a significant impact on the treatment of atopic dermatitis, such as accelerated healing of scratch-induced wounds, the regression of AD symptoms, and suppression of the dysregulated Th2 immune response.

Table 1. Substances and their proven properties.

Substance	Compound	Source	Subject of research	Proven mechanism of action
Quercetin	Flavonoid	Fruits and vegetables (especially capers and rocket)	Immortalized human HaCaT keratinocytes	Induction of the expression of natural antioxidants.
Apigenin	Flavonoid	Barley sprouts	RAW264 cells (mouse macrophages)	Inhibition of NO production and inhibition of the expression of IL-1β, IL-6, iNOS, and COX-2.
Erigeron annuus (herb)	Flavonoids, coumarins, and sterols	*Erigeron annuus*	Immortalized human HaCaT keratinocytes	Reduction of MDA levels and an increase in SOD activity. Reduction of free radical production in cells and their neutralization.
Aristotelia chilensis (berries)	Coumarins, flavonoids, MUFA, anthocyanins, PUFA, delphinidin	*Aristotelia chilensis*	RAW 264.7 (mouse macrophages)	Free radical scavenging capacity of 99.6% at 1000ppm. Inhibition of NO production.
Resveratrol	Polyphenol	Plants (eg. grapes, peanuts, tea)	Human epidermal keratinocytes	Reducing and blocking the production of free radicals in cells. Inhibition of COX-2, PGE2 expression, and reduction of MMP-1, MMP-9, and IL-8 levels.
Hibiscus cannabinus L. (plant)	Phenols, flavonoids, anthocyanins, myricetin	*Hibiscus cannabinus* L.	Immortalized human HaCaT keratinocytes	Reduction of free radical production in cells. Decrease in the levels of IL-1β, IL-4, IL-6, IL-8, IL-13 and CXCL10, CCL5, CCL17, CCL22, MCP-1.

The cited research had certain limitations. The most significant issue is the fact that the attributes of quercetin were only studied in vitro. The study of plants, including *Aristotelia chilensis*, focused on plant extracts rather than individual components. Research on the antioxidant properties of resveratrol, used on keratinocytes derived from foreskin, which are not exposed to particulate matter (PM**)**

under natural circumstances, and the PM itself was collected from a road tunnel in Warsaw, which may vary depending on the location.

In addition, hydrogel dressings combined with various substances are effective in reducing oxidative damage, improving skin barrier function, and alleviating inflammation (Table 2). However, they have their limitations and challenges that must be overcome for this therapy to be effective. Due to the location of skin lesions mainly in flexural folds, hydrogels should have good adhesion. They should be characterized by elasticity, softness, resistance to mechanical damage caused by scratching, and should remain on the affected skin for as long as possible and in antiseptic conditions. However, they should not cause secondary skin damage during removal (Jia et al., 2023).

Table 2. Properties of hydrogels.

Hydrogel	Added compound	Properties
HCPF hydrogel	Polydopamine nanoparticles (PDA NP) and liposomes containing a focal adhesion kinase inhibitor (FAKi-lipo)	Reduction of oxidative stress. Improvement of the epidermal barrier. Suppression of inflammation. Antibacterial features.
Zn-MOF hydrogel	Metal-organic framework nanomaterials	Reduction of epidermal hyperplasia, serum IgE levels, and mast cell infiltration. Antibacterial features.
CeNP hydrogel	Cerium oxide nanoparticles (CeNPs)	Faster wound healing. Reduction of IgE levels, Th2-type inflammatory cytokines, and a decrease in mast cell infiltration.

4. CONCLUSION

In summary, the studies suggest that the compounds mentioned above may be promising candidates for further exploration for possible therapeutic applications in the treatment of inflammatory conditions associated with atopic dermatitis. The reason for this is threefold. Firstly, they protect against oxidative stress. Secondly, they can regulate inflammatory processes. Thirdly, their natural origin contributes to their low toxicity, and local-activity hydrogels don't cause systemic side effects.

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Conflict of interest

The authors declare that they have no conflicts of interest, competing financial interests or personal relationships that could have influenced the work reported in this paper.

Data and materials availability

All data associated with this study will be available based on reasonable request to the Corresponding Author.

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