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LITERATURE REVIEW

The role of polyphenols in atopic dermatitis: A literature review

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Abstract

Background: Atopic dermatitis (AD) is a chronic inflammatory skin with the appearance of pruritic eczema lesions, mostly found in young children, and impact their quality of life (QoL). In concordance with numerous treatment options, some adverse effect might. Recently, it has been discovered that polyphenols may provide satisfactory results for AD therapy and patient's QoL.
Objectives: This literature review objective to summarize recent research the use of polyphenols for AD therapy.
Methods: This is a literature review. Literature search was conducted in Pubmed, EBSCOHOST, Proquest, and Google Scholar, using keywords: "atopic dermatitis", "atopic eczema" and "polyphenols". Inclusion criteria were: 1) Randomized clinical trials, case reports, case series, literature reviews, systematic reviews, meta-analysis, cohorts, and experimental studies, 2) Available in full text, 3) Written in English, 4) Research studies with intervention conducted in human, 5) Research studies from early 2000s. While article with lack of available data is excluded. The author use Dermatology Life Quality Index (DLQI) to assess the role of polyphenols in QoL for AD.
Results: The use of polyphenols in AD shows satisfactory results through their antioxidant, anti-allergic and anti-inflammatory properties. Several studies have observed improvements in sleep disturbance scores, itchiness, and levels of skin moisture and elasticity levels in patients with AD.
Conclusions: Polyphenols use in AD provide satisfactory results in reducing symptoms that interfere with QoL. However, due to the limited number of studies conducted on human, further studies of larger-scale participants are needed to confirm the effect of polyphenols in AD treatment.

Keywords: atopic dermatitis, atopic eczema, polyphenols

Introduction

Atopic dermatitis (AD) is a chronic skin condition that may negatively impacts quality of life (QoL). Prevalence of AD has increased approximately three-fold in the last 30 years decades, with 15-30% of cases are found in children and 2-10% in adults.[1] This skin condition often appears in 3-4 months old babies and continues to develop until the age of 2 years. Despite the exact mechanisms of AD pathogenesis remain unclear, several literatures suggest it is a result of combination between epidermal barrier dysfunction, immune dysregulation (increased inflammatory cells including monocytes, eosinophils, macrophages, mast cells, Th1 and Th2 cells), and environmental factors.[3]

Dermatological features of AD include itching, inflammation and erythema.[2,3] This symptoms is associated with QoL impairment such as the itching may affect mood and sleep hygiene, and the lesions may cause embarrassment, thus impacting on psychological wellbeing and social relationship.[4] Current therapeutic options generally consist of corticosteroids and

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antihistamines, however their long-term use potentially cause localized adverse effects including skin atrophy, telangiectasia, hypertrichosis, and dependence on topical steroids.[2] Therefore, several therapeutic options have emerged, such as polyphenols, probiotics, and vitamins that results in satisfactory findings.[5]

Polyphenols are substances that are widely distributed in variety of plants. The type of polyphenol content depends on the type of plant: isoflavones (soybeans), lignans (nuts and cereals), flavanols (tea, chocolate and apples), flavavones (citrus), flavonols (tea and apples), hydroxynamide acids (coffee, plums, and pears), quercetin (apples, grapes, and cherries), and anthocyanins (berries). Polyphenols play an important role in suppressing inflammatory processes and they have shown anti-oxidant, anti-microbial, anti-carcinogenic, neuroprotective, anti-allergic, anti-aging and anti-diabetic effects.[6] In this literature review, authors intend to further elaborate the role of polyphenols as AD therapy.

Methods

This is a literature review. Literature search was conducted in Pubmed, EBSCOHOST, Proquest, and Google Scholar, using keywords: "atopic dermatitis" and "atopic eczema". Inclusion criteria were: 1) Randomized clinical trials (RCT), case reports, case series, literature reviews, systematic reviews, meta-analysis, cohorts, and experimental studies, 2) Available in full text, 3) Written in English, 4) Research studies with intervention conducted in human. While article with lack of available data is excluded. The author uses Dermatology Life Quality Index (DLQI) to assess the role of polyphenols in quality life for AD.

Discussion

Atopic Dermatitis

Atopic dermatitis is a common, chronic, and often recurring condition. The incidence of AD has increased in recent decades, especially in developing countries.[8] Atopic dermatitis has become a global health problem regarding its high-costs treatment, ability to negatively impact quality of life, and the resulting psychosocial distress. WHO estimates that AD affects 230 million people worldwide.[9] The prevalence in children ranges between 15-20%, while in adults it ranges between 1-10%. Globally, prevalence of AD has increased two to three-fold in recent decades.[10] The interaction between genetic, immune and environmental factors plays an important role in this increasing number of AD cases. Family history of atopic disease is a well-established main risk factor for the development of AD. In addition, other risk factors include low humidity, intake of foods with high sugar and unsaturated fats, repeated exposure to antibiotics before the age of five, and high social status.[11]

The pathogenesis of AD is complex, involving skin barrier disruption, dysregulation of the immune and cutaneous systems, dysbiosis of the skin bacterial microbiome, and genetic factors. Disruption of the skin barrier subsequently leads to chronic inflammation with epidermal hyperplasia and cellular infiltrates such as dendritic cells, eosinophils, and T cells. In the acute phase, Th2 cells produce IL-4, IL-5, IL-13, IL-25, and IL- 31. Meanwhile, in the chronic phase, Th2 will be converted into Th1. Furthermore, there is a reduction of microbiota in AD, resulting in colonization by *Staphylococcus*, especially *S. aureus*, in 90% of patients with AD.[11] The clinical features of AD in the acute setting are acute eczema and wet pruritic lesions on dry skin. While, chronic AD consists of dry reddish or brownish lesions, cracked skin accompanied by lichenification, and prurigo nodularis. Pruritic skin especially at night may results in sleep disturbances which in turn weakens the body and may lead to mental health problems.[8]

There is no specific examination for AD apart from inspection of clinical features, however elevated serum IgE levels can be seen specifically in patient with AD. There are several criteria to help in diagnostic process, where criteria by Hanifin and Rajka and American Academy of Dermatology Consensus are the most widely used among those criteria.[8] The dry, itchy, and eczematous skin of AD has a profound impact on

QoL. The most commonly used tools is Dermatology Life Quality-Index (DLQI). DLQI assesses the impact of skin disease on symptoms and feelings, daily activities, leisure, work and school, personal relationships and the impact of treatment. DLQI score for AD patients ranges from 0 (no impact of the disease on QoL) to 30 points (extreme impact of the disease on QoL).[13]

Polyphenols

Polyphenols are chemical substances that are widely found in plants. To date, thousands of types of polyphenols have been identified. Variety of plants have been identified containing polyphenols, including nuts, berries, grapes, tea, olives and lemons.[13] Polyphenols are divided into different groups according to the number of phenol rings they contain. Polyphenols are mainly classified into two groups, flavonoids and non-flavonoids. Flavonoids can be subdivided into different subgroups depending on the position of the hydroxyl group and on the basis of the structural features of the C ring. These subgroups are: flavanols, flavones, isoflavones, flavones, anthocyanidins, and flavanols. The carbon atoms of flavonoids are arranged in a C6-C3-C6 configuration with two aromatic rings bound to three carbon atoms, thus leading to the formation of an oxygenated heterocycle ring C. Flavonoids are found in variety of berries, grapes, tea, soybeans and onions.[14]

Non-flavonoids are further divided into phenolic acids, lignans and stilbenes. Phenolic acid is divided into two different classes based on the C1-C6 (benzoic) and C3-C6 (cinnamic acid hydroxy derivatives) groups. Phenolic acid is found widely in onions and berries. Lignans are plant secondary metabolites synthesised by oxidative coupling of two phenylpropane units and occur mostly in the free form, which are mostly found in flaxseed, sesame and sunflower seeds. Stilebene is also a small class of plant secondary metabolites derived from the phenylpropanoid pathway, some of which are associated with mechanisms of defence in the plant, found in many berries and nuts.[15] Dietary polyphenols are found in free form and/or bound to polysaccharides and/or proteins. The process of absorption of flavonoids (except flavonols) in the small intestine are not well absorbed in the intestine, because they are highly hydrophilic to penetrate the walls of the digestive tract, resulting in fairly low bioavailability. Polyphenols that are not absorbed in the small intestine are able to reach the colon to help promote the growth of gut microbiota, such as *Lactobacillus* and *Bifidobacterium* which act as probiotics, thus finally reducing pathogenic microbes, such as *Clostridium histolyticum* and *Clostridium perfringens*.[14]

Process of polyphenol metabolism occurs in hepatocytes and enterocytes in the liver through phases I and II of biotransformation. Most of the dietary polyphenols are found in the form of ester bonds, glycosides, and polymers, where in these forms, they cannot be directly absorbed, where only about 5-10% of monomer form can be directly absorbed in the small intestine. This absorption process requires hydrolysis process assisted by digestive enzymes and gut microbiota. Alpha rhamnosidase, beta-glucosidase, and beta-glucoronidase are enzymes that aid the hydrolysis process. After the formation of aglycogens, they are then transferred to enterocytes via passive diffusion or through portal vein flow. Polyphenols are degraded with the help of gut microbiota into simple aromatic acids, followed by a conjugation process consisting of hydroxylation, methylation, sulfation and glucuronidation in liver cells to become O-glucoronate or O-sulfonate. Finally, it is then distributed throughout the organs and excreted in the urine.[18]

The bioavailability of polyphenols depends on the chemical structure of each type, where their bioavailability from highest to lowest in order are: isoflavones, flavonols, flavones, and anthocyanins.[19] In addition to the type of polyphenol, bioavailability also affected by food processing, interactions with other food ingredients, digestive enzymes, health conditions, and gut microbiota species.[14]

Polyphenols have multiple functions in lowering the symptoms of atopic dermatitis. Firstly, they act as antioxidant by inhibiting fat oxidation, decreasing hydroperoxide formation,

inhibiting ROS formation by inhibiting enzyme production, inducing the formation of antioxidant enzymes, regenerating alpha tocopherol and ascorbic acid, regulating transduction signal of the antioxidant defense system. Polyphenols stabilising free radicals and lower their reactivity.[14]

One has shown that quercetin has an antioxidant effect by preventing cell death secondary to oxidative stress in the keratinocyte layer, also other research have shown that quercetin 3-O-2-alpha-L-rhamnopyranoside inhibits apoptosis of keratinocyte by inhibiting caspase 8 and mitochondrial pathway. ROS (reactive oxygen species) is stimulated by NADPH oxidase as a messenger in several cellular signaling pathways, including NF kB and AP1 in inflamed skin. Transcriptional factor Nrf2 is released from the cytosolic protein Keap 1 into the nucleus, which then binds to transactive antioxidant enzyme genes. Activated Nrf2 facilitates phase II enzymes, such as HO-1. Studies in mice showed that Nrf2 loss results in high formation of NFkB including TNF-alpha, IL1b, and cyclooxygenase. NRf2 is responsible for inhibiting regulation of HMGB1 to produce macrophage and/or monocyte. Quercetin have been proven effective in suppressing inflammatory process by activating Nrf2 signaling and inhibiting both NFκB and MAPK pathways.[2]

The second function of polyphenols against dermatitis is by reducing inflammatory process. Polyphenols inhibit enzymes that activate pro-inflammatory mediators, such as COX-2, LOX, iNOS, NF kB, activated protein-1 (AP-1), antioxidant phase II detoxifying enzyme activation, MAPK (mitogen activated protein kinase), protein kinase-C , and erythroid 2 related factor.[19] Quercetin suppresses proinflammatory cytokines in mast cells (NFκB and p38MAPK). Application of quercetin derivatives reduce inflammatory cytokines including IL-4, 5, 13, IgE, eosinophil and COX2 levels in mice with atopic dermatitis. HMGB1, RAGE, ERK1/2 NF kB act as inflammatory mediators that enhance proinflammatory cytokines in mice with atopic dermatitis. Quercetin inhibits proinflammatory cytokines such as IL-1beta, IL-6, and TNF alpha and increases IL-10 levels.[2]

The role of polyphenols in allergic reactions works by inhibiting the production of signaling factors and cytokine; along with inhibiting gene expression in mast cells, basophils, and T cells. Polyphenols bind to allergen proteins, therefore turning them into insoluble proteins with lower potential. Among polyphenol structure, there are several potent components in inhibiting activation of pyrogallol allergic reactions, epigallocathecin gallate, a galloyl group in the benzene ring, and 2,3-cis configuration. One study found that quercetin significantly suppressed expression of inflammatory cytokines such as IL-4, IL-5 and NF kB in mice.[16]

Effect of polyphenols on atopic dermatitis

Skin is the largest organ of human body that is continuously exposed to the external environment. Inflammatory skin is caused by infiltration of T cells, mast cells, and eosinophils. Itching sensation is one of the most debilitating symptoms in AD that may affect the quality of life of patients in addition to precipitate complications including secondary infection. A study by Talamonti about quality of life using DLQI categorization, only two AD patients reported no negative influence of skin disease on their QoL, while 26 reported a small effect, 36 reported a moderate effect, and 110 reported a very large effect. As is commonly believed, the intense itching associated with AD often causes patients to experience severe sleep disturbances, leading to daytime sleepiness and sleep-related impairment. Sleep disturbances consequently results in functional impairment and profoundly worsens QoL for AD patients. It is also associated with unsatisfactory performance in school and work, reduced general health and safety, and considerable cost.[17]

Studies by Singh[5] suggest that inflammatory effects found in AD can be reversed with polyphenols use either as dietary intake or topical agents. Meanwhile, polyphenols act in inhibiting T cells production and inhibiting inflammatory cytokine, IL-2. Green tea extract contains

flavanols such as catechin and epicatechin. One of catechin derivatives – epigalocatechin galate (EGCG) – is an active substance found in green tea extract that has been shown to prevent inflammation of the skin layers. Catechin and EGCG are known to inhibit CD11b molecules binding into circulating T cells and B cells, thereby inhibiting their migration to areas of inflammation. EGCG also plays a role in inhibiting the release of histamine by mast cells and basophils, thus prevents IgE antigen complexes formation that potentially leads to allergic reactions. Photoprotective effect on the skin is observed with topical application. Moreover, green tea is also able to reduce hyperkeratosis and hyperplasia in inflammatory area of the skin.[5,21]

Avenanthramides, one compounds of polyphenol among many, which is predominantly found in wheat, are known to exert anti-inflammatory activity in the skin. This type of polyphenol works by inhibiting NF-kB activation and reducing pro-inflammatory cytokines such as TNF-a and IL-8. Furthermore, other forms of polyphenols such as Quercetin and Luteolin also have similar properties in reducing itchiness and redness caused by an elevated skin temperature. Evaluations conducted on topical application of Quercetin have shown to reduce irritation and improving the function of skin barrier. In addition to their anti-inflammatory properties, polyphenols also possess antioxidant effects. Consumption of high-dose cocoa drinks may help to maintain skin moisture and increase blood flow of cutaneous tissues. Lesional skin of patients with AD was more frequently colonized with *S. aureus*. Generally, antibiotics are used as treatment strategy for treating secondary infections. However, a study found that polyphenols may also inhibit enterotoxin activity from staphylococcal bacteria.[5]

A study by Kojima et al.,[22] assessed the benefit of apples containing polyphenols to treat allergies in patients with AD on 24 patients (10 patients in the control group and 14 patients in the ACT (Apples Condensed Tannin) group). This study includes participants with the age of 8-18 years, without any history of allergic rhinitis or bronchial asthma. The research was carried out for 10 weeks, where they provided identical treatment between the 2 groups on the first 2 weeks using bufexamac ointment, half-doses of aclometasone dipropionate ointment, as well as the antihistamine hydroxyzine hydrochloride, given to each subject from the beginning to the end of the observation. Control group kept receiving the similar treatment given for those first 2 weeks. While the ACT group received ACT supplement 10 mg/kgBW/day divided into 2 doses for 8 weeks. Participants was monitored every 2 weeks to assess any lichenification, inflammation, cracking, itching, and sleep disturbance scores. Assessment of eosinophils, serum IgE, SGPT and SGOT were only performed at the beginning and the end of study period. This study concluded that there was no significant difference in terms of gender, age, serum IgE values, eosinophils, degree of AD, and duration of AD between control group and intervention group who received ACT. However, reduced inflammation, lichenification, and cracking scores were observed in the ACT group. Similarly, itching and sleep disturbance scores were also lower compared to the control group.

Additional study by Mehrbani[23] on using whey protein and *dodder* extract for AD patients was conducted on 52 patients with moderate to severe AD for 30 days. Moisture, elasticity, itchiness, sleep disturbance scores, changes in skin color, pH and skin sebum levels are all documented every 15 days. By the end of the study, 42 patients remained, 24 patients of dodder whey group and 18 patients of the control group. Final result of this study showed some significant differences of skin moisture level, skin elasticity, sleep disturbance scores, and itching in the group that received whey protein and dodder extract compared to control group. In terms of safety profile, there were 13 patients experienced anorexia and 4 patients with dyspepsia in the intervention group using whey dodder. However, blood pressure, kidney function, liver function, and body weight were not evaluated in this study.[23]

Conclusion

Polyphenols may alleviate the symptoms presenting in patients with AD and improve their quality of life. Due to the limited number of studies in human, further studies involving larger-scale respondents are required to confirm the effect of polyphenols in AD treatment.

Conflict of interest

Authors declared no conflict of interest regarding this article

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