



Management and treatment of atopic dermatitis with modern therapies, complementary and alternative medicines: a review

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Abstract

Atopic dermatitis (AD) is a common dermatological disease characterized by relapsing pruritus and rash accompanied by cutaneous physiological dysfunction. This disease could affect certain population worldwide, including infants, children and adults. The prevalence of AD has been increased rapidly over the past few decades and the severity of the disease, symptoms, and effects on patients' quality of life may vary among individuals. AD could be caused or triggered by several factors, such as genotypic, climatic, food allergens and environmental. Many treatments are available to alleviate the symptoms and severity of AD, including topical therapy, immunosuppressant and systemic therapy, phytotherapeutic approach, traditional Chinese medicine (TCM), as well as complementary and adjunct therapies. Topical therapies involve moisturizers, emollients, topical corticosteroids, topical pimecrolimus and tacrolimus and antipruritic/antihistamine therapy. Whereas, systemic therapies and immunosuppressant prescribed for AD treatment include cyclosporine A, azathioprine and methotrexate. Nowadays, not only the modern medicines are used for treatment of AD but also the phytotherapy using herbs and TCM are commonly incorporated into the therapy. In addition some studies have been showed that complementary/adjunct therapies are effective as preventive approaches for managing AD. In this review some examples of these therapies and approaches will be discussed with relevant supporting literatures.

Keywords Atopic dermatitis · Herbal therapies · Anti-inflammatory · Topical corticosteroids · Traditional Chinese medicine

Introduction

Atopic dermatitis (AD) is a chronic inflammatory skin disorder that affect certain population worldwide. This skin disorder is a significant social and financial burden to the patients, their families and the whole community (Boguniewicz et al. 2007; Boguniewicz and Leung 2011; Lewis-Jones 2006; Mancini et al. 2008). AD can affect both adults and children at any age and the prevalence is up to 20% worldwide (DaVeiga 2012). Significant increase in prevalence of AD, ranging from 0.07% to 1.09% in 48 countries has been reported (Spergel 2010). Some literatures reported that some developed and developing countries have high prevalence rate of

AD which showed that this dermatological disease is a considerable problem worldwide (Boguniewicz and Leung 2011; Odhiambo et al. 2009; Williams et al. 2008). In United States, the lifetime prevalence in 6–12 years old children is 17%. In Southeast Asia, the prevalence of AD has been increased recently across different age groups. In Singapore, Malaysia and north-eastern Thailand, the lifetime prevalence of chronic rash in 5–15 years old children is about 12.5%, 17.6% and 17.2%, respectively. However, the prevalence is stable in children when they are older, at 12–15 year old in Singapore, and 13–14 years old in north-eastern Thailand (Teeratakulpisarn et al. 2004; Trakultivakorn et al. 2007; Wang et al. 2004). In Malaysia, the prevalence is the highest in 6–7 years old in children, and it is stable in older children, aged 13–14 years old (Deckers et al. 2012; Quah et al. 2005; Teeratakulpisarn et al. 2004).

The National Survey of Children's Health suggests that the high prevalence rate of disease is related to genetic, lifestyle and environmental factors. But it is proposed that the lifestyle and environmental factors are the main causes of increasing prevalence of AD.

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Causes of AD

Scientifically, AD is characterized by increased level of serum immunoglobulin E (IgE) after sensitization by certain factors. Various factors and reasons can trigger the flare of AD but the exact cause is still unknown. Multiple reasons and causes have been proposed which are closely related to the flare of AD.

Genotypic factors

Genetic factors could contribute to the development of AD. Cookson et al. (2001) reported that evidences supporting a role for filaggrin (FLG) in genetic susceptibility to eczema. It is been identified that genetic linkage with polymorphic markers within the epidermal differentiation complex on chromosome 1q21, where the *FLG* gene is located (Cookson et al. 2001). *FLG* mutation is reported to be significantly correlated with AD and other allergy related diseases (Irvine 2007; Nomura et al. 2008; Nomura et al. 2007; Palmer et al. 2006). Kamer et al. (2013) reported that 49.1% of the AD cases in children are associated with family history of atopic disease and allergy. These AD children usually will have immediate family members who are also suffering from allergy: mothers (35.4%), fathers (25.5%), siblings (24.5%) and grandparents (18.7%) (Kamer et al. 2013). Allergens-specific antibodies concentration in these children increases when they have come in contact or consumed the highly allergic food and inhaled allergens, such as cow milk proteins, egg white, egg yolk, carrot, soy, house dust mites and moulds. Monozygotic and dizygotic twin pairs would have different probability of having AD, which could be related to the genetic makeup differences between the twin pairs. Monozygotic twin pairs are resulted from one zygote, which separated independently at the early stage of development into growing cell aggregations, giving rise to two individuals of the same sex and identical genetic constitution. Therefore, if the twin partner has the atopy disease, the other twin sibling is also at the higher risk of having the disease, due to the identical genetic makeup. However, the risk for dizygotic partner is slightly lower, and no difference is noticed in the frequency seen in ordinary brothers and sisters (Larsen et al. 1986).

Climate and food allergens

Flohr and Mann (2014) reported that climate is also closely associated with the prevalence of AD. Cross-sectional studies in Spain and Taiwan indicated that AD symptoms are correlated positively with latitude and negatively with annual outdoor temperature and climate (Flohr and Mann 2014). Some cases of AD in children happened more frequently in summer whilst some in winter. FLG is the main source of several major

components of natural moisturizing factor in the stratum corneum, including pyrrolidone carboxylic acid and urocanic acid. It plays an essential role in skin barrier function. UV light is believed to have immunosuppressive effect and it promotes the conversion of FLG, and causes the breakdown of FLG trans-urocanic acid into the immunosuppressive cis-urocanic acid isoform (Flohr and Mann 2014). Combination of various factors including outdoor temperature, ultra-violet (UV) light, humidity, pollen count due to seasonal change are believed could trigger the flare of AD.

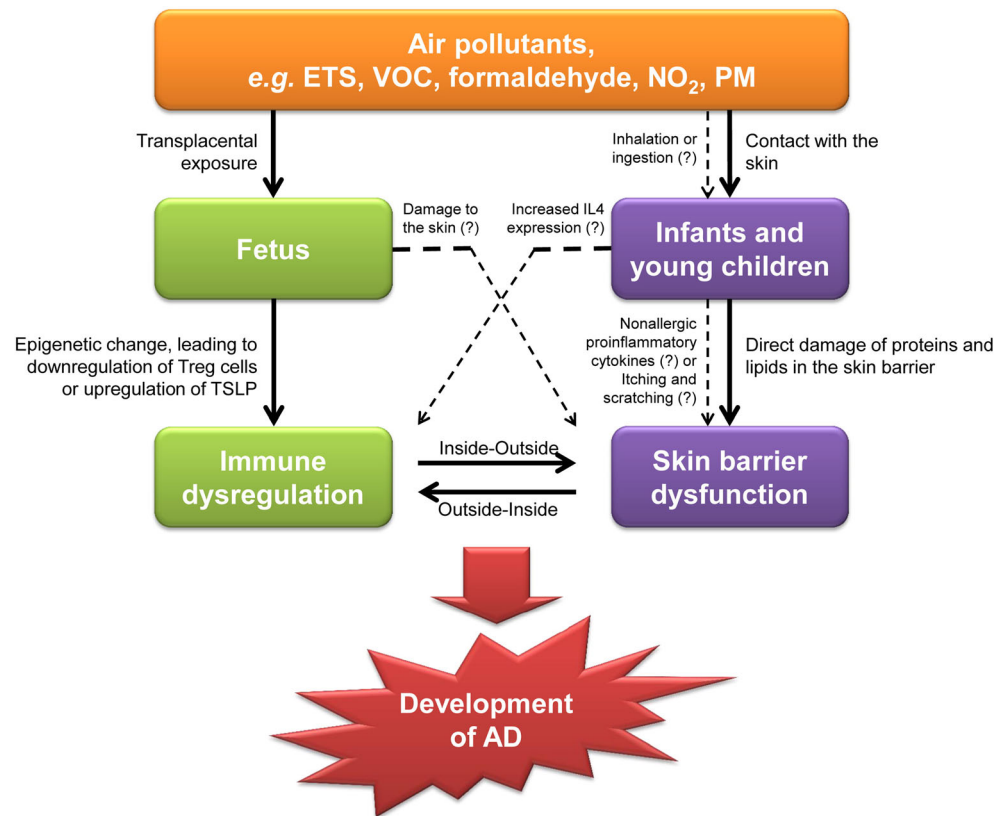
Irritants and allergens in food could trigger the itchiness and scratching, induce the release of proinflammatory cytokines from atopic keratinocytes. Highly allergenic food such as eggs, milk, wheat, soy, and peanuts are the major types of food that could potentially trigger eczema in children (Leung et al. 2004). However, consumption of refined grains, cured and red meats, saturated and unsaturated fatty acids, and fast-food have also been reported could increase the risk of AD. In addition, diet which is low in anti-inflammatory n-3 polyunsaturated fatty acids (n-3 PUFA) and high in proinflammatory n-6 polyunsaturated fatty acids (n-6 PUFA) such as linoleic acid are also correlated with higher AD risk (Flohr and Mann 2014; Leung et al. 2004; Palmer et al. 2012). Intake of n-6 PUFA by the mother during pregnancy would cause the infant to born with higher risk to AD, as discovered in the study of Japanese children at 2 years old reported by Flohr and Mann (2014). Authors explained that it is due to the high level of n-6 PUFA precursor but low level of n-3 PUFA that caused the children to be more susceptible to AD.

Environmental

Urbanisation has always been considered as one of the contributing factors to the rise of AD in many countries. Hygiene-related exposures, such as parasites, bacteria, virus infections, the use of vaccination, antibiotics, and pollutants (including sulfur oxide, nitrogen oxides, carbon monoxide, volatile organic compounds, particulate matter, toxic metals, ammonia, and radioactive pollutants) will also increase the prevalence of AD (Ahn 2014). A cohort study in West Germany revealed that exposure to nitrogen dioxide in children and prevalence of AD are interrelated (Flohr and Mann 2014; Morgenstern et al. 2008). It also showed that pollutants including fine-particles and cigarette smoke are believed to cause impairment in skin barrier, resulting in skin inflammation.

Ahn (2014) has proposed the possible mechanisms which explained how air pollutants could trigger the development of AD (Fig. 1). Author has explained that transplacental exposure to pollutants during pregnancy could cause epigenetic changes, such as reduction in regulatory T cells, and upregulation of thymic stromal lymphopoietin (TSLP) protein would result in immune dysregulation. Exposure to various pollutants by infants and young children via skin contact or

Fig. 1 A proposed mechanism by which exposure to air pollutants affects the development of AD. Reproduced with permission from Elsevier



inhalation would cause damage to the proteins and lipids in the skin barrier. Exposure to these pollutants may cause the release of nonallergic proinflammatory cytokines, increase the expression of interleukin-4 (IL-4), trigger the skin itchiness and lead to scratching behaviour, and hence contribute to the development of AD (Ahn 2014).

Treatment for AD

Severity of AD can be managed in various ways. AD is normally treated using the modern methods, such as topical and systemic therapies. However, many alternative and complementary therapies are adopted in management of AD, such as the usage of probiotic supplementation, phototherapy and acupuncture.

Skin is the largest organ in the body. It serves three main functions, namely protection against environmental allergens and irritants, regulation of body temperature and sensations (Akdis et al. 2006). Topical and systemic therapies are used to protect the weakened skin barrier in AD patients.

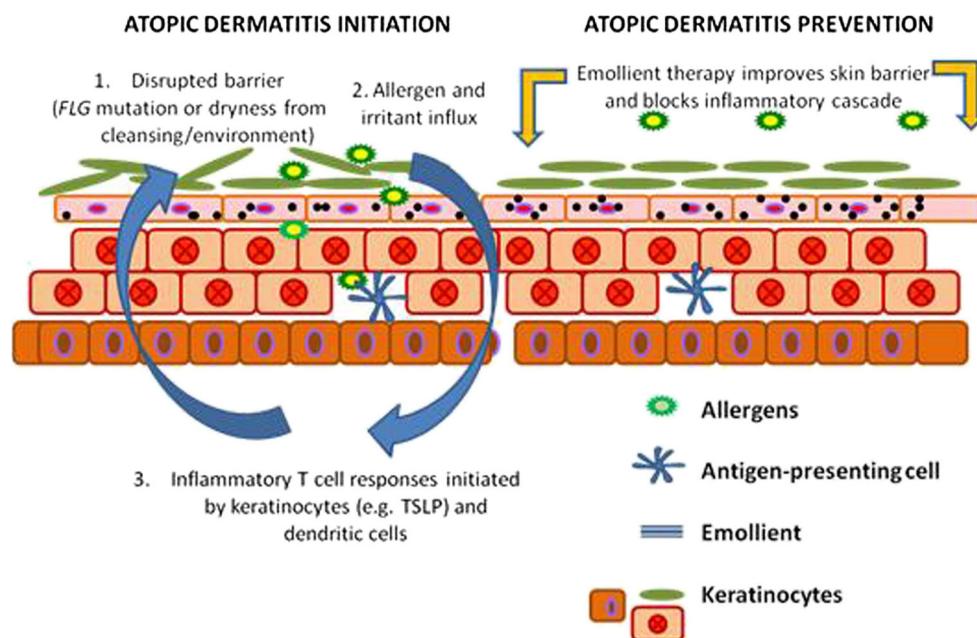
Topical therapies

Moisturizers and emollients Moisturizers and emollients including creams, ointments and lotions are usually used as topical therapy for AD. Emollients contain occlusive and

humectants that could enhance the skin barrier, provide a lipid layer on the skin surface to reduce the water loss and increase the skin moisture content, whereas the humectants could retain the moisture of the stratum corneum layer (Akdis et al. 2006; Rubel et al. 2013) (Fig. 2). The types of emollient used are depending on the skin condition, degree of dryness and climate humidity of the patients. For instance, greasy emollients, i.e. creams are suitable for dry skin, while more creamy textures such as lotions are used for inflamed skin. Simpson et al. (2014) reported that daily use of moisturizers and emollients could significantly reduce the cumulative incidence of AD and relative risk by 50%, as they target on the subclinical skin barrier dysfunction and prevent the early inflammation. Sufficient skin hydration and skin barrier enhancement could potentially inhibit the irritation by pollutants and penetration of allergens. Hence it will eventually prevent the onset of skin inflammation. (Simpson et al. 2014).

Topical corticosteroids Topical corticosteroids are the first-line therapy for AD. Topical corticosteroids are formulated in creams, ointments and gels with known amount of corticosteroids and hormones which possess anti-inflammatory, vasoconstriction and immunosuppressant properties. A survey conducted in Southeast Asia in 2006 reported that 91–100% of patients are using topical corticosteroids in managing AD (Chan et al. 2006). However, prolong topical corticosteroid exposure could induce various side effects, including local

Fig. 2 Skin barrier protection might prevent atopic dermatitis development. *FLG*, Filaggrin. Reproduced from Simpson et al. (2014). Figure reproduced is under Creative Commons Attribution License



irritation, atrophy changes, telangiectasia, striae, purpura and stellate pseudoscars, hyper/hypopigmentation, and rosacea (Coondoo et al. 2014). Among the topical corticosteroids prescribed, hydrocortisone is the most commonly used, followed by betamethasone valerate (Charman et al. 2000). Luger et al. (2004) reported that 95.6% of the AD patients are using topical corticosteroids and 50% of the patients were on topical corticosteroids almost everyday for a year. This showed that the amount of continuous exposure to topical corticosteroids by the AD patients is likely to be higher than the recommended dosage in clinical practice and treatment guidelines (Luger et al. 2004). Therefore, the usage of topical corticosteroids should be carefully monitored, in terms of dosage, potency, duration, and frequency of application.

Topical pimecrolimus and tacrolimus Topical pimecrolimus and tacrolimus are topical calcineurin inhibitors. They are non-steroid selective inhibitors of inflammatory cytokines which can be used to decrease inflammations (Kapp et al. 2002; Wahn et al. 2002). Pimecrolimus and tacrolimus regulate the activity of several transcription factors that control cell division and trigger the early stages of T cell activation, selectively inhibit activation of T cells and mast cells, suppressing inflammatory cytokines and other mediators of the allergic inflammatory reaction, without causing atrophogenic potential like topical corticosteroids. Kapp et al. (2002) discovered that pimecrolimus treatment group has fewer flares compared to conventional treatment group which uses emollients and moderately potent topical corticosteroids. The flare-free period for topical pimecrolimus users is significantly longer than conventional treatment group (Wahn et al. 2002). However, increase and prolong use of

topical pimecrolimus and tacrolimus has also been associated with the increased risk of lymphoma (Arellano et al. 2007). 18 lymphoma cases associated with the prolong use of pimecrolimus and tacrolimus have been reported, including hepatoblastoma, metastatic sweat gland carcinoma, nodular follicular lymphoma, histiocytic lymphoma, basal cell carcinoma, squamous cell carcinoma etc. (Ormerod 2005).

Antipruritic/antihistamine therapy Pruritus is a common symptom of AD. The itch-scratch cycle would worsen and damage to the skin, causing skin dryness and increasing water loss. The disrupted skin barrier creates an ideal environment for skin pathogens to cause infection and triggers severe itching. Sedating and non-sedating antihistamines are prescribed as antipruritic therapies in AD. Sedating antihistamines are frequently prescribed to ease the skin itchiness, especially at bedtime. The sleep-inducing effect could relieve the itchiness at night and facilitate peaceful sleep. During daytime, non-sedating antihistamine such as loratadine is prescribed. Some antihistamines may bring adverse effect. For instance, doxepin is prescribed as antihistamine for AD patients, as it possesses very potent H_1 and H_2 histamine receptor blocking properties (Leslie et al. 2015). It is usually prescribed for patients with lichen simplex chronicus, nummular dermatitis and contact dermatitis. However, if topical doxepin is applied to large areas, patients may experience drowsiness, localised burning and allergic contact dermatitis. Prolong exposure (more than 8 days) may increase the risk of contact allergy (Leslie et al. 2015). Hence, the efficacy of the use of antihistamines towards AD should be carefully evaluated.

Immunosuppressant and systemic therapies

Cyclosporin A (CsA) CsA is also recommended as the first-line treatment for short-term use. It is an immunosuppressant that inhibits the proliferation of T lymphocytes. CsA has been reported could affect B cells and dendritic cells, inhibit the growth pathways in keratinocytes and induce rapid clinical reversal (Khatti et al. 2014). Significant improvement in the immune and epidermal phenotypes is noticed within 2 weeks of treatment period. Another study also supported that short term use of CsA showed clinical improvement in severity between 53% and 95% (Roekevisch et al. 2014).

Azathioprine (AZA) AZA is the second line treatment after CsA (Roekevisch et al. 2014). It is a purine synthesis inhibitor that inhibits the proliferation of leukocytes (Schram et al. 2011). Several randomised trials have reported that patients under AZA have improved skin conditions (26–37%) compared to placebo group (Berth-Jones et al. 2002; Meggitt et al. 2006). In the recent report, 39% reduction of Severity scoring of atopic dermatitis (SCORAD) scores in AD patients were noticed (Schram et al. 2011). The use of AZA can be gradually reduced and discontinued if the AD is under controlled.

Methotrexate (MTX) MTX is frequently used as the third-line treatment (Roekevisch et al. 2014). It is a strong dihydrofolate reductase inhibitor and a folic acid antagonist that could reduce the T-cell proliferation (Lyakhovitsky et al. 2010; Schram et al. 2011). Lyakhovitsky et al. (2010) reported statistically significant reduction in SCORAD after the treatment of MTX in children and adult AD patients (mean reduction is 28.65 ± 23.2 units). Improvement of SCORAD is also reported by Schram et al. (2011). The skin conditions of AD patients improved after the treatment. MTX possesses anti-inflammatory action, where the increased adenosine release and accumulation at the inflamed site would inhibit lymphocyte proliferation and pro-inflammatory cytokines TNF- α , IL-6, and IL-8 production (Lyakhovitsky et al. 2010).

Phytotherapeutic (herbal) approach and traditional Chinese medicines (TCM)

In recent years, AD patients begin to seek for alternative therapies for the treatment. There has been considerable interest in herbal remedies and TCM. Upon the conventional therapies, patients are turning to these potential adjunct therapies when they realised that side effects of modern therapies may be long term and irreversible. Hence, patients opt for safer alternative therapies, to reduce the exposure to corticosteroids and other modern therapies. Herbal remedies and TCM are currently among the most popular therapies used as alternative treatments.

Phytotherapeutic (herbal) approach

German chamomile (*Matricaria chamomilla*) German chamomile (Fig. 3) is used to treat various inflammation diseases, including gastrointestinal tract symptoms, oral inflammation and skin dermatitis. Anti-inflammatory activity is examined in animal studies using German chamomile showed that it could inhibit the histamine release from basophilic polymorphonuclear leukocytes (Shenefelt 2011). German chamomile oil has been reported could alleviate AD symptoms in mice model. Lee et al. (2010) reported that German chamomile oil could significantly reduce the serum histamine level and frequency of scratching on facial and back skin of AD induced mice model. In addition, the number of neutrophils and lymphocytes and hyperplasia of the epidermis are significantly decreased in treated group in mice model (Lee et al. 2010). Studies have reported that German chamomile oil exhibited 60% as active as 0.25% hydrocortisone when it is been applied topically, and it could reduce the symptoms of dermatitis with the application of sodium lauryl sulfate (Brown and Dattner 1998).

Aloe vera *Aloe vera* (Fig. 3) is well known to have the ability to hydrate the skin and retain the water content of the epidermis. It can be applied topically on the skin in the form of cream, gel and lotion. Vazquez et al. (1996) reported that *Aloe vera* exhibits anti-inflammatory activity and it is capable to modulate immunological responses in AD by reducing the IL-5 or IL-10 levels in NC/Nga mice (Kim et al. 2010). Panahi et al. (2012) discovered that significant reduction in prevalence of dermatitis severity is noticed before and after the study. Similar finding has also been reported and the authors suggested that topical application of *Aloe vera* gel may suppress chronic AD by a selective reduction of the Th2 response (Finberg et al. 2015). These results showed that the use of *Aloe vera* is effective in soothing the symptoms of AD.

Coconut oil Ordinary coconut oil has been used to relieve the symptom of AD. It is normally been used as an emollient to soothe and relieve the itchiness and moisturize the skin (Naafs 2006). Virgin coconut oil (VCO) is extracted from fresh coconut and it is considered as the highest quality and healthiest form of coconut oil. Intahphuak et al. (2010) have reported that VCO could exhibit moderate anti-inflammatory effects on acute inflammatory model, where ethyl phenylpropionate (EPP)-induced ear edema in rats and carrageenin- and arachidonic acid induced paw edema are used. Reduction is observed at 15 and 30 mins after the application of 1, 2 and 4 mg/20 μ L VCO/ear, and at 60 and 120 min after the application of 2 and 4 mg/20 μ L VCO/ear. The inhibitory effect displayed in dose-dependent manner. It can also exhibited an inhibitory effect on chronic inflammation by reducing the transudative weight, granuloma formation,



Fig. 3 Plants used in phytotherapeutic treatment in AD. **a** German chamomile, **b** *Aloe vera*, **c** Coriander

and serum alkaline phosphatase activity (Intahphuak et al. 2010; Zakaria et al. 2011). Clinical trial conducted by Evangelista et al. (2014) investigated the effects of topical application of VCO on SCORAD index values and skin capacitance. SCORAD signs included intensity and extent of eczema, itchiness and sleep loss. These signs are analysed since the extent of eczema correlated well with intensity and partially with itchiness and sleep loss. Results showed that the mean SCORAD indices reduced by 68.23% in patients using VCO, and 93% of the patients showed positive response towards the use of VCO in AD. VCO group also showed reduction in transdermal water loss (TEWL), from 26.68 to 7.09. With the increase in skin capacitance and reduction in TEWL, the skin will be less prone to noxious substances and development of AD can be avoided.

Coriander (*Coriandrum sativum*) One of the uses of coriander (Fig. 3) is to treat skin disorders (Rajeshwari and Andallu 2011). Linalool is the major composition in coriander oil, up to 60–75% of its composition (Reuter et al. 2008). Coriander oil is reported to possess antimicrobial activity towards *Streptococcus pyogenes* and *Staphylococcus aureus* and it comprises of good skin tolerability (Casetti et al. 2012). Linalool in coriander oil has been reported could reduce the carrageenin-induced edema in rats and exhibited anti-inflammatory activity (Reuter et al. 2008). Park et al. (2014) also reported that standardised coriander extract could inhibit dermatitis-skin and scratching behaviour. In the contact dermatitis induced mouse model, coriander is found to inhibit the T-helper-1 (Th1) and Th2-mediated cytokines and reduce the inflammatory mediators, including serum IgE, TNF- α , IFN- γ , IL-1, IL-4, and IL-13 levels (Park et al. 2014). AD is characterised by skin inflammation and superficial skin infections which may be triggered by the colonised *S. aureus*, hence the combination of anti-inflammatory, antibacterial properties and skin tolerability of coriander oil would offers an option in AD treatment.

Traditional Chinese medicines (TCM)

Use of TCM in dermatological disease treatment is a complex intervention as it uses formulation of combination of herbs

and each herb consists of numerous phytochemicals. Research on AD therapy using TCM has been reported more than 20 years ago by Sheehan et al. (1992). Patients who were subjected to traditional Chinese herbal therapy which consisted of standardised formulation of identified plant materials commented that at the end of the study, they itched less and have better sleep after the treatment. Authors claimed that the various properties and effects exhibited by plant materials i.e. anti-inflammatory, antimicrobial, immunosuppressive, and sedative could be responsible for the improved results (Sheehan et al. 1992). Besides, Chan and colleagues tested the inflammatory mediators suppressive action of PentaHerb formula (PHF), a formulation comprises of five species of traditional herbs of various botanical parts, and it is reported that PHF could inhibit the release of histamine and prostaglandin D₂. Authors also noticed that modulation of mast cells by PHF could suppress the allergen induced inflammation (both acute and chronic) and improve the clinical efficacy in AD treatment (Chan et al. 2008).

Studies have also reported that patients who are under TCM treatment have reduced the usage of corticosteroids. It was found that the children who are under TCM treatment has significantly reduced in corticosteroid usage (by 42%) compared to placebo group (increased by 34.5%) during the one-year follow up period (Chen et al. 2015). Decreased exposure to corticosteroids could also reduce their potential adverse effects, especially to young patients (infants and children). Schneider et al. (2016) recently reported a young patient with severe AD who responded poorly to topical steroids, oral and topical antibiotics, but his condition improved immediately and remarkably after preliminary treatment with TCM.

Literatures have reported that the side effect of TCM treatment is absent or minor and they subsided faster upon discontinuation of the treatment (Armstrong and Ernst 1999; Gu et al. 2013; Ho and Ong 2015; Tan et al. 2013). Hence, it is believed to be a safer alternative therapy to AD. To date, many controlled studies have reported the effectiveness of TCM in AD therapies (Armstrong and Ernst 1999; Bass III 2014; Chen et al. 2015; Cheng et al. 2011; Gu et al. 2017; Lin et al. 2014).

Complementary/adjunct therapies

Various complementary or adjunct therapies are being utilised as part of the therapies to AD.

Probiotic supplementation Supplementation with *Lactobacillus* strains probiotic bacterial products has recently been explored as a complementary therapy for AD. It is believed that supplementation with probiotics would improve the immunomodulatory properties of patients (Weston et al. 2005). Weston and colleagues investigated the effect probiotic supplementation in AD patients, and they reported that great improvement in SCORAD index is noticed in treated group, while no difference is noticed in placebo group at the end of treatment period. Other studies also showed similar findings where it is reported that supplementation can reduce the severity, alleviate the symptoms and decrease the SCORAD index of subjects (Foolad and Armstrong 2014; Kim et al. 2014; Niccoli et al. 2014). Studies suggested supplementation of probiotics during pregnancy and early infancy may act as a primary preventive measure against AD. This has also been extensively reported in meta-analysis studies by Lee et al. (2008), Pelucchi et al. (2012), Foolad et al. (2013) and Panduru et al. (2015). Rø and colleagues discovered recently that young children who are supplemented with maternal probiotics displayed a significant lower Th22 cells. This finding suggested that reduction in Th22 due to maternal probiotic supplementation is significantly related to AD in children. The explanation given is that early colonisation of beneficial gut microflora is essential for building up the immune system and maintain the Th cell balance (Gensollen et al. 2016; Rø et al. 2017).

Phototherapy Phototherapy, the therapeutic treatment using ultraviolet A (UVA) and ultraviolet B (UVB) has been used to treat AD. Use of phototherapy in AD was reported in 1948, first begun with the use of broadband ultraviolet light B (BBUVB) equipped with carbon arc lamps. Over the years, multiple types of phototherapy are reported to be effective towards AD, including BBUVB, Goeckerman regimen (i.e. coal tar and broadband UVB), narrow-band UVB, monochromatic excimer light, UVA-1 and combination of UVA/UVB (Fernández-Guarino et al. 2016; Rodenbeck et al. 2016). Phototherapy is served as the second-line treatment when skin condition failed to response to the first-line therapies, such as emollients, topical corticosteroids, and topical calcineurin inhibitors (Rodenbeck et al. 2016; Sidbury et al. 2014). Fernández-Guarino et al. (2016) proposed that phototherapy is effective against AD with the following justifications: (1) induces immunosuppressive responses such as apoptosis of inflammatory T-cells, (2) inhibition of Langerhans cells antigen-presenting function, (3) suppresses the production of type-1 cytokine, (4) inhibits the colonization of *S. aureus*

and *Pityrosporum orbiculare*, (5) improves the skin barrier function. Recent study conducted by Bogaczewicz and colleagues reported that patients who underwent phototherapy with UVA1 have significantly improved SCORAD index and pruritus, and increased in the expression of thymus and activation-regulated chemokine (TARC) and IL-4 (Bogaczewicz et al. 2015, 2016).

Acupuncture Acupuncture has been reported could reduce itch in AD. Lee and colleagues noticed there is a significant decrease in severity of AD and improvement in visual analogue scale (VAS), Investigator's Global Assessment (IGA) and Eczema Area and Severity Index (EASI) lichenification scores (Lee et al. 2011). Pfab et al. (2012) have performed the comparison of anti-itch effect of verum acupuncture with placebo, and the study demonstrated that it could significantly reduce the skin itchiness, in both histamine-induced itchiness and allergen itch in AD patients. There is study which uses acupuncture as an adjunctive treatment for AD. Salameh et al. (2008) performed a study on the use of Chinese herbal medicine and acupuncture in AD treatment for 12 weeks. It is noticed that tremendous improvement in Dermatology Life Quality Index (DLQI), EASI and VAS after the treatment. The mean DLQI, EASI and VAS have decreased from 12.5 to 7.6 (39.1% reduction), 4.99 to 1.81 (63.5% reduction), and 6.8 to 3.7 (44.7% reduction), respectively without significant adverse effects are reported at the end of the study (Salameh et al. 2008). The exact mechanism of acupuncture in treating AD by reduction in itch and skin response to allergen is still unknown. But Pfab et al. (2012) proposed that it may be related to the anti-inflammatory and inhibitory effect of itch related mediators.

Conclusion

Prevalence of AD showed significant increase in many countries including Asia. Flare of AD is characterized by increased of serum IgE level and it is usually trigger by various reasons, including genetically inheritance, climate, food allergens, and environmental. Inherited or acquired filaggrin deficiency has been described to essentially contribute to the pathogenesis of AD. Therefore, many therapies are discovered and made available to sooth the symptoms, including modern treatments, phytotherapeutics approaches and adjunct therapies. Examples of modern treatment used include topical therapies, such as moisturizers, emollients, topical corticosteroids, topical pimecrolimus and tacrolimus, antihistamines, and immunosuppressants. In addition, studies have reported that herbal treatments and TCM are also been used as complementary therapies, and scientific evidences have reported the positive outcomes of the treatments in AD

management. Examples discussed in the review including German chamomile, *Aloe vera*, coconut oil and coriander. Various complementary and adjunct therapies are also been used as part of the treatment options for AD, such as probiotic supplementation, phototherapy and acupuncture. Scientific findings of the treatments and therapeutic options have been critically reviewed.

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Compliance with Ethical Standards

Ethical Statement No ethical issue involved in this review.

Conflict of Interest The authors declare that they have no conflict of interests.

Declarations We declared that this manuscript, or parts thereof, has not been submitted or published elsewhere for publication.

Abbreviations AD, Atopic dermatitis; AZA, Azathioprine; BBUVB, Broadband ultraviolet light B; CsA, Cyclosporine A; DLQI, Dermatology Life Quality Index; EASI, Eczema Area and Severity Index; EPP, Ethyl phenylpropionate; FLG, filaggrin; IFN- γ , Interferon gamma; IGA, Investigator's Global Assessment; IgE, Immunoglobulin E; IL-1, Interleukin-1; IL-10, Interleukin-10; IL-13, Interleukin-13; IL-4, Interleukin-4; IL-4, Interleukin-4; IL-5, Interleukin-5; IL-6, Interleukin-6; IL-8, Interleukin-8; MTX, Methotrexate; NO₂, Nitrogen dioxide; PHF, PentaHerb formula; PUFA, Polyunsaturated fatty acids; SCORAD, Severity scoring of atopic dermatitis; TARC, Thymus and activation-regulated chemokine; TCM, Traditional Chinese medicines; TEWL, Transdermal water loss; Th-1, T-helper-1; Th-2, T-helper-2; Th22, T-helper 22; TNF- α , Tumor necrosis factor alpha; TSLP, Thymic stromal lymphopoietin; UV, Ultra-violet; UVA, Ultraviolet A; UVB, Ultraviolet B; VAS, Visual analogue scale; VCO, Virgin coconut oil

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