



The formulae and biologically active ingredients of Chinese herbal medicines for the treatment of atopic dermatitis

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ABSTRACT

Atopic dermatitis (AD) is a common relapsing inflammatory skin disease characterized by severe pruritus that seriously affects the quality of patients' life. There is an increasingly large amount of research demonstrating that traditional Chinese medicine (TCM) including herbal formulae and bioactive ingredients exerts pharmacological effects on atopic dermatitis. It has been a long history of TCM being used to treat atopic dermatitis, especially in preventing disease recurrence, maintaining long-term remission, and reducing disease burden. Nowadays, both of TCM monomer preparations and traditional formulae are still widely used. This review focuses on TCM as well as its bioactive ingredients for the treatment of AD, from the perspectives of animal model construction, pharmacodynamic mechanisms and clinical studies of formulae. To be more specific, the regulation and molecular mechanisms of the herbal formulae and bioactive ingredients of TCM are investigated, and the latest clinical research on TCM formulae is discussed. Furthermore, it provides a summary of the strengths and utilities of TCM, and will be useful for doctors who use Chinese medicine for treatment or researchers who select candidates for clinical treatments or further high-quality clinical studies.

1. Introduction

Atopic dermatitis (AD) is a chronic itchy, inflammatory skin dermatitis involving both children and adults which is extremely difficult to treat. It is one of the most common chronic skin diseases, affecting up to 25 % of children and 2–3 % of adults in most countries of the world [1]. Here, we consider atopic eczema to be synonymous with atopic dermatitis (AD).

AD is caused by the heredity of the individual, various environmental factors and stimulated by allergens leading to dysfunctions in aspects of skin barrier and immune system [2,3], which is accompanied by cytokine release by two main types of T lymphocytes (Fig. 1). Recently, it has been proposed that the pathogenesis of AD derives from a complex interplay of trinitarian factors: the skin barrier, allergy, and pruritus [4].

AD is categorised into extrinsic and intrinsic clinical phenotypes according to the presence or absence of allergen-specific IgE antibodies [5]. Extrinsic or allergic AD is typified by high total serum IgE

levels, as these IgE being specific for environmental and food allergens generates allergic bronchial asthma or allergic rhinoconjunctivitis in 70–80 % of AD patients [6]. In contrast, intrinsic or non-allergic AD is typified by normal IgE levels and the absence of specific IgEs; it does not give rise to respiratory symptoms, and patients have negative skin-prick test responses to common aeroallergens or food allergens [7,8]. However, the clinical features that indicate the severity of both AD types are not significantly different in children and adults [9].

Currently, the guidelines of care for the management of AD from the Journal of the American Academy of Dermatology comprise recommendations for the use of topical therapies such as emollients, antihistamines, calcineurin inhibitors, glucocorticoids, phototherapy, antimicrobials and antiseptics. It has also been noted that there is an increasing risk of infection, lymphoma, pruritus, and nonmelanoma skin cancer development in AD patients [10]. The absence of a cure for AD underscores the need for further research into treatments for this disease.

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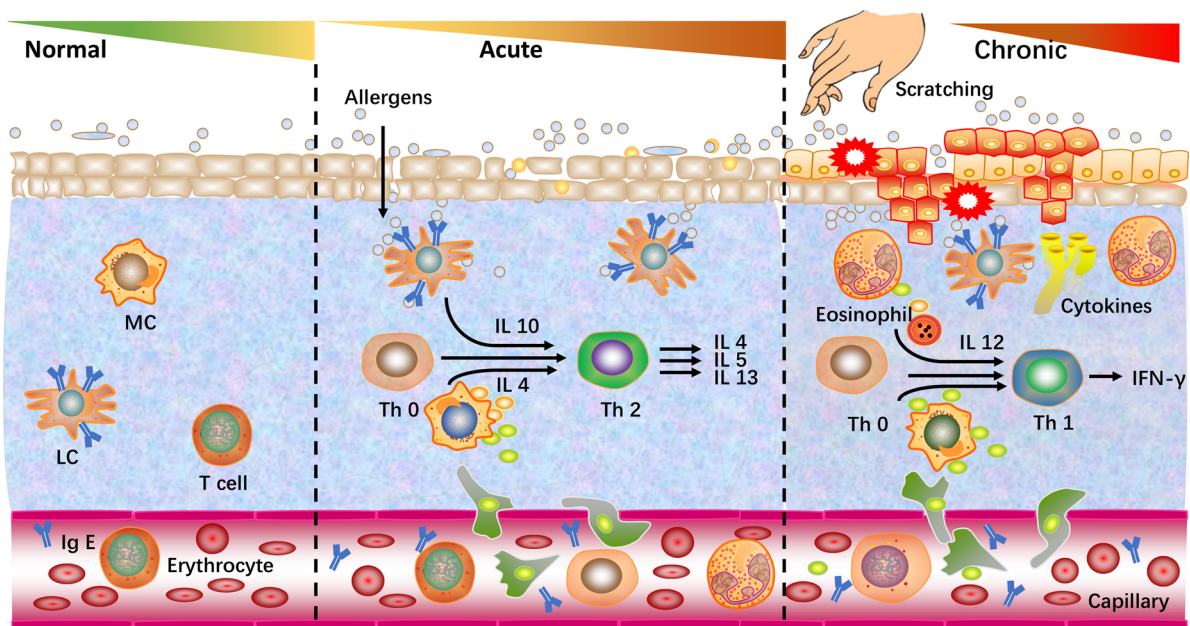


Fig. 1. Skin during the acute and chronic stages of immune cell migration and T-cell-mediated atopic dermatitis.

Traditional Chinese medicine (TCM) has been used in clinical practice for thousands of years, including for the routine management and treatment of AD [11]. Anti-inflammatory treatments that inhibit specific steps of the inflammatory cascade are a promising strategy for improving control of AD. Such agents, which include a variety of natural products used in TCM, have been the most extensively studied. However, due to the dearth of scientific evidence for clear and specific mechanisms of action for TCM in the treatment of AD, its widespread application is limited. This article thus reviews current and previous studies in the area, including those explore TCM treatment formulae and ingredients, to give a comprehensive summary of the biologically active ingredients in AD therapies. This will afford a new insight for further research into the utility of TCM for the treatment of AD *in vivo* and *in vitro*.

2. Pathogenesis of AD

AD is a chronic, pruritic, and inflammatory skin disease that commonly manifests as red, burning, dry, swollen and cracked skin. The pathogenesis of AD is a complex interplay of multiple contributing factors, such as skin barrier defects, infections, immunological factors (i.e., T helper cells, eosinophils, immunoglobulin E, cytokines, chemokines), susceptible genes (e.g., filaggrin genes) and environmental factors (e.g., food and aeroallergens, seasonal and climatic change) [11–13]. Moreover, the immune part of the process is dynamic, including innate and adaptive immunity via T cells, antibodies and immunoregulatory cytokines.

Specialised epithelial cells at the interface between the skin and the environment are considered to be the important first line of defence for the innate immune system. Cutaneous inflammation is another feature of AD, and is characterised by sequential and progressive patterns of mixed inflammatory cell infiltration in skin lesions, especially several effector T cell subsets, such as pro-inflammatory Th9, Th17 and Th22 cells [14,15]. Additionally, new techniques for identifying novel T-lymphocyte subsets, chemokines and cytokines have discovered many additional potential biomarkers that may be used to explore therapeutic

and diagnostic approaches for AD. Some examples of these potential biomarkers are the serum levels of chemokines, filaggrin, interleukins (IL)-12, -13, -16, -18, -25, -31, and -33, and thymus and activation-regulated chemokine (TARC) [16–23].

3. Experimental animal models to study of TCM treatments for AD

To date, a number of murine models of AD have been established, including transgenic mice, and other models including Nc/Nga, NOA, C57BL/6 and BALB/c mice [24–27]. These animal models display some of the typical histopathological features of AD and are useful in research, but the pathogenetic mechanisms of AD remain incompletely understood. What have been known is that the pathogenesis of AD is characterised by the infiltration of dermal macrophages and eosinophils, the participation of Langerhans cells and dendritic cells (DCs), the activation of T lymphocytes and the augment of mast cells [28]. The occurrence of AD is also related to genetic factors, food consumption and environmental factors. Basic AD therapy comprises topically increased hydration, with use of anti-inflammatories such as topical corticosteroids (TCS) and calcineurin inhibitors (TCI) which are recommended for exacerbation management, and more recently for proactive therapy in specific cases [29].

In recent years, many studies have shown that some TCMs and their active ingredients have important anti-inflammatory functions against multiple targets, on account of these long history of treating inflammatory diseases in China [30]. Due to their therapeutic effects and relatively low toxicity, a variety of compounds such as natural polysaccharides, polyphenol et al. have been widely used in the biomedical fields for AD treatment. Searches were therefore conducted on the PubMed database using the following search terms: ‘atopic dermatitis’, ‘atopic eczema’, ‘traditional Chinese medicine’, ‘herbal medicine’, ‘extract’, ‘isolate’, ‘Kampo medicine’ (the Japanese study of TCM), and ‘Korean medicine’. After screening the results, 90 studies of bioactive ingredients in Chinese herbal medicine and Chinese formula medicine were included for analysis.

4. Bioactive ingredients in a single Chinese herbal medicine for the treatment of AD

4.1. Effect on eosinophils, mast cells and cytokines involved in AD regulation

Linoleic acid and linolenic acid in coriander are demonstrated to protect human keratinocytes against H₂O₂-induced oxidative stress, and significantly reduce levels of the Th2-mediated inflammatory cytokines IgE, TNF- α , INF- γ , IL-1, IL-4, IL-13 [31]. There is also evidence for the efficacy of evening primrose oil, which is rich in γ -linolenic acid, in treating AD and blocking skin irritation may via counteracting inflammatory responses beyond the intestinal milieu [32]. Schizandrin, as a bioactive component of *Schizandra chinensis* Baill, is found to inhibit passive cutaneous anaphylaxis (PCA) and thus suppress the urge to scratch, perhaps through preventing mast cell degranulation and cytokine expressions such as TNF- α and IL-4 [33]. In addition, maximal blood concentrations of schizandrin occurs only 0.5 h after oral administration. Yang, J. H. reported that the extract of *Sanguisorbae Radix* (SR) can decrease the accumulation of eosinophils in mouse AD skin lesions; it can also reduce the level of IgE and the extent of mast cell infiltration indicated by determination of β -HEX, the hallmark of degranulation, which is suppressed in IgE/Ag-activated bone marrow mononuclear cells [34]. Cimifugin is the main component of Chinese medicine Fang Feng. In the initial stage of AD, cimifugin suppresses TSLP, IL-33 mRNA expression, reduces the infiltration of inflammatory cells, decreases the level of IL-4, IL-5, IL-13, and attenuates the junction deficiency between epithelial *in vivo* and *in vitro* (i.e., reduce gap separation or loosen connections) to decrease the susceptibility of epithelial cells to allergens. Furthermore, cimifugin treatment reduces levels of impaired proteins such as CLDN1, CLDN-1, and occludin, culminating in enhancing the penetration of low molecular compounds, such as FITC (approximately 389.4-Da) into cells [35]. HPLC analysis of extracts from *Coptidis rhizoma* and *Glycyrrhiza uralensis*, revealed that these contain four bioactive components – palmitine, berberine, liquiritin and liquiritigenin – which are found to: regulate Th2 differentiation (thus reducing the level of IL-4); maintain the lipid barrier (thereby increasing levels of the liver-X-receptor and decreasing PKC-positive reactions); decrease levels of degranulated mast cells (by inhibiting the production of substance P-positive nerve fibres and MMP-9); suppress the levels of TNF- α , p-I κ B, iNOS, and COX-2; and upregulate apoptosis (via increasing cleavage of caspase-3 and other pro-apoptotic molecules, and decreasing Bcl-2 positive reactions under high-fat diet conditions [36]. *Angelicae dahuricae Radix* (ADR) is used in Chinese and Korean medicine to counter the harmful effects of external insults. It is shown to inhibit the progression of AD by reducing infiltration of mast cells, inflammatory cells and CD4⁺ into sensitised lesions, decreasing the number of white blood cells (WBCs) in blood to suppress inflammatory responses, and suppressing the level and mRNA expression of IL-4, IL-6, IL-10, and TNF- α [37]. Alpinetin and cardamonin, two bioactive products extracted from *Alpinia katsumadai* Hayata, can decrease IgE and histamine levels *in vivo*, and also lower NO, PGE₂ production and suppress TARC and histamine *in vitro* [38]. Methanol extracts of *Rehmanniae Radix* can reduce the level of IgE, IL-2, IL-4, as well as the number of degranulated mast cells and CCR3⁺ eosinophils. Notably, topical application of hydrodistilled extracts has greater immunomodulatory effects than pharmacopuncture [39]. Ha et al. demonstrated that topical administration of an ethanol extract of *Luffa cylindrica* significantly reduced IgE levels and the production of plasma histamine. In addition, it inhibited the release of PGE₂, thus suppressing cyclooxygenase (COX) activity, and reduced not only the levels of AD-related chemokines (RANTES and TARC) but also the

amount of proinflammatory cytokines IL-4, IL-5 and IL-13 [40]. Chlorogenic acid and isochlorogenic acid A, as two biologically active components in *Artemisia capillaris* (AC), can inhibit NO and histamine production in LPS-stimulated RAW264.7 cells and PMA/A23187-stimulated MC/9 mast cells, respectively and reduce plasma levels of IgE and histamine by topical application [41]. *Alpinia intermedia* extracts have β -pinene as its primary constituent, which can significantly reduce the number of neurites that form on the surface of each cell, and inhibit mast cell degranulation as well as TSLP mRNA expression in skin tissues [42]. The crude polysaccharide extract of white wax scale (CWPS), which is insect exudate consisting of glucose, mannose and galactose, can significantly decrease levels of Th17 lymphocytes and suppress Th17 mRNA expression in skin lesions. Oral administration of CWPS in mice also inhibits mast cell accumulation and IL-6 mRNA expression in epidermal tissue [43]. Lee et al. confirmed that *Angelicae dahuricae* extracts suppressed the function of a chemoattractant (TARC) to regulate the recruitment of Th2-type cells into AD lesions, and therefore inhibited mRNA expression of inflammatory cytokines [44]. Ethanol extracts of the white mulberry *Morus alba* (MAE), which consist of flavonoids, alkaloids, glycosides, steroids, terpenoids, volatile oils and tannins, can decrease NO and PGE₂ production and suppress TARC levels in TI-stimulated HaCaT cells [45]. Naringin, the most prominent active compound in *Drynaria fortunei*, decreases serum levels of IgG1, IgE, IL-6, downregulates expression of the mRNA of IL-4, IL-6 and TNF- α in ear lesions, and consequently inhibits the infiltration of inflammatory cells into skin lesions [46].

4.2. Effect on chemokines and immunosuppressive involved in AD regulation

Gallic acid, one of the main biological actives in Cortex Moutan, is shown to have anti-tumorigenic and anti-allergic inflammatory effects, involving suppression in release of pro-inflammatory cytokine IL-6, chemokine CCL7 and CXCL8 [47]. Similarly, berberine, a biological active in Cortex Phellodendri, is shown to inhibit the release of IL-6, CXCL8, CCL2 and CCL7 (all $p < 0.05$) [47]. Topical application of a *Forsythia suspensa* extraction suppresses the expression of chemokines, cytokines and adhesion molecules in keratinocytes by inhibiting the production of TARC, MDC, RANTES, IL-4, VCAM-1 and ICAM-1, consequently prevents the migration and infiltration of leukocytes into lesions in a DfE-induced AD mouse model [48]. Caffeic acid, which can be extracted from *Ilex dentata* (ID), inhibits the expression of chemokines such as IL-8, MDC and TARC by blocking p38/ERK phosphorylation and NF- κ B activation, reduces the number of ICAM-1 and MMP-9 infiltration into keratinocytes. Moreover, water extracts of ID can reduce the levels of IgE and IL-1 β released in serum [49]. Extensive *in vivo* and *in vitro* experiments showed that oral administration of *Poria cocos* extracts had significant immunosuppressive effects via potentiating the generation and maintenance of functional Foxp3+CD4⁺ Tregs in an aryl hydrocarbon receptor (AhR)-dependent manner [50]. Valencene (VAL), which is isolated from *Cyperus rotundus*, can inhibit the loss of filaggrin to rescue the epidermal barrier. In addition, involucrin expression is also increased by topical application of VAL. Crucially, the expression of Th2 chemokines such as TARC/CCL17, MDC/CCL22, and proinflammatory chemokines such as CXCL8, GM-CSF and I-CAM is suppressed by blockade of the NF- κ B pathway [51].

4.3. Effect on signal transduction pathways involved in AD regulation

Capsiate, which is isolated from *Capsicum annuum* L., has inhibitory effects on IgE-mediated mast-cell activation and the protein kinase R (PKR)-like ER kinase (PERK) pathway, which results in suppression of

pro-inflammatory cytokine expression in activated bone marrow-derived mast cells. Capsiate also has anti-proliferative and anti-differential effects on CD4 + T-cells, leading to suppress cell differentiation mediated by Th1, Th2 and Th17 [52]. Choi et al. reported that treatment of AD with cultivated ginseng can significantly reduce levels of TARC in *in vitro* AD model by inhibiting TARC mRNA expression in TNF- α - and INF- γ -induced HaCat cells, which further inhibits the pro-activational binding of NF- κ B to target genes coding for inflammatory cytokines [53]. It is also revealed that *Pseudostellaria heterophylla* (PH) water extracts downregulates the expression of NF- κ B, p-I κ B α , and MAPK proteins in dorsal skin lesions; inhibits the expression of mRNAs of various cytokines such as INF- γ , IL-4, IL-8, IL-1 β , TNF- α ; and reduces the levels of IgE in serum and the number of mast cells as well as CD4 + infiltration into lesions [54]. Lee et al. isolated a novel glycolipoprotein fraction, gintonin, from *Panax ginseng*, which displayed strong inhibition of eosinophil and mast cell infiltration, and also inhibited microglial activation and proinflammatory cytokine production. Additionally, oral administration of gintonin not only decreased the level and activity of serum autotaxin (ATX), but also reduced the levels of IgE, histamine IL-4, and TNF- γ . Moreover, red ginseng extract (RGE) decreased ERK, JNK, p38 and NF- κ B activation via blockade of the MAPK/ NF- κ B pathway in keratinocytes and mast cells [55,56]. Compounds extracted from *Saussurea lappa* are demonstrated to markedly downregulate PI3K α and IL20R β expression and regulate the expression of genes related to cytokine-cytokine receptor interactions and JAK-STAT signalling by microarray analysis [57]. Tao et al. demonstrated that calycosin, a bioactive component of *Astragali Radix*, reduced the expression of TSLP/IL-33 mRNA as well as the release of TSLP/IL-33 itself, and protected epithelial tight junctions (TJs) by inhibiting the disruption of TJ protein (ZO-1 expression). In addition, calycosin significantly inhibited the expression of MyD88 and TAK1, which are key TLR4 adaptor proteins linking receptors to downstream kinases *in vitro* [58]. The ethanol extracts of *Artemisia argyi* (AAFE) ameliorate transforming growth factor- β 1 (TGF- β 1) immunoreactivity in ear tissue and reduce levels of IgE as well as histamine in serum in mouse model. Moreover, AAFE reduces the levels of IL-4, IL-6, INF- γ , and IL-1 β , and the expression of the mRNA of IL-4, IL-6, IL-13 and IL-1 β , and inhibit phosphorylation process of Lyn/Syk, MAPKs (ERK, JNK and p38), PI3K/Akt and I κ B α in DNCB-induced mouse model [59]. Ethanolic extracts (EAH) of *Artemisia apiacea* Hance, a traditional herbal medicine, are traditionally used for treating malaria, jaundice, and eczema through inhibiting RANTES, IL-6, IL-8, and TARC *in vivo* in a dose-dependent manner. Additionally, EAH can suppress the activation of p38, ERK, STAT-1 and the degradation of I κ B- α , and the translocation of inflammatory factors such as NF- κ B p65 in a HaCat cell model. Furthermore, EAH can regulate chemokine formation via inhibiting the activation of ERK and NF- κ B pathways [60]. Sur et al. used UPLC to detect 21 compounds from TCM *Polygala tenuifolia* Willd (PTW), which had the effects of restoring skin water content, countering inflammation, and inhibiting the increase of lymph node weight, which results in reducing IgE and histamine levels in serum. In addition, PTW can strongly inhibit degranulation in HMC-1 cells and subsequently suppress tryptase secretion and PKA activity, and selectively suppress MAPK phosphorylation via regulation of the PKA/p38 MAPK signalling pathway [61]. PG102, a water-soluble extract from *Actinidia arguta*, can decrease lymphocyte infiltration into inflamed tissue, and dampen the responses of inflammatory T cells, but elevate the expression level of Foxp3 and other Treg-related genes. Furthermore, oral administration of PG102 enhances the induction of CD4 + Foxp3 + Tregs from naïve CD4 + CD62L + T cells, probably via inhibition of mTOR activation and STAT5 phosphorylation rather than via interacting with the TGF- β signalling pathway [62]. Some more mechanisms of bioactive ingredients in TCMs are described in Table 1.

5. Bioactive ingredients in traditional formulae for the treatment of AD

The effects of biologically active constituents in TCM formulae are more comprehensive compared with the effects of monomer in TCMs, and therefore the mechanisms of TCM formulae are more complex and harder to elucidate. A retrospective study revealed that the most frequently prescribed herbal formula and single herb extract for AD patients in Taiwan from 2002 to 2011 were Xiao-Feng-San (Eliminate Wind Powder) (16.98 %) and Bai-Xian-Pi (Cortex Dictamnii) (12.68 %), respectively. The most commonly used therapeutic principles of herbal formulae and single herbs were ‘releasing exterior’ (20.23 %) and ‘clearing heat’ (41.93 %), respectively [63]. According to TCM, AD patients are congenitally weak in physique, rendering them susceptible to both external and internal pathogenic factors such as wind, cold, heat and dampness. The ‘relapsed and chronic’ characteristic is believed to injure the yin and blood, so as to generate dryness [64].

5.1. Effect on eosinophils, mast cells, cytokines and chemokines involved in AD regulation

The Pentaherbs formula, comprising five traditional Chinese herbal medicines, has been shown to have effects against *Staphylococcus aureus* ATCC 25923 and methicillin-resistant *Staphylococcus aureus* (MRSA) ATCC BAA-43 t [65]. An oxazolone (OXA)-mediated AD-like dermatitis murine model was established to elucidate the efficacy of Pentaherbs against AD. The five herbal extracts in Pentaherbs are Flos Lonicerae, Herba Menthae, Cortex Moutan, Rhizoma Atractylodis, and Cortex Phellodendri, in a ratio of 2:1:2:2:2. Oral administration of Pentaherbs can relieve OXA-induced ear redness, alleviate ear swelling, reduce epidermal thickening, and significantly reduce the infiltration of eosinophils as well as levels of AD-related cytokines and chemokines [47]. Deoxyshikonin is the main bioactive composition of Shiunko ointment, and is found to be very effective at removing necrotic tissue and regenerating damaged epithelial tissue by increasing the expression of VEGFR2 and phosphorylation of Akt and p38 [66]. Makino et al. [67] found that *Ophiopogon tuber* and *Schisandra* fruit suppress the increase of serum total immunoglobulin E (IgE) and antigen-specific IgG1 in NC/Jic mouse model stimulated by Df-antigen, which culminates in lower levels of lesional IL-1 α and tumour necrosis factor- α (TNF- α) mRNA than those in the control group. This suggests that these substances contain compounds that inhibit AD-like symptoms by correcting the Th2-skewed Th1/Th2 imbalance. Zhou et al. reported that Sanpao herbs reduced the level of IgE in serum and suppressed the development of AD-like lesions in mice model [68]. Similarly, Yoku-kansankachimpinhang, a Korean formula consisting of *Atractylodes*, *Angelica dahurica* root, *Bupleurum* root, *Citrus unshiu* peel, *Cnidium* rhizome, *Glycyrrhiza*, *Poria sclerotium*, *Pinellia* tuber and *Uncaria* hook, helps attenuate chronic pruritus in AD and is shown to have potent inhibitory effects against neurite growth *in vivo and vitro* [69]. “KM110329” is a mixture of four herbal medicines: *Houttuynia cordata*; *Rehmannia glutinosa*; *Prunus yedoensis*; *Rubus coreanus* at the ratio of 1:1:1:1. Topical application of KM110329 significantly decreases the eosinophil cell count in blood, lowers the number of mast cell, and inhibits inflammatory cell infiltration into dermal tissue. Beyond that, KM110329 ethanol extracts suppresses IL-4, IL-13, IL-17 mRNA expression and reduces levels of inflammatory cytokines such as TNF- α , IL-6 and IL-8, as confirmed by ELISA and RT-PCR analyses [70]. A Chinese decoction named Qingre-Qushi (QRQS) has specific inhibitory effects on IgE, IgG, IgG1, and IgG2a antibodies, and significantly downregulates IL-33 mRNA expression via suppressing IL-33/ST2 transduction [71].

Table 1
Bioactive molecules in traditional medicines described in the text and their observed mechanisms of activity.

Bioactive molecule	Molecular formula	Origin	Observed activity	Murine model	Author/Year
alantolactone	$C_{15}H_{20}O_2$	<i>Saussurea lappa</i>	Remarkably downregulate PI3K α and IL20R β expression; regulate the expression of genes related to cytokine-cytokine receptor interactions and JAK-STAT signalling	Biostr-AD-induced male Nc/Nga mice	Lim et al. [57] 2015
caryophyllene	$C_{15}H_{24}$				
costic acid	$C_{15}H_{22}O_2$				
costunolide	$C_{15}H_{20}O_2$				
dehydrocostus lactone	$C_{15}H_{18}O_2$	<i>Inula helenium</i> L.			
alantolactone	$C_{15}H_{20}O_2$	<i>Alpinia katsumadai</i> Hayata	Significantly reduce the elevated levels of IgE, INF- γ , and TNF- α in serum and inhibit mRNA expression of IL-4, IL-5, IL-13 in skin lesions	DNCB-induced female ICR mice	Wang et al. [86] 2018
isolanolactone	$C_{15}H_{20}O_2$		Decrease NO and PGE2 production in LPS-stimulated RAW 264.7 cells;	<i>D. farinosa</i> -induced	Lim et al. [38] 2012
alpinetin	$C_{16}H_{14}O_4$		inhibit TARC in HaCaT cells, and levels of histamine in HMC-1 cells;	Nc/Nga mice;	
cardamonin	$C_{16}H_{14}O_4$		lower IgE and histamine levels in mice serum		
trans-anethole	$C_{10}H_{12}O$	<i>Illicium verum</i> Hook. F.	Markedly reduce the serum level of IgE, histamine, IL-6 and ICAM-1; decrease expression of IL-4, IL-6, TNF- α , TARC, RANTES, ICAM-1, and VCAM-1, but not IFN- γ .	<i>D. farinosa</i> -induced Nc/Nga mice;	Sung et al. [87] 2012
apigenin	$C_{15}H_{10}O_5$	<i>Spirodela polyrhiza</i>	Decrease the infiltration of mast cells; reduce plasma IgE levels, and decrease the secretion of cytokines such as IL-4, IL-6, and TNF- α ; inhibit the expression of pro-inflammatory mediators (NF- κ B, phosphor-I κ B- α , MAPKs)	DNCB-induced 7-week-old female BALB/c mice	Lee et al. [88] 2016
luteolin	$C_{15}H_{10}O_6$				
artemisinin	$C_{15}H_{22}O_5$	<i>Artemisia apiacea</i>	Inhibit RANTES, IL-6, IL-8, and TARC; suppress the activation of p38, ERK, STAT-1, degradation of I κ B- α , and translocation of inflammatory factors NF- κ B p65, as well as activation of ERK and NF- κ B pathways	DNCB-induced 5-week-old Male BALB/c mice	Yang et al. [60] 2018
ethanolic extracts					
berberine	$C_{20}H_{18}NO_4$ +	<i>Cortex phellodendri</i>	Inhibit the release of IL-6, CXCL8, CCL2 and CCL17	OXA-induced adult female BALB/c mice	Tsang et al. [47] 2015
bryonolic acid	$C_{30}H_{48}O_3$	<i>Luffa cylindrica</i>	Inhibit the release of PDE2; reduce plasma IgE levels and histamine production; decrease the levels of AD-related chemokines (RANTES and TARC) and cytokines (IL-4, IL-5, IL-13)	<i>D. farinosa</i> -induced 8-week male Nc/Nga mice	Ha et al. [40] 2015
echinocystic acid	$C_{30}H_{48}O_4$				
oleanolic acid	$C_{30}H_{48}O_3$	<i>Angelicae dahuricae</i> Radix	Inhibit histamine and IgE levels in plasma; suppress NO production in LPS-treated RAW 264.7 cells and TARC in TNF- α /IFN- γ -treated HaCaT cells	<i>D. farinosa</i> -induced Nc/Nga mice	Lee et al. [44] 2011
byakangelicin	$C_{17}H_{18}O_7$				
imperatorin	$C_{16}H_{14}O_4$				
isoperatorin	$C_{16}H_{14}O_4$				
nodakenin	$C_{20}H_{20}O_9$				
oxypeucedanin	$C_{16}H_{14}O_5$				
oxypeucedanin hydrate	$C_{16}H_{16}O_6$				
caffeic acid	$C_9H_8O_4$	<i>Ilexis dentata</i>	Reduce the level of IgE and IL-1 β in serum; suppress the expression of IL-8, TARC, MDC, ICAM-1 and MMP-9; decrease TNF- α and IL-8 levels in mast cells	DNFB-induced BALB/c mice	Jeon et al. [49] 2015
caffeic acid	$C_9H_8O_4$	<i>Salvia plebeia</i>	Decrease IgE and IgG2a levels; inhibit inflammatory infiltration into skin lesions and histamine in serum; suppress Th1/Th2/Th17 phenotype CD4 $^{+}$ T lymphocytes expansion in lymph node; inhibit the expression of Th1/Th2/Th17 cytokines in lesional tissue; downregulate NF- κ B and STAT1	DfE/DNCB induced 6-week-old female BALB/c mice	Choi et al. [89] 2014
homoplantagin	$C_{22}H_{22}O_{11}$				
luteolin	$C_{15}H_{10}O_6$				
luteolin-7-glucoside	$C_{21}H_{20}O_{11}$				
calycosin	$C_{16}H_{12}O_5$	<i>Astragali Radix</i>	Markedly inhibit TSLP and IL-33 mRNA expression; inhibit the disruption of ZO-1 to protect tight junctions; inhibit the LPS-induced phosphorylation of NF- κ B and IKB- α	FITC-induced BALB/c mice	Tao et al. [58] 2017
campesterol	$C_{28}H_{48}O$	<i>Rehmanniae radix</i>	Methanol extraction decrease the number of mast cells, CCR3 $^{+}$ eosinophils immunoreactions, and IgE, IL-2, IL-4 levels by pharmacopuncture	<i>D. farinosa</i> -induced Nc/Nga mice	Kim et al. [39] 2013
stigmasterol	$C_{29}H_{48}O$				
β -sitosterol	$C_{29}H_{50}O$				
Capsiate	$C_{18}H_{26}O_4$	<i>Capsicum annuum</i> L.	Decrease the number of mast cells, CD4 $^{+}$ T cells, eosinophil, IgE levels, IL-4, TSLP, and suppress the gene expression of CCL11, CCL17, and CCL12	DNFB-treated Nc/Nga mice	Lee et al. [52] 2015
catalposide	$C_{22}H_{26}O_{12}$	<i>Catalpa ovata</i>	Markedly reduce the levels of IgE in serum; significantly inhibit Th2 cytokines IL-4, IL-5, IL-13, Th2 chemokine TARC and pro-Th2 cytokine TSLP, as well as pro-inflammatory cytokines IL-1 β , IL-6 and TNF- α	DfE-induced 4-week-old Nc/Nga male mice	Yang et al. [90] 2013
(COE) ointment					
cimifugin	$C_{16}H_{16}O_6$	<i>Saposhnikovia divaricata</i>	Inhibit the expression of TSLP, IL-33 mRNA; decrease the level of IL-4, IL-5, IL-13; restore TJs such as CLDN1, CLDN1-1, and occludin	0.6 % FITC- treated BALB/c mice	Wang et al. [35] 2017

(continued on next page)

Table 1 (continued)

Bioactive molecule	Molecular formula	Origin	Observed activity	Murine model	Author/Year
chlorogenic acid	$C_{16}H_{18}O_9$	<i>Artemisia capillaris</i>	Inhibit both NO and histamine;	<i>D. farina</i> -sensitised	Ha et al. [41]
isochlorogenic acid a	$C_{25}H_{24}O_{12}$		Reduce plasma IgE and histamine levels	8-week-old male Nc/Nga mice	2014
chrysophanol	$C_{15}H_{10}O_4$	<i>Rumex crispus</i> and <i>Cordyceps militaris</i>	Reduce inflammatory cell infiltration into skin lesions; significantly reduce the levels of histamine, IgE, TSLP, IL-4, IL-6, and TNF- α in serum; markedly inhibit the levels of TSLP, ICAM-1, MIP-2 protein expression; significantly suppress the expression as well as the activities of caspase-1	DNFB-induced female BALB/c mice	Han et al. [91]
AST2017-01	—				2018
cordycepin acid;	—	<i>Cordyceps</i>	Inhibit the release of histamine, secretion of IL-4, INF- γ , and production of IgE;	DNFB-treated 6-week-old male Nc/Nga mice	Wu et al. [92]
3'-amino-3'-deoxyadenosine; homocitrullyl			However, did not directly inhibit the progress of degranulation		2011
aminoadenosine; ophiocordin;					
ergostrol;					
cordyheptaepptide					
crocin	$C_{44}H_{64}O_{24}$	<i>Gardenia jasminoides</i>	Inhibit the increase of thymus activity, and the activation of IL-4, IL-13; suppress the activation of NF- κ B and STAT6 by blocking of NF- κ B/STAT6 signalling pathways	<i>D. farina</i> -sensitised 6-week-old male Nc/Nga mice	Sung et al. [93]
					2018
cupressuflavone	$C_{30}H_{18}O_{10}$	<i>Juniperus rigida</i>	Accelerat recovery of the function of the skin barrier; inhibit the overproduction of serum IgE and IL-4; potently downregulate IL-4 expression and β -hexosaminidase release	OXA/DNCB-induced BALB/c mice	Lee et al. [94]
isocutellarein-7-O- β -xylopyranoside	—				2018
daidzein	$C_{15}H_{10}O_4$	<i>Glycine max</i> Merr.	Significantly reduce the levels of PKC and IL-4, which contribute to decreased levels of inflammatory factors such as substance P, inducible iNOS and MMP-9; downregulate IL-12, TNF- α , IL-4 and p-I κ B levels	Df-induced Nc/Nga mice	Jung et al. [95]
genistein	$C_{15}H_{10}O_5$		Reduce the level of cytokines such as IL-4, IL-6, TNF- α , INF- γ , and plasma IgE; suppress the expression of NF- κ B, phospho-I κ B α , and phospho-MAPKs (ERK, p38, and JNK) in skin lesions	DNCB-induced 5-week-old female BALB/c mice	Lee et al. [96]
decursin	$C_{19}H_{20}O_5$	<i>Angelica sinensis</i>	Significantly increase aryl hydrocarbon receptor (AhR) expression; stabilise the expression of <i>foxp3</i>		2015
ergosterol	$C_{28}H_{44}O$	<i>Portia cocos</i>	Reduce the levels of TNF- α , IgE in serum, and suppress the levels of histamine and the mast cell count, as well as cut down the expression levels of proteins such as TARC, MDC, RANTES, IL-4, VCAM-1 and ICAM-1 in skin lesions	DNCB and <i>D. farina</i> -induced Four-week-old female BALB/c mice	Bae et al. [50]
triterpenoid compounds	$C_{29}H_{36}O_{15}$	<i>Forsythia suspensa</i> fruits		DfE-induced Nc/Nga mice	2016
forsythiaside	$C_{27}H_{34}O_{11}$				Sung et al. [48]
phyllyrin	$C_{21}H_{24}O_6$				2016
pinoselin	$C_{30}H_{22}O_6$				
gallic acid	$C_7H_6O_5$	Cortex Moutan	Suppress the release of pro-inflammatory cytokine IL-6, chemokine CCL7 and CCL8	OXA-induced adult female BALB/c mice	Tsang et al. [47]
geniposide	$C_{17}H_{24}O_{10}$	<i>Gardenia jasminoides</i>	Significantly reduce the levels of IgE, histamine, and the degranulation of mast cells; downregulate expression of IL-4, IL-6, TNF- α , and INF- γ mRNA in skin lesions	<i>D. farina</i> -induced Nc/Nga mice	Sung et al. [97]
					2014
ginsenosideRh2	$C_{55}H_{92}O_8$	<i>Panax ginseng</i>	Increase flaggrin protein levels; inhibit the mRNA expression of TARC and both IL-4 and IL-10 in splenocytes; reduce IgE, IL-10 and IL-4 levels in serum; decrease the expression of IL-6, TSLP, TARC, TNF- α mRNA; suppress MAPKs (ERK1/2, JNKs, and p38MAPK) signalling pathways, which further inhibit Ikatos transcriptional activity	DNCB-induced Nc/Nga mice	Choi et al.
ginsenoside Rg3	$C_{42}H_{72}O_{13}$				Park et al.
					[53] [98,99]
					2013, 2019
gintonin	—	<i>Panax ginseng</i>	Inhibit microglial activation and reduce the levels of proinflammatory cytokines; decrease the level of IgE, histamine, IL-4, INF- γ in serum; reduce the levels and activity of ATX	DNFB-induced Nc/Nga mice	Lee et al. [55]
					2017
indirubin	$C_{16}H_{10}N_2O_2$	<i>Polygonum tinctorium</i>	Potently inhibit TSLP via blockage of caspase-1/receptor-interacting protein 2; reduce the levels of TSLP, IL-4, IL-6, and caspase-1 in skin lesions; significantly decrease serum IgE and histamine levels	DNFB-induced 6-week-old male Nc/Nga mice	Han et al. [100]
					2014
indirubin	$C_{16}H_{10}N_2O_2$	<i>Polygonum tinctorium</i>	Significantly reduce IgE and IL-4 levels in serum; suppress the expression of mast cells-derived caspase-1 by oral administration; inhibit the production and mRNA expression of TSLP by blockage of caspase-1 signalling pathway in activated HMC-1 cells	DNFB-induced Nc/Nga	Han et al. [101]
kaempferol	$C_{15}H_{10}O_6$				2014
tryptanthrin	$C_{15}H_8N_2O_2$				

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Table 1 (continued)

Bioactive molecule	Molecular formula	Origin	Observed activity	Murine model	Author/Year
lancerin	$C_{19}H_{18}O_{10}$	<i>Polygala tenuifolia</i> Willd (PTW)	Restore skin water content, reduce inflammation, and lymph node weight; reduce IgE and histamine levels in serum; markedly inhibit the degranulation of HMC-1 cells, tryptase secretion, and PKA activity; selectively suppress MAPK phosphorylation	Trimellitic anhydride (TMA) + immobilisation (IMO) stress-exacerbated 12-week-old BALB/c mice	Sur et al. [61] 2017
sibiricoses A1, A5, A6	$C_{28}H_{28}O_{15}$				
polygalaxanthones III, XXXII	$C_{33}H_{38}O_{17}$				
tenuifolioside A	$C_{35}H_{44}O_{19}$				
tenuifolioside C	–				
tenuifolioses M, S, T, E, J, I, B, D, A	–				
onjisaponins Sg, Ng, V, O, J	–				
sengin III	–				
liquiritigenin	$C_{15}H_{12}O_4$	<i>Coptidis Rhizoma</i> and <i>Glycyrrhiza uralensis</i>	reduce the level of IL-4; increase the levels of liver-X-receptor and decrease PKC-positive reactions; inhibit the production of Substance P, positive fibres and MMP-9; reduce the level of TNF- α , p-IkB, iNOS, and COX-2; increase the of cleavage caspase-3 and other pro-apoptotic proteins, and decrease Bcl-2 positive reactions	DNFB-induced Nc/Nga mice	Cha et al. [36] 2016
liquiritin	$C_{23}H_{22}O_9$				
palmatine	$C_{23}H_{22}NO_4+$				
linolenic acid	$C_{18}H_{30}O_2$	<i>Coriandrum sativum</i> L.	Significantly reduce the levels of Th-1 and Th2-mediated inflammatory cytokines such as IgE, TNF- α , INF- γ , IL-1, IL-4, IL-13	DNCB-induced Male ICR mice	Park et al. [31] 2014
linoleic acid	$C_{18}H_{32}O_2$				
momordin Ic	$C_{41}H_{64}O_{13}$	<i>Kochia scoparia</i>	Significantly reduce the mRNA expression levels of pro-inflammatory cytokines such as IL-1 β , TNF- α ; inhibit the expression of NF- κ B and MAPKs(ERK1/2, p38, and JNK)	DNCB-induced 7-week-old female BALB/c mice	Choi et al. [102] 2014
naringin	$C_{27}H_{32}O_{14}$	<i>Drymaria fortunei</i>	Decrease the serum levels of IgG1, IgE, IL-6; downregulate the expression of IL-4, IL-6 mRNA, and TNF- α levels in ear lesions	<i>D. farinosa</i> -induced Nc/Nga mice	Sung et al. 2012 [46]
oregonin	$C_{24}H_{30}O_{10}$	<i>Alnus japonica</i>	Decrease the eosinophil count in blood; reduce the levels of IgE and Th2-related cytokines in serum; lower IL-4, IL-5, IL-13 levels in skin lesions	Biostrir AD-induced 5-week-old female Nc/Nga mice	Choi et al. [103] 2011
polysaccharide	$(C_6H_{10}O_5)_n$	<i>Eriocerus pela</i>	Decrease IgE levels in serum and limit mast cell and eosinophil infiltration into dermal tissue; inhibit Th1, Th17 activation, and some cytokine (IL-17A, INF- γ , IL-6) mRNA expression	DNCB-induced BALB/c mice	Lin et al. [43] 2017
quercetin	$C_{15}H_{10}O_7$	<i>Dendrobium tosaense</i>	Upregulate INF- γ production, downregulate IL-4 production; inhibit IgE or IgG over-production; reduce the degranulation of mast cells	OVA/TNCB- induced female BALB/c mice	Wu et al. [104] 2013
rutin	$C_{27}H_{30}O_{16}$	<i>Broussonetia kazinoki</i>	Decrease mast cells infiltration into skin lesions; reduce plasma IgE and IL-4; suppress TARC production in TNF- α /IFN- γ -treated HaCat cells; lower IL-4, IL-5, IL-13 expression; inhibit the production of TARC, MDC, and RANTES	<i>D. farinosa</i> -induced Nc/Nga mice	Lee et al. [105,106] 2014
valencene	$C_{15}H_{24}$	<i>Cyperus rotundus</i> L.	Rescue the loss of flaggrin as well as involucrin; reduce the levels of IgE, IL-1 β , IL-6, IL-13 in skin tissue; inhibit TARC/CCL17, MDC/CCL22, and CXCL8, GM-CSF and I-CAM	DNCB-induced Nc/Nga mice	Yang et al. [51] 2016
ziyuglycoside I	$C_{41}H_{66}O_{13}$	<i>Sanguisorba officinalis</i> L.	Suppress the accumulation of eosinophils; significantly reduce the level of IgE; potentially cut down β -HEX release	DNCB-induced BALB/c mice	Yang et al. [34] 2016
β -pinene	$C_{10}H_{16}$	<i>Alpinia intermedia</i>	Inhibit mast cell degranulation and TLSP mRNA expression; significantly reduce the number of neurites	house dust-mite-induced NC/Tnd mice	Amagai et al. [42] 2017
1,6-O,O-diacetylbritannilactone	$C_{19}H_{26}O_6$	<i>Inula japonica</i>	Attenuate airway hyper-responsiveness and plasma IgE levels; reduce leukotriene C ₄ production; suppress phosphorylation of cytosolic phospholipase A ₂ , as well as that of phospholipase C and γ -mediated Ca ²⁺ influx	OVA-induced 6-week-old female BALB/c mice	Jin et al. [107] 2017
Artemisia argyi Folium (AAFE) ethanol extract	–	<i>Artemisia argyi</i>	ameliorate transforming growth factor- β 1 (TGF- β 1) immunoreactivity in ear tissue; reduce IgE and histamine levels in serum; reduce the level of IL-4, IL-6, INF- γ , and IL-1 β , as well as the expression of IL-4, IL-6, IL-13 and IL-1 β mRNA; inhibit phosphorylation of Lyn/Syk, MAPKs (ERK, JNK and p38), PI3K/Akt and IkB α	DNCB-induced BALB/c mice	Han et al. [59] 2016

(continued on next page)

Table 1 (continued)

Bioactive molecule	Molecular formula	Origin	Observed activity	Murine model	Author/Year
ADR water extracts	—	<i>Angelicae dahuricae</i> Radix	Decrease the infiltration of inflammatory cells, mast cells, and CD4 + cells into sensitised lesions; reduce the levels of IgE, IL-4, IL-6, IL-10, IL-12 as well as the expression of IL-4, IL-6, TNF- α mRNA; lower the WBC in blood	DNCB-induced BALB/c mice	Ku et al. [37] 2017
AS (Bu-OH) butanol extract	—	<i>Artemisia scoparia</i>	Significantly inhibit serum levels of histamine, IgE, TSLP, IL-4, IL-6, and expression levels of TSLP, IL-4, IL-6 and TNF- α mRNA in skin lesions; markedly suppress the activities of caspase-1	DNFB-induced BALB/c mice	Ryu et al. [108] 2018
AXE water extract	—	<i>Amomum xanthioides</i>	Selectively reduce IgE, IgG2a and histamine levels in serum, and reduce the expression of TNF- α , INF- γ , IL-4, IL-13, IL-31 and IL-17A mRNA; downregulate the gene expression of TNF- α , IL-1 β , IL-6, IL-8, CCL-17 and CCL22	Df + DNCB-induced BALB/c mice	Choi et al. [109] 2017
CA water extract	—	<i>Cynanchum atratum</i>	Ameliorate total serum IgE levels; significantly reduce mast cell infiltration and pro-inflammatory cytokines levels (IL-6, IL-1 β , TNF- α , IL-4); decrease the expression of NF- κ B, phospho-I κ Ba and MAP kinase	DNCB-induced 6-week-old female BALB/c mice	Choi et al. [110] 2017
CCE ethanolic extracts	—	<i>Cinnamomum cassia</i>	Reduce the levels of serum IgE, histamine, and TNF- α ; suppress the expression of IL-4, TNF- α , and TARC mRNA in lesions	8-week-old male Nc/Nga mice	Sung et al. [111] 2011
dibenzocyclooctadiene-type lignans	—	<i>Schizandra chinensis</i>	Suppress passive cutaneous anaphylaxis (PCA) and itching; inhibit TNF- α and IL-4 protein expression and mRNA expression	Anti-DNP-induced male ICR mice	Lee et al. [33] 2007
ginsenosides KRG water extract	—	<i>Panax ginseng</i>	Decrease the levels of TNF- α , IFN- γ and substance P; reduce the infiltration of FOXP3+ regulatory T (Treg) cells and CD1a + Langerhans cells into lesions; lower IgE levels in serum; decrease lymphocyte infiltration; oral administration significantly suppress protein expression of TSLP and TNF- α , as well as TSLP mRNA expression in lesions	TNCB-induced 8-week-old female Nc/Nga mice	Lee et al. [112,113] 2011, 2013
maesil (fermented with <i>Saccharomyces cerevisiae</i>)	—	<i>Prunus mume</i>	Significantly reduce the eosinophil ratio and IgE levels in serum; decrease the number of <i>Staphylococcus aureus</i> recovered from skin tissue; downregulate the expression of IL-4, INF- γ , and TNF- α mRNA; increase the concentration of IL-10 and concurrently decrease IL-4 concentrations in serum	DNCB-induced 6-week-old female Nc/Nga mice	Jung et al. [114] 2010
<i>Morus alba</i> (MAE) ethanol extracts	—	<i>Morus alba</i> L.	Decrease NO and PGE ₂ production; suppress TARC levels in TI-stimulated HaCaT cells; lower IgE and histamine levels in skin tissue	Biostr-AD induced Nc/Nga mice	Lim et al. [45] 2014
NGE water extracts	—	<i>Cervus nippon</i>	Reduce the infiltration of inflammatory cells, mast cells and CD4 + T cells into skin lesions; downregulate the mRNA expression of inflammatory cytokines such as IL-4, IL-6, IL-10, IL-12, and TNF- α ; reduce serum IgE concentrations	DNCB-induced 6-week-old male BALB/c mice	Hong et al. [115] 2018
PG102 water extracts	—	<i>Actinidia arguta</i>	Decrease lymphocyte infiltration into inflamed tissue; decrease the responses of inflammatory T cells and elevate the expression level of Foxp3 and other Treg-related genes; enhance the induction of CD4 + Foxp3+ Tregs from naïve CD4 + CD62L + T cells	DNCB/DFE-induced 4-week-old female BALB/c mice	Bae et al. [62] 2016
PH water extracts	—	<i>Pseudostellaria heterophylla</i>	Suppress the levels of mast cells, IgE and CD4+ expression; inhibit the mRNA expression of INF- γ , IL-4, IL-8, IL-1 β , TNF- α ; downregulate NF- κ B, p-I κ Ba, and MAPKs in lesions	DNCB-induced BALB/c mice	Choi et al. [54] 2017
SCE water extract	—	<i>Schizandra chinensis</i>	Inhibit the levels of IgE, IgM, and histamine in serum; reduce mast cell infiltration into skin lesions; reduce histamine receptor (H1R, H3R, H4R) mRNA expression, the splenic expression of IL-4, IL-5, and the level of high-affinity IgE receptor B protein (Fc ϵ R1).	DNCB-induced 6-week-old male Nc/Nga mice	Kang et al. [116] 2012
<i>S. lappa</i> methanolic extract	—	<i>Saussurea lappa</i>	Significantly downregulate the mRNA expression of inflammatory chemokines and cytokines such as TARC, MDC, RANTES, IL-8, and reduce histamine, IgE, and TARC levels in serum	Biostr-AD-induced Nc/Nga mice	Lim et al. [117] 2014
TF ethanolic extract	—	<i>Tribulus terrestris</i>	Inhibit mast cell degradation and inflammatory cell infiltration; reduce TEWL; significantly suppress Orai-1 activation and the induction of TRPV3 activation.	Oxazolone-induced SKH-1 hairless mice	Kang et al. [118] 2017

(continued on next page)

Table 1 (continued)

Bioactive molecule	Molecular formula	Origin	Observed activity	Murine model	Author/Year
7, 8, 4'-trihydroxyisoflavone	-	soybeans	Decrease the count of eosinophils and suppress mast cell infiltration into skin lesions as well as the levels of TARC chemokines; significantly reduce TEWL; lower the levels of IL-4, IL-5, IL-13, IL-12, INF- γ	DNCB-induced Nc/Nga mice	Kim et al. [119] 2014

TNF- α : tumour necrosis factor- α ; PERK: extracellular signal-regulated kinase pathway; PCA: passive cutaneous anaphylaxis; MDC: macrophage-derived chemokine; (ICAM): intercellular adhesion molecule; RANTES: Regulated upon activation normal T cell expressed and secreted; VCAM-1: vascular cell adhesion molecule-1; NF- κ B: nuclear factor kappa-B; MAPK: mitogen-activated protein kinase; MMP-9: matrix metalloprotein-9; ERK: extracellular regulated protein kinases; JNK: c-Jun N-terminal kinase; Fc ϵ RI: high-affinity IgE receptor; TEWL: transepidermal water-loss; TARC: Thymus- and activation-regulated chemokine; p-I κ B α : phospho-inhibitory subunit of NF κ B α .

5.2. Effect on chemokines and immunosuppressive involved in AD regulation

A novel herbal medicine for topical administration, C2RLP, containing *Cornus officinalis*, *Rosa multiflora*, *Lespedeza bicolor*, *Platycladus orientalis* and *Castanea crenata* in a ratio of 4:1:1:1:1, can lower the production of IL-4, NO, TARC, and PGE₂, and inhibit the release of β -hexosaminidase, which is a hallmark of mast-cell degranulation. In addition, high concentration of C2RLP can suppress iNOS-mRNA expression and DPPH free-radical release [72]. Topical Jawoongo treatment has similar efficacy to the immunosuppressant drug tacrolimus in reducing inflammatory cell and mast cell infiltration into skin lesions. In addition, Jawoongo can lower overall WBC counts and the number of all WBC subtypes (neutrophils, basophils, eosinophils, monocytes and lymphocytes) as well as reduce the levels of IgE, IL-6, IL-10, IL-12 in serum and CD4⁺ in skin. Moreover, Jawoongo ointment down-regulates levels of IL-2, IL-4, IL-13 and TNF- α in mouse skin [73]. Yokukansan (YKS), a traditional Japanese medicinal formula, can reduce the frequency of aberrant grooming behaviours of mice, which suggests that YYS has a tranquilizing effect on the central nervous system. In addition, YYS is demonstrated to have a partial agonist effect against 5-HT_{1A} receptors, which leads to inhibition of the N-methyl-D-aspartate (NMDA) receptor and enhances the activity of the glutamate transporter-1 (GLT-1). It's therefore proposed that YYS can modulate the extracellular glutamate concentration in the skin of Nc/Nga mice that is socially isolated under conventional conditions [74].

5.3. Effect on signal transduction pathways involved in AD regulation

Researchers found that using topical application of Jaun ointment (JO) combined with low-temperature argon plasma (LTAP) can moderately reduce eosinophil homing and the level of various pro-inflammatory cytokines in mice model. Moreover, LTAP combined with JO treatment can completely block phosphorylation of p50 and suppress the nuclear localisation of NF- κ B, which was greater than the effect of treatment with JO alone, since LTAP technology ensured sufficient penetration of anti-inflammatory compounds into the epidermal layer [75]. Topical application of Atofrellage (AF), a herbal formula, can remarkably inhibit basophils and eosinophils in peripheral blood during an inflammatory event, and decrease the levels of pro-inflammatory cytokines such as TNF- α , IL-1 β , IL-6 in serum. Moreover, AF normalises inflammatory signals in skin tissues, such as those of ERK, p38 MAP kinase, JNK, and NF- κ B [76]. The probable mechanism of the anti-allergic activity of KIOM-MA128, the fermented form of KIOM-MA, is found to involve in inhibitory effects on both Fc ϵ RI and arachidonate cascades in Ag/IgE-activated mast cells *in vivo and vitro*. This process may comprise multiple targets, such as LYN, FYN, SYK, MAPKs, cPLA₂ and COX-2 [77]. Dangguibohyul-tang (DBT), which contains *Astragalus membranaceus* (AM) and *Angelica sinensis* (AS) in a ratio of 5:1, significantly decreases the levels of cytokines IL-4, IL-6, IFN- γ , TNF- α , and IL-1 β , as well as the levels of inflammatory mediators such as NF- κ B, phospho-I κ B α , and phospho-MAPKs [78]. Moreover, DBT regulates the NF- κ B signalling pathway and suppresses the phosphorylation of MAPK signalling molecules, and thus is more effective than either AM or AS by topical application [78]. Topical application of Huang-Lian-Jie-Du-Tang, a popular traditional Chinese medicine specified in the Zhou Hou Bei Ji Handbook, downregulates the expression levels of IL-1 α , IL-1 β , IL-2, IL-4, IL-5, IL-6, IFN- γ and TNF- α and restores the ratio of splenic CD4⁺/CD8⁺ T-lymphocytes. Additionally, HLJDT can block the activation of MAPK (p38, ERK, JNK), I κ B- α and NF- κ B (p65), decrease the expression of IL-1 α , IL-1 β , IL-6 and TNF- α mRNA, and reduce phosphorylation levels of ERK, p38, JNK, I κ B- α and p65 in the MAPKs/NF- κ B pathway [79]. More mechanisms of bioactive ingredients in Chinese formulae are shown in Table 2.

Table 2
Bioactive molecules in traditional TCM formulae and their observed mechanisms of activity.

Traditional Formula	Bioactive compounds/herbs	Constituents	Observed activity	Murine Model	Author/Year
Atorellage	gallic acid; caffeic acid; hyperoside	<i>R. javanica</i> ; <i>K. scoparia</i> ; <i>C. montieri</i> ; <i>H. cordata</i> ; <i>S. tenuifolia</i> ; <i>S. flavescens</i> ; <i>R. palmatum</i> ; <i>L. erythrorhizon</i> ; <i>T. chebula</i> ; <i>T. kirlowii</i>	Potently inhibit elevated levels of basophils and eosinophils in peripheral blood, as well as levels of pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6) in serum; normalise ERK, p38 MAP kinase, JNK, and NF- κ B signals in skin tissues	DNCB-induced Nc/Nga mice	Kim et al. [76] 2015
Bakumijijogan	marronside; loganin; paeoniflorin; benzoylpaeoniflorin; paeonol; shizandrin; gomisin A	<i>Rehmannia</i> root; <i>Cornus</i> fruit; <i>Discocoria</i> rhizome; <i>Alisma</i> rhizome; <i>Portia sclerotium</i> ; <i>Moutan</i> bark; <i>Ophiopogon</i> tuber; <i>Schisandra</i> fruit	slightly decreasing IL-1 α and TNF- α expression and notably increasing IFN- γ expression	Df antigen-induced NC/Jic mice	Makino et al. [67] 2008
Byakko-ka-ninjin-to (BN)	–	Gypsum Fibrosum 5 g. <i>Anemarrhena</i> Rhizoma 5 g; <i>Panax</i> ginseng 3 g; <i>Glycyrrhiza uralensis</i> 2 g; <i>Oryza sativa</i> L. 10 g <i>Cornus officinalis</i> (fruit); <i>Rosa multiflora</i> (stem); <i>Lespedeza bicolor</i> (aerial part); <i>Platycladus orientalis</i> (leaves); <i>Castanea crenata</i> (leaves) 4:1:1:1:1	Decrease scratch frequency and decrease temperature by 1.97 °C; do not affect expression level of myocyte-specific enhancer binding factor 2C (MEF2C) mRNA Lower the production of IL-4, NO, PGE-2, and TARC; inhibit β -hexosaminidase release;	Substance P-induced NC/Jic mice	Tohda et al. [120] 2000
C2RLP ointment	–	<i>Houttuynia cordata</i> ; <i>Rehmannia glutinosa</i> ; <i>Betula platyphyllo</i> ; <i>Rubus coreanus</i>	Suppress IL-4 and IL-13 mRNA expression; reduce IgE production in plasma; in HMC-1 cell line, inhibit cytokine production and expression of IL-4, IL-6, IL-8, and IL-13 mRNA	DNCB-induced BALB/C mice	Mechesso et al. [72] 2019
CP001	catalpol; ellagic acid; quercitrin	<i>Houttuynia cordata</i> ; <i>Rehmannia glutinosa</i> ; <i>Betula platyphyllo</i> ; <i>Rubus coreanus</i>	Suppress IL-4 and IL-13 mRNA expression; reduce IgE production in plasma; in HMC-1 cell line, inhibit cytokine production and expression of IL-4, IL-6, IL-8, and IL-13 mRNA	DNCB induced BALB/c mice	Kim et al. [121] 2014
Dangguibohyul-tang (DBT)	formononetin; decursin	<i>Astragalus membranaceus</i> (AM); <i>Angelica sinensis</i> (AS) 5:1	Reduce total IgE levels and number of mast cells in serum; significantly decrease the levels of IL-4, IL-6, IL-8, and IL-13 mRNA	DNCB induced 6-week-old female BALB/c mice	Choi et al. [78] 2016
Gami-Cheongyeul-Sodok-Eum (GCSE)	decursin; decursinol angelate; nodakenin; berberine; baicalin; glycyrrhizin; liquiritigenin; baicalin; wogonin	<i>Angelicae Gigantis</i> Radix; <i>Astragali</i> Radix; <i>Atractylodis Rhizoma</i> Alba; <i>Coptidis Rhizoma</i> ; <i>Forsythiae Fructus</i> ; <i>Glycyrrhizae Radix</i> ; <i>Lonicerae Flos</i> ; <i>Portulacae Herba</i> <i>Scutellariae Radix</i> ;	Downregulate pathogenic cytokines such as IL-4, IL-5, IL-10, IL-13, IL-17, TNF- α and INF- γ ; increase the expression of Foxp3	DNCB + Df-induced Female BALB/c mice	Hwang et al. [122] 2013
Hochuekkito (HET) water extracts	–	<i>Astragali</i> Radix; <i>Atractylodis Rhizoma</i> Ginseng Radix; <i>Angelicae Radix</i> ; <i>Bupleuri Radix</i> ; <i>Zizyphi Fructus</i> ; <i>Aurantii Nobilis</i> ; <i>Pericarpium</i> ; <i>Glycyrrhizae Radix</i> ; <i>Cimicifugae Rhizoma</i> ; <i>Zingiberis Rhizoma</i>	Reduce the increase in TEWL and stratum corneum carbonylated protein (SCCP), decrease stratum corneum water content (SCWC) and stratum corneum catalase activity (SCCA); HET has low ability to scavenge H ₂ O ₂ , and decrease the expression level of cyclooxygenase-2 mRNA	70 mJ/cm ² of ultraviolet (UV)-B light-induced 6-week-old HR-1 male hairless mice	Yangihara et al. 2013 [123]
HTD treatment	liquiritin liquiritigenin	<i>Coptis japonica</i> ; <i>Glycyrrhiza uralensis</i>	Increase the level of liver X receptor (LXR) and FLG, but decrease the level of protein kinase C (PKC); significantly reduce the levels of IL-4, IL-13, STAT-6 and cluster of differentiation 40 (CD40); suppress mast-cell degranulation, and the levels of Fc ϵ RI, substance P, MMP-9 and 5-HT; decrease the levels of NF- κ B, p65, p-I κ B and iNOS	DfE-induced 3-week-old male Nc/Nga mice	Ahn et al. [124] 2017
Huang-Lian-Jie-Du-Tang	wogonin; berberine; baicalin; palmatine; chloride jatrorrhizine; hydrochloride; wogonoside; geniposide;	<i>Coptis chinensis</i> Franchi; <i>Scutellaria baicalensis</i> ; <i>Phellodendron amurense</i> ; <i>Gardenia jasminoides</i>	Downregulate the expression levels of IL-1 α , IL-1 β , IL-2, IL-4, IL-5, IL-6, IFN- γ , and TNF- α ; restored the ratio of splenic CD4+ /CD8 + T-lymphocytes; block the activation of MAPK (p38, ERK, JNK), I κ B- α , and NF- κ B (p65); decrease the expression of IL-1 α , IL-1 β , IL-6, mRNA and TNF- α mRNA; reduce the phosphorylation level of ERK, p38, JNK, I κ B- α , and p65	DNCB-induced 8-week-old male KM mice	Fan et al. [79] 2019

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Table 2 (continued)

Traditional Formula	Bioactive compounds/herbs	Constituents	Observed activity	Murine Model	Author/Year
Jageum-Jung (JGJ)	gallic acid; methylgallate; militarin; ellagic acid; PGG; ingenol; muscone; eudesmin	<i>Melaphis chinensis</i> Bell; <i>Gremastrea variabilis</i> Nakai; <i>Knoxia valerianoides</i> Thorel; <i>Euphorbia lathyris</i> L.; <i>Moschus moschiferus</i> L.	Inhibit the production as well as mRNA expression of IL-8, IL-6, and significantly inhibit both TARC and RANTES; suppress nuclear translocation of NF- κ B and STAT-1; inhibit the granulation of mast cells	DNCB-induced 5-week-old male BALB/c mice	Yang et al. [125] 2018
Jaun-oilment	shikonins; lithospermic acid; decursin	radix of <i>Lithospermum erythrorhizon</i> Siebold; Zucc and <i>Angelica gigas</i> Nakai [Here, please check if you mean: <i>Angelica gigas</i> Nakai and <i>Angelica acutiloba</i> (Siebold & Zucc.) Kitag.	Moderately reduce the extent of eosinophil homing and the levels of IgE, CCL17, INF- γ , LTAP-JO; completely suppress the nuclear localisation of NF- κ B and block phosphorylation of p50.	DNCB induced Nc/Nga mice	Choi et al. 2017 [75]
Jawoongo-oilment	decursin	<i>Lithospermum</i> root; <i>Angelica gigas</i> Nakai	Reduce the infiltration of inflammatory cells and mast cells into skin; lower WBC and the counts of each WBC subtype in blood; reduce the levels of IgE, IL-6, IL-10, IL-12 in serum and CD4 + in skin; downregulate IL-2, IL-4, IL-13 and TNF- α in mouse skin	DNCB induced 6-week old BALB/c mice	Ku et al. [73] 2018
KIOM-MA128 (Fermented with <i>Lactobacillus rhamnosus</i>)	–	Glycyrrhizae radix; Polygoni cuspidati Rhizoma; Sophorae radix; Cnidii rhizome; Arctii fructus	regulate Fc ϵ RI and arachidonate cascades; suppress the degradation process and the production of histamine, IL-4, IL-6, TNF- α , PGD ₂	The Ag/IgE-mediated PCA reaction in ICR-mice	Park et al. [77] 2016
KM110329	ethanol extracts	<i>Houttuynia cordata</i> ; <i>Rehmannia glutinosa</i> ; <i>Prunus yedoensis</i> ; <i>Rubus coreanu</i> ;	Significantly decrease eosinophil cell counts in blood; lower mast cell count and inflammatory cell infiltration into the dermis; inhibit IL-4, IL-13, IL-17 mRNA expression and serum IgE levels	OVA induced female BALB/c mice/ DNCB induced male BALB/c mice	Kim et al. [70] 2012
Pentaherbs	gallic acid; chlorogenic acid; berberine	Flos Lonicerae; Herba Menthae; Cortex Moutan; Rhizoma Atractylodis; Cortex Phellodendri	Suppress the release of pro-inflammatory cytokine IL-6, and chemokines CCL2, CCL7, CXCL8	(OXA)-Induced adult female BALB/c mice	Tsang et al. [47] 2015
Qingre-Qushi	esculetin; chlorogenic acid	<i>Hedyotis diffusa</i> ; <i>Xanthium sibiricum</i> ; <i>Taraxacum</i> ; <i>Sophora flavescens</i> ; <i>Xanthium Pavillon</i>	Inhibit specific IgE, IgG, IgG1, and IgG2a antibodies in serum as well as the expression of IL-33, ST2, IL-1RAcP, IL-4, and IL-13 mRNA in skin; regulate the IL-33/ST2 signalling axis	OVA-induced BALB/c mice	Chen et al. [71] 2017
SanPaoCao	physalin; flavonoids; lignans; catechins	<i>Cardiospermum halitacabum</i> ; <i>Physalis minima</i> ; <i>Jussiaea repens</i>	Reduce the level of IgE in serum; Suppress the severity of dermatitis-like lesions	DNCB-induced BALB/c mice	Zhou et al. [68] 2014
Shiunko ointment	deoxyshikonin	Lithospermi Radix; Angelicae Gigantis Radix; sesame seed oil; beeswax; swine oil;	Promote wound healing by increasing the expression of VEGFR2 and phosphorylation of Akt and p38	<i>Streptozotocin</i> -Induced Diabetes Mice	Park et al. [66] 2018
SSC201	–	Stemonae Radix; Spirodela Herba; Cnidii Fructus	Upregulate IL-12 expression; downregulate the expression of IL-4, IL-5, IL-13, chemokines and IgE; inhibit the infiltration of T cells, eosinophils (CCR3 ⁺), mast cells (CD117 ⁺ / Fc ϵ R1a ⁺) into lesional tissue	DNCB-induced Nc/Nga mice	Park et al. [126] 2014
Taglisdog-eum	ginsenoside Rb1 ginsenoside Rg1 glycyrrhizin liquiritigenin paeoniflorin	<i>Panax ginseng</i> ; <i>Astragalus membranaceus</i> ; <i>Paeonia lactiflora</i> ; <i>Angelica gigas</i> ; <i>Atractylodes macrocephala</i> ; <i>Citrus unshiu</i> ; <i>Forsythia viridissima</i> ; <i>Lonicera japonica</i> ; <i>Poria cocos</i> ; <i>Angelica dahurica</i> ; <i>Glycyrrhiza uralensis</i>	Reduce lymphocyte infiltration into inflamed sites; decrease serum IgE level and the expression of IL-4, IL-5, IL-13 in skin lesions; inhibit the translocation NF- κ B into the nucleus	DNCB-induced female BALB/c mice	Hwang et al. [127] 2013

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Table 2 (continued)

Traditional Formula	Bioactive compounds/herbs	Constituents	Observed activity	Murine Model	Author/Year
Yokukansan (YKS)	-	4.0 g: <i>Atractylodes lancea</i> ; 4.0 g Hoelen; 3.0 g: <i>Cnidium</i> rhizome; 3.0 g: Japanese Angelica root; 2.0 g <i>Bupleurum</i> root; 1.5 g <i>Glycyrrhiza</i> root; 3.0 g <i>Uncaria</i> thorn	Ameliorate TEWL in skin lesions; excite 5-HT1A receptors; inhibit the NMDA receptor and enhance the activity of glutamate transporter-1 (GLT-1); inhibit the infiltration of mast cells and eosinophils; significantly suppress serum corticosterone levels	Nc/Nga mice socially isolated under conventional conditions	Funakushi et al. [74,128] 2011,2009
Yokukansankachimpinhang	rhynchophylline; hirsutine; saikosaponin A; saikosaponin D	<i>Atractylodes</i> ; <i>Angelica dahurica</i> root; <i>Bupleurum</i> root; <i>Citrus unshiu</i> peel; <i>Cnidium</i> rhizome; <i>Glycyrrhiza</i> ; <i>Poria sclerotium</i> ; <i>Pinellia</i> tuber; <i>Uncaria</i> hook	Markedly suppress neurite growth	NGF-induced neurite growth SD rats	Murayama et al. [69] 2015

PEG2: polyethylene glycol; TNF- α : tumour necrosis factor- α ; pERK: extracellular signal-regulated kinase pathway; RANTES: Regulated upon activation normal T cell expressed and secreted; NF- κ B: nuclear factor kappa-B; MAPK: mitogen-activated protein kinase; ERK: extracellular regulated protein kinases; JNK: c-Jun N-terminal kinase; Fc ϵ RI: high-affinity IgE receptor; TEWL: transepidermal water loss; TARC: thymus- and activation-regulated chemokine; p-IkB α : phospho-inhibitory subunit of NF Kappa B α .

6. Clinical trials investigating Chinese herbal medicine for AD

A wealth of experience and knowledge has been accumulated on TCM treatments for AD. TCM treatment formulae are based on the individual physiological and pathological characteristics of the patient with AD, and as one of the key therapeutic components of complementary or alternative medicine (CAM), TCM is becoming increasingly popular for the treatment of inflammatory skin diseases [80]. The TCM approach is focused on differentiating the chief syndrome, analysing its presentation, and then devising treatment strategies. Herbal formulae are used to strengthen the body against disease, with a strong emphasis on optimising qi (vital energy) and the yin-yang balance (negative and positive equilibrium) to ensure health and well-being.

The aetiology of AD according to TCM is 'wind', 'dampness' and 'heat' [81]. Clinical trials investigating Chinese herbal medicine for AD are shown in Table 3. Researchers have found that the formulae and single herbs in Chinese medicine have stable efficacy of treatment and other useful features (e.g., minimal toxicity, few adverse reactions) when used for the prevention and treatment of AD. Herbal medicines such as Cogongrass rhizome (Bai Maogen), Radix Paeoniae Alba (Bai Shao), Cortex Moutan Radix (Dan Pi) and Herba Houptuynia (Yu Xingcao) are common treatments for allergy and sedative for pruritus [82–85]. According to TCM theory, TCMs can be useful for cleansing and clearing the 'wind', 'dampness' and 'heat', thus helping to improve a person's general health and wellness as well as treating specific diseases or common ailments.

7. Conclusions and perspective

In this review we summarised multiple TCM bioactive herbal ingredients and formulae for the treatment of AD via oral or topical administration. Most TCMs exert anti-inflammatory, anti-allergic, anti-oxidative, and anti-angiogenic effects, which can attenuate AD through various mechanisms such as restoring skin barriers, balancing Th1/Th2 cells levels, as well as regulating cytokine and chemokine expression, with few side-effects. Given these multifaceted effects and the associated scientific evidence of efficacy, TCM may be a potential treatment for AD in clinical settings.

Bioactive ingredients of TCMs for AD decrease plasma total IgE and histamine, probably by suppressing mast cell degranulation and the PERK pathway, which most inhibit eosinophil accumulation and pro-inflammatory cytokine expression in damaged skin tissues. Some TCM constituents, e.g., capsiate, have anti-proliferative and anti-differential effects on CD4 + T cells, which can further lead to inhibition of Th1-, Th2-, Th17-mediated cell differentiation. In addition, the effects of TCM constituents on decreasing the levels as well as expression of cytokines such as TNF- α , INF- γ , IL-4, IL-5, IL-6, IL-13, IL-33 and IL-1 α , chemokines such as CCL2, CCL7, CCL8, TARC/CCL17 and MDC/CCL22, and pro-inflammatory factors such as RANTES, VCAM-1 and ICAM-1 in skin lesions treated with TCMs, have been most studied. The blockade of the MAPK/NF- κ B pathway in keratinocytes can decrease ERK, JNK, p38 and NF- κ B activation. Some researchers have focused on determining which mechanisms correct the Th1/Th2 imbalance skewed toward Th2. Ultimately, their findings may lead to the use of TCMs to attenuate skin pruritus and irritation, restore the skin barrier, and thereby improve AD patients' quality of life.

Data from clinical trials has shown that TCMs can decrease the severity of diseases and improve quality of life; therefore, it is possible that TCM may become an alternative choice of therapy for the treatment of AD. Furthermore, with no or only mild adverse effects, such as nausea and diarrhoea, occurring in the trials with traditional medicines (with no statistical differences between treated and non-treated groups), which indicates that TCM formulae may be a safe option for improving the overall condition of AD patients.

The variety of bioactive compounds detected in herbal ingredients and herbal formulae by researchers are just a small part of TCM,

Table 3
Clinical study on the treatment of AD with traditional Chinese Medicine.

Formula	Herbs	Population	Outcome	Adverse effects	Author/Year
Decoction of TCM containing ten herbs	<i>Ledebouria sesclodes</i> , <i>Potentilla chinensis</i> , <i>Anethum clematidis</i> , <i>Rehmannia glutinosa</i> , <i>Paeonia lactiflora</i> , <i>Lophatherum gracile</i> , <i>Dictamnus dasycarpus</i> , <i>Tribulus terrestris</i> , <i>Glycyrrhiza uralensis</i> , <i>Schizonepeta tenuifolia</i>	47 patients between the ages of 1.5 and 18.1 years	The results suggest that there is a wider therapeutic potential for these TCM herbs in atopic eczema and other skin diseases	No evidence of haematological, renal or hepatic toxicity	Sheehan MP 1992 [129]
Formula containing ten herbs	<i>Ledebouria sesclodes</i> , <i>Potentilla chinensis</i> , <i>Clematis armandii</i> , <i>Rehmannia glutinosa</i> , <i>Paeonia lactiflora</i> , <i>Lophatherum gracile</i> , <i>Dictamnus dasycarpus</i> , <i>Tribulus terrestris</i> , <i>Glycyrrhiza glabra</i> , <i>Schizonepeta tenuifolia</i>	40 patients between the ages of 16 and 65 years	Traditional Chinese herbal therapy seems to be benefit for patients with AD	No side-effects were reported by the patients although many commented on the unpalatability of the decoction	Sheehan, M. P. 1992 [130]
Zemaphyte containing ten herbs	<i>Ledebouria sesclodes</i> , <i>Potentilla chinensis</i> , <i>Clematis armandii</i> , <i>Rehmannia glutinosa</i> , <i>Paeonia lactiflora</i> , <i>Lophatherum gracile</i> , <i>Dictamnus dasycarpus</i> , <i>Tribulus terrestris</i> , <i>Glycyrrhiza glabra</i> , <i>Schizonepeta tenuifolia</i>	40 patients between the ages of 7 and 50 years	Zemaphyte does not seem to benefit Chinese patients with stubborn AD	The treatment was safe with few side-effects, but its mode of action was unclear	Fung, A. Y. 1999 [131]
Formula containing five herbs	<i>Flos loniceriae</i> , <i>Herba menthae</i> , <i>Cortex moutan</i> , <i>Rhizoma atracylodes</i> , <i>Cortex phellodendri</i>	90 patients between the ages of 5 and 21 years	The concoction is efficacious in improving the quality of life and reducing topical corticosteroid use in children with moderate-to-severe AD	No serious adverse effects were observed	Hon, K. L. E. 2007 [132]
Hochu-ekki-to containing eleven herbs	<i>Ginseng radix</i> , <i>Atractylodes rhizoma</i> , <i>Astragali radix</i> , <i>Angelicae radix</i> , <i>Zizyphi fructus</i> , <i>Bupleuri radix</i> , <i>Glycyrrhizae radix</i> , <i>Zingiberis rhizoma</i> , <i>Cimicifugae rhizoma</i> , <i>Aurantii nobilis Pericarpium</i>	91 patients between the ages of 20 and 40 years	The overall skin severity scores of treated patients are not statistically different; use of Hochu-ekki-to significantly reduce the dose of topical steroids and/or tacrolimus used for AD treatment, without leading to aggravation of AD	Only mild adverse events such as nausea and diarrhoea were noted in both groups, without statistical difference	Kobayashi, H. 2010 [133]
Formula containing five herbs	<i>Flos loniceriae</i> , <i>Herba menthae</i> , <i>Cortex moutan</i> , <i>Rhizoma atracylodes</i> , <i>Cortex phellodendri</i>	85 patients between the ages of 5 and 21 years	The concoction is efficacious in reducing topical corticosteroid usage in children with moderate-to-severe AD	No significant difference in the frequency of adverse events	Hon, K. L. 2011 [134]
Formula containing thirteen herbs	<i>Saposhnikovia divaricata</i> , <i>Schizonepeta tenuifolia</i> , <i>Angelica sinensis</i> , <i>Rehmannia glutinosa</i> , <i>Sophora flavescens</i> , <i>Atractylodes lancea</i> , <i>Cryptotympana pustulata</i> , <i>Linum usitatissimum</i> , <i>Anemarrhena asphodeloides</i> , <i>Gypsum fibrosum</i> , <i>Clematis armandii</i> , <i>Glycyrrhiza uralensis</i> , <i>Arctium lappa</i>	69 patients between the ages of 8.4 and 22.6 years	The formula may be an alternative choice of therapy for severe, refractory, extensive and nonexudative AD	No side effects from treatment, although some commented on the unpalatability of the medication	Cheng, H. M. 2011 [135]
Formula (PTQXT) containing nine herbs	<i>Radix pseudostellariae</i> , <i>Forsythia suspensa</i> , <i>Ramulus uncaria</i> , <i>cum uncis</i> , <i>Medulla junci</i> , <i>Herba lophatheri</i> , <i>Semen coicis</i> , <i>Rhizoma dioscoreae</i> , <i>Concha ostreae</i> , <i>Radix glycyrrhizae</i>	275 patients between the ages of 5 and 25 years	PTQXT is effective in decreasing the severity of the disease and improving the QOL in patients with moderate-to-severe AD	No severe adverse events occurred during the trial	Liu, J. 2015 [136]

whereas many more active ingredients and the precise targets and mechanisms of action of TCM in AD treatment remain to be discovered in the future.

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Declaration of Competing Interest

The authors declare that they have no competing interests.

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