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Review

Herbal Medicines Prevent the Development of Atopic Dermatitis by Multiple Mechanisms*

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ABSTRACT Atopic dermatitis (AD) is among the most common skin disorders in humans. Although a variety of regimens are available for the treatment of AD, preventive approaches are limited. Recent studies have demonstrated that certain naturally-occurring herbal medicines are effective in preventing the development of AD via divergent mechanisms, such as inhibiting cytokine and chemokine expression, IgE production, inflammatory cell infiltration, histamine release, and/or enhancement of epidermal permeability barrier function. Yet, they exhibit few adverse effects. Since herbal medicines are widely available, inexpensive and generally safe, they could represent an ideal approach for preventing the development of AD, in both highly developed and developing countries.
KEYWORDS herbal medicines, T cells, cytokines, permeability barrier, dermatitis

Various types of eczematous dermatitis are among the most common skin disorders in human. These disorders include atopic dermatitis (AD), nummular eczema, seborrheic dermatitis and contact dermatitis.[1,2] A variety of anti-inflammatory approaches are available to treat these disorders. For example, topical glucocorticoids are commonly used to treat allergic contact dermatitis, irritant contact dermatitis and AD. Moreover, oral cyclosporin A reportedly increases regulatory T cells in AD, and is effective in treating both AD[3,4] and allergic contact dermatitis.[5] Furthermore, immunomodulators, such as tacrolimus and pimecrolimus, also are effective in treating AD in both adults and children.[6-9] Finally, tumor necrosis factor α (TNF-α) inhibitors, such as infliximab, are effective in treating AD.[10,11] The effects of these anti-inflammatory approaches in treating eczematous dermatoses are not always sufficient. Moreover, each of these anti-inflammatory approaches carries a substantial risk of side effects. These adverse effects provide a rationale for alternative approaches to both treat and/or prevent these disorders. Though both systemic and topical administrations of herbal medicines alleviate AD, allergic and irritant contact dermatitis,[12-16] herbal regimens that prevent the development of dermatitis, including AD, are not greatly appreciated by the medical community. Certain topical medicinal herbal preparations reportedly prevent the development of contact dermatitis in human,[17-20] and the preventive effects of herbal medicines on the development of contact dermatitis and AD-like dermatitis has also been convincingly demonstrated in murine disease models.[21,22] Most studies on the preventive effects of herbal medicines on the development of AD-like lesions have been carried out in murine models, including repeated topical applications of a hapten or allergen to pre-sensitized murine skin,[1,23] or in NC/Nga and filaggrin deficient mice, which develop AD-like skin lesions with AD-like, Th2-dominant immunophenotype under appropriate condition.[24] Numerous studies have demonstrated that either systemic or topical administration of herbal medicines prevents the development of AD as evaluated by clinical symptoms, stratum corneum biophysical properties, cytokine expression and inflammatory cell infiltration in these murine AD models.

In a review of the patients' quality of lives, as well as cumulative medical costs, prevention is more important than treatment of these eczematous diseases. This paper updates current knowledge about the utility of herbal medicines in preventing the development of AD, and the mechanisms that appear to account for their benefits. These studies demonstrate the potential utility of herbal medicines for the prevention of AD.

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Clinical Symptoms

The benefits of herbal medicines in preventing the development of clinical symptoms have been assessed primarily in AD mouse models. For example, mice topically treated repeatedly with house dust mites, or haptens, such as 2,4-dinitrochlorobenzene (DNCB) or oxazolone develop AD symptoms. In addition, NC/Nga mice develop AD like lesions in a conventional (non-specific pathogen free) environment. It has been reported that mice pre-fed with azuki bean extract (250 mg•kg^{-1}•day^{-1}) for 2 weeks display a greater than 70% reduction in dermatitis score in a repeated DNCB-induced model of AD.[25] Likewise, mice pre-fed with apigenin for 4 weeks also demonstrated a dramatic reduction in dermatitis scores during the development of AD induced by repeated topical 2,4,6-trinitrochlorobenzene (TNCB) challenges.[26] Moreover, either oral *Rumex japonicus houtt*, or *Actinidia arguta* or persimmon leaf extract dramatically reduced the amount of scratching behavior in different AD models.[27-29] Orally given *Alpinia katsumadai Hayata* extract, along with topical allergen challenges for 4 weeks, also significantly lowered dermatitis scores in NC/Nga mice with spontaneous AD.[22] However, when 6-week old NC/Nga mice were fed with *Lithospermum erythrorhizon* extract for 10 weeks, the appearance of their skin, as well as the extent of their scratching behavior were nearly normalized.[30]

In most comparative studies, the effect of oral herbal extracts in the prevention of AD development was compared favorably to potent topical or systemic glucocorticoids.[31-36] For example, oral herbal extracts display similar or superior effect to oral prednisolone in preventing the increase in ear inflammation[33] and dermatitis score during the development of AD.[28,34] In another comparative study, oral Yokukansan (Yi-Gan-San in Chinese) was more effective than the H1 blocker, fexofenadine hydrochloride, in reducing the amount of scratching, as well as dermatitis scores in NC/Nga mice.[37] Similarly, oral ginseng extract displayed similar effect to cyclosporin A for dermatitis symptoms in an AD mouse model.[38]

Not only do oral, but also topical herbal medicines prevent the increase in dermatitis scores of AD. For instance, topical *Angelicae Dahuricae Radix* extract effectively decreased dermatitis scores and ear thickness, with an comparable effect as topical tacrolimus in a dust mite-induced AD model.[39] Additionally, intraperitoneally administrations of herbal extracts prevented the expected increase in AD severity scores and ear thickness induced by topical DNFB.[40,41] All these studies indicate that either systemic or topical herbal medicines prevent the development of clinical symptoms of AD. Herbal medicines shown to be effective in preventing the development of AD-like symptoms are shown in Table 1.

Stratum Corneum Function

Stratum corneum (SC) biophysical properties reflect different epidermal functions. Studies indicate that elevated transepidermal water loss (TEWL) levels, an indicator of epidermal permeability barrier function, correlate positively with the severity of AD phenotype,[64,65] while SC hydration correlates negatively with the severity of AD.[66] Therefore, changes in both barrier function and SC hydration have been used to evaluate the therapeutic and preventive effect of herbal medicines on AD. A number of studies have demonstrated that orally administrations of herbal extracts attenuate the expected deterioration in barrier function in murine AD models. Funakushi, et al[37] reported that oral administrations of herbal extract, Yokukansan, for 3 weeks significantly inhibited the increase in TEWL in NC/Nga mice. Likewise, oral administration of an extract from *actinidia arguta* at a dosage of either 50 or 100 mg/kg for 16 days prevented the expected deterioration in barrier function in a rat AD model induced by magnesium deficiency.[27] Similarly, an oral extract from persimmon leaves also normalized barrier function in NC/Nga mice.[29] Moreover, orally administrated *Lithospermum erythrorhizon* extract, started one day prior to oxazolone challenge not only reduced basal TEWL rates, but also accelerated barrier recovery rates in an AD model.[67] Furthermore, topically co-applications of bamboo extract with DNCB lowered TEWL rates in a repeated DNCB-treated mouse AD model.[68] As stated above, decrease in SC hydration is another feature of AD.[1,69,70] Oral Yokukansan prevented the usual reduction of SC hydration in NC/Nga mice, in parallel with an inhibition in the development of AD.[43] Notably, the effect of oral red ginseng extract in preventing a TNCB-induced increase in TEWL was comparable to that of oral cyclosporin A.[38] The mechanisms accounting for improving barrier function are not clear. One study showed that *Lithospermum erythrorhizon* increased epidermal ceramide content resulting from reduction of ceramidase expression in NC/Nga mice.[30] Together, these studies demonstrate that either systemic or topical herbal medicines prevent the development of AD, as indicated by prevention in expected AD-associated changes in epidermal permeability barrier function and SC hydration. These studies further suggest that assessment of SC biophysical properties could comprise a useful non-invasive approach to evaluate the potential efficacy of herbal medicines in preventing

Table 1.   List of Herbal Medicines that Display Preventive Effects on the Development of AD in Murine AD Models

No.	Herbal extract	Route of administration	AD model	Dermatitis score	Ear thickness	Number of scratching	Reference
1	*Alpinia katsumadai Hayata* (草豆蔻)	Orally	House dust mite-treated NC/Nga mice	↓	↓	N/D	22
2	*Vigna angularis* (红豆)	Orally	DNCB-treated NC/Nga mice	↓	↓	N/D	25
3	Apigenin from *Flos Chrysanthemi* (菊花)	Orally	PCI-treated NC/Nga mice	↓	N/D	N/D	26
4	*Lithospermum erythrorhizon* (紫草)	Orally	NC/Nga Mice	N/D	N/D	↓	30
5	*Radix Glycyrrhizae* (甘草), *Zingiber officinale* (生姜), *Citrus sunki* (酸橘), *Magnolia officinale* (厚朴), *Atractylodes japonica* (苍术), *Zizyphus jujuba* (大枣)	Orally	DNFB-treated NC/Nga mice	↓	N/D	↓	31
6	*Atractylodes Japonica* (苍术)	Orally	TNCB-treated NC/Nga mice	↓	N/D	↓	32
7	*Astragalus membranaceus* (黄芪)	Orally	DNFB-treated NC/Nga mice	↓	↓	N/D	33
8	Fruits of *Cudrania tricuspidata* (柘树)	Orally	House dust mite-treated NC/Nga mice	↓	N/D	N/D	34
9	*Actinidia arguta* (猕猴桃)	Orally	TNCB-treated NC/Nga mice; NC/Nga mice; magnesium deficient rat	↓	N/D	↓	35, 36, 27, 42
10	*Rumex japonicus houtt* (土大黄)	Orally	PCI-treated NC/Nga mice	↓	↓	↓	28
11	*Atractylodes lancea rhizome* (苍术), *Poria* (茯苓), *Cnidium officinale* (川芎), *Radix Angelicae sinensis* (当归), *Radix Bupleuri* (柴胡), *Radix Glycyrrhizae* (甘草), and *Ramulus uncariae cum uncis* (钩藤)	Orally	NC/Nga mice	↓	N/D	↓	37,43
12	Persimmon leaf (柿叶)	Orally	NC/Nga mice	↓	↓	↓	29
13	*Panax red ginseng* (红参)	Orally	TNCB-treated NC/Nga mice	↓	↓	N/D	38
14	*Ramulus uncariae cum uncis* (钩藤)	Orally	DNFB-treated NC/Nga mice	↓	↓	N/D	44
15	*Saururus chinensis* (LOUR.) BAILL (三白草)	Orally	PCI-treated NC/Nga mice	↓	↓	↓	45
16	*Betula platyphylla* var. japonica (白桦)	Orally	PCI-treated NC/Nga mice	↓	↓	↓	46
17	Ginsenoside Rh1 from *Radix ginseng* (人参)	Orally	OX-treated hairless mcie	↓	↓	N/D	47
18	*Radix Angelicae sinensis* (当归), *Moutan Cortex* (牡丹皮), *Rehmannia glutinosa Libosch* (地黄), *Glycyrrhizae Radix* (甘草), *Flos Lonicerae* (金银花), *Radix Ledebouriellae Divaricatae* (防风), *Spirodelae Herba* (浮萍), *Forsythiae Fructus* (连翘), *Radix Paeoniae rubra* (赤芍), *Rhizoma Ligusticum wallichii* (川芎), *Schizonepetae Herba* (荆芥), *Bombyx Batryticatus* (僵蚕), *Menthae Herba* (薄荷), *Bubali Cornu* (水牛角) and *Radix Scutellariae* (黄芩)	Orally	DNCB-treated NC/Nga mice	↓	↓	N/D	48
19	*Radix Platycodi* (桔梗)	Orally	DNCB-treated NC/Nga mice	↓	↓	N/D	49
20	*Chelidonium majus* (白屈菜)	Orally	DNCB-treated NC/Nga mice	↓	↓	↓	50
21	*Euglena gracilis* Z (小眼虫)	Orally	TNCB-treated NC/Nga mice	↓	↓	N/D	51
22	Naringenin	Intraperitoneally	DNFB-treated NC/Nga mice	↓	↓	N/D	40
23	Rosmarinic acid	Intraperitoneally	DNFB-treated NC/Nga mice	↓	↓	N/D	41
24	*Radix Angelicae Dahuricae* (白芷)	Topically	House dust mite-treated NC/Nga mice	↓	↓	N/D	39
25	Silymarin	Topically	House dust mite-treated NC/Nga mice	↓	↓	N/D	52
26	*Lindera obtusiloba* (三桠乌药)	Topically	DNCB-treated BALB/c; House dust mite-treated BALB/c	↓	↓	N/D	53
27	*Broussonetia kazinoki* Sieb (小构树, 楮)	Topically	House dust mite-treated NC/Nga mice	↓	↓	N/D	54

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No.	Herbal extract	Route of administration	AD model	Dermatitis score	Ear thickness	Number of scratching	Reference
28	*Illicium verum* (八角)	Topically	House dust mite-treated NC/Nga mice	↓	↓	N/D	55
29	*Drynaria fortunei* (骨碎补)	Topically	House dust mite-treated NC/Nga mice	↓	↓	N/D	56
30	*Vernonia amygdalina* leaf (南非叶)	Topically	DNCB-treated NC/Nga mice	↓	↓	↓	57
31	*Sophora alopecuroides* L. (苦参)	Topically	DNFB-treated NC/Nga mice	↓	↓	N/D	58
32	*Chelidonium majus* (白屈菜)	Topically	DNCB-treated NC/Nga mice	↓	↓	↓	50
33	*Pleurotus eryngii* (灵芝)	Topically	DNCB-treated NC/Nga mice	↓	↓	N/D	59
34	*Radix ginseng* (人参), *Astragalus membranaceus* (黄芪), *Radix Paeoniae rubra* (赤芍), *Angelica gigantis Radix* (当归), *Atractylodis Rhizoma Alba* (白术), *Citri Unshius Pericarpium* (陈皮), *Forsythiae Fructus* (连翘), *Lonicerae Flos* (金银花), *Poria cocos* (茯苓), *Radix Angelicae Dahuricae* (白芷), *Glycyrrhiza uralensis* (甘草)	Topically	DNCB-treated BALB/c	↓	↓	N/D	60
35	*Cortex Cinnamomi* (肉桂)	Topically	House dust mite-treated NC/Nga mice	↓	N/D	N/D	61
36	*Rehmannia glutinosa* Libosch (地黄)	Topically	House dust mite-treated NC/Nga mice	↓	↓	N/D	62
37	*Radix ginseng* (人参)	Topically	DNCB-treated NC/Nga mice	↓	↓	N/D	63

Notes: N/D: non-determined; DNFB: 2,4-dinitrofluorobenzene; DNCB: 1-chloro-2,4-dinitrobenzene; TNCB: trinitrochlorobenzene; OX: oxazolone; PCl: 1-chloro-2,4,6-trinitrobenzene (picryl chloride)

the development of AD. Herbal medicines that prevent the increase in TEWL during the development of AD-like lesions are shown in Table 2.

Inflammation
Inflammatory Cell Infiltration

Although AD is generally considered as a Th2 cytokines mediated immune disorder,[71] other inflammatory cells such as Th1, Th17, mast cells and B cells also are involved in the pathogenesis of AD.[71-75] Although AD is a Th2 dominant allergic disorder, characterized by elevated interleukin (IL)-4, 5 and 13 levels, mast cells also produce Th2 cytokines[76] and release histamine upon stimulation,[77,78] all of which contribute to the development of AD.[79,80] Accordingly, the preventive effects of herbal medicines on the development of AD also reflect an inhibition in

inflammatory cell activation, differentiation and infiltration.

Studies have shown that orally administered extracts of herbal medicines inhibit inflammatory cell infiltration by eosinophils and mast cells in various murine AD models, including magnesium deficiency, NC/Nga mice or repeated DNFB applications.[27,28,37,43,44-47] Pokharel, et al[48] showed that oral Sopungyangjae-Tang extract at a dosage of 40 mg/day for 12 weeks completely diminished inflammatory infiltration of the epidermis in a NC/Nga model. Even intraperitoneally administrated naringenin significantly reduced the number of CD4+ T cells, CD8+ T cells, total mast cells and degranulated mast cells in a NC/Nga model.[40] Oral herbal medicines not only reduce inflammatory cell infiltration in skin, but also decrease circulating inflammatory cells. It has been demonstrated

Table 2. Herbal Medicines that Prevent the Deterioration in Barrier Function During AD Development

Herbal extract	Route of administration	AD model	TEWL	Reference
Actinidia arguta	Orally	Magnesium deficient rats	↓	27
Atractylodes lancea rhizome, *Poria*, *Cnidium officinale*, *Radix Angelicae sinensis*, *Radix Bupleuri*, *Radix Glycyrrhizae*, and *Ramulus uncariae cum uncis*	Orally	NC/Nga mice	↓	37
Persimmon leaf	Orally	NC/Nga mice	↓	29
Panax red genseng	Orally	TNCB-treated NC/Nga mice	↓	38
Lithospermum erythrorhizon (柴草)	Orally	OX-treated hairless mice	↓	67
Bambusae caulis in Liquamen (竹沥)	Topically	DNCB-treated hairless mice	↓	68

that oral extract of *Actinidia arguta* prevented the increase of activated B (CD45RA$^+$ positive) and CD11b$^+$ cells in peripheral blood mononuclear cells (PBMC) and the skin of AD rats.[27] Furthermore, *Actinidia arguta* extract induced a 30% reduction in CD4$^+$IL-4$^+$ cells and over 40% reduction in CD19$^+$IgE$^+$ B cells in the splenocytes of ovalbumin-sensitized mice.[81] Oral *Rheum rhabarbarum* extract caused an almost 200% reduction in neutrophil, and an over 85% reduction in eosinophil counts in the blood during the development of AD.[42] Moreover, oral extracts from the fruit of *Cudrania tricuspidata* exhibited similar effect to oral prednisolone in inhibiting mast cell infiltration in the NC/Nga model.[34] Another study showed that efficacy of oral ginsenoside Rh1 was comparable to prednisolone on inflammatory cell infiltration in an oxazolone-induced AD model.[47] Moreover, there was no difference in the extent of inhibition of cutaneous CD11a$^+$ cell infiltration between oral *Panax ginseng* extract and oral cyclosporin A.[38]

Not only do systemic administration, but also topical applications of herbal medicines reduce inflammatory cell infiltration during the development of AD. Qi, et al[68] showed that topical bamboo extract inhibited the expected increase in neutrophils and eosinophils in peripheral blood mononuclear cell (PBMC). Reduction in mast cell infiltration, induced by topical extracts from *Silybum marianum* or *Lindera obtusiloba*, has been reported in NC/Nga mice and in an DNCB-induced AD model.[52,53] Interestingly, the inhibitory effect of topical extracts from *Broussonetia kazinoki* Sieb. on mast cell infiltration is superior to conventional immunosuppressor, tacrolimus, in NC/Nga mice.[54] Again, the efficacies of topical *Illicium verum* extract and *Drynaria fortunei* extracts on inhibition of mast cell infiltration were also comparable to tacrolimus during the development of house duct mite-induced AD.[55,56] In addition to inflammatory cell infiltration, the epidermal thickness normalized in *Angelicae Dahuricae Radix* extract-treated mice to an extent that was comparable to tacrolimus-treated skin in an AD model.[39] Taken together, these studies reveal that either systemic or topical administrations of herbal medicines prevent the development of AD by inhibiting inflammatory cell infiltration.

Cytokine/Chemokine Expression

T cells, eosinophils, mast cells, cytokines and chemokines play crucial role in the development of AD.[82-84] Thus, blockade of cytokine production or action has become a common approach in preventing and treating AD.[85,86] Alternatively, approaches that stimulate the production of anti-inflammatory cytokines, such as IL-10, also could be beneficial in AD. Several studies have shown that herbal medicines, that prevent the development of AD, also down-regulated pro-inflammatory cytokine expression. The pro-inflammatory cytokine, TNF-α binds to its receptors on T cells, B cells and antigen-presenting cells thereby regulating inflammatory responses. It is reported that oral ginseng extract is as effective as cyclosporin A in the reduction of cutaneous levels of both protein and mRNA for TNF-α, as well as thymic stromal lymphopoietin (TSLP), an epidermal cytokine that stimulates T cell maturation, in a hapten-induced AD model.[38] Pretreatment with topical *Vernonia amygdalina* leaf extracts remarkably lowered serum TNF-α levels and even normalized serum IL-4 levels in NC/Nga AD model.[57] In contrast, IL-10 is anti-inflammatory cytokine. Accordingly, inhibition of IL-10 action increases TNF-α and IL-1β production.[87] Oral or topical applications of some herbal extracts increase IL-10 levels in serum[49] and skin[58] while decreasing cutaneous mRNA levels of IL-4 and TNF-α.[49]

Although most herbal medicines, that simultaneously exhibit preventive benefit on the development of AD, lower pro-inflammatory cytokine levels, the effects of herbal medicines on cytokine and its mRNA expression varies among the herbal ingredients (Table 3). Majority of herbal medicines down-regulate Th2 cytokines, such as IL-4, IL-5 and IL-13. The influence of herbal medicines on Th1 cytokines such as interferon-γ (IFN)-γ varies dramatically. Some herbs increase IFN-γ,[31,88] while others decrease IFN-γ,[33,40,44] or cause a little changes in IFN-γ.[26,28,38] Yet, it is worth noting that both oral and topical apigenin inhibit the development of AD in murine models,[26,89] but oral administrations of apigenin did not change serum levels of a wide range of cytokines,[26] suggesting that the inhibitory effect of some herbal medicine, such as apigenin, on the development of AD could be independent of cytokines. The influence of herbal medicines on cytokine mRNA expression also varies among tissues. It has been shown that topical Taglisodog-eum extract lowers mRNA levels of IL-31, IFN-γ and TNF-α in skin lesion, but not CD4$^+$ T cells in draining lymph nodes.[60] Some herbal medicines induce down-regulation of some cytokine mRNA expression is attributable to inhibition of NF-κB activation.[60,63,64]

In addition to cytokines, chemokines also play crucial role in the development of AD.[90-92] For example, macrophage inflammatory protein 1 (MIP-1/CCL3) can activate granulocytes (neutrophils, eosinophils and basophils) and induce the synthesis and release of other pro-inflammatory cytokines such as IL-1, IL-6 and TNF-α.[93,94] Regulated upon

activation normal T cell expressed and presumably secreted (RANTES, CCL5) can activate and recruit inflammatory cells into inflamed skin sites.[95] Both thymus activation regulated chemokine (TARC/CCL17) and the macrophage-derived chemokine, MDC/CCL22, are AD associated chemokines that recruit Th2 cells.[96] Increased levels of these chemokines have been observed in AD patients.[94,97-100] Accordingly, some herbal medicines that prevent the development of AD also down-regulate chemokine expression. A number of studies have demonstrated that both oral and topical applications of some herbal extracts decrease both protein and mRNA levels for these chemokines (Table 3). Moreover, the effect of oral administration of *Cudrania tricuspidata* extract on serum TARC levels was comparable to oral prednisolone in NC/Nga mouse model of AD.[34] Topical applications of either *Illicium verum* extract or tacrolimus induce a comparable extent of inhibition in mRNA expression for TARC and RANTES.[55] Taken together, these evidence suggest that either oral or topical applications of herbal medicines can inhibit cytokine and/or chemokine expression, resulting attenuation of AD development.

IgE Levels

IgE is synthesized by B cells and further modulated by Th2 cytokines, such as IL-4 and IL-13,[101,102] but a large portion of allergen-specific IgE is also produced by CD138$^+$ plasma cells.[103] IgE plays a crucial role in the development of AD. IgE molecules bind to the high affinity IgE receptor (Fc ε RI) on the surface of mast cells and dendritic cells, stimulating histamine release.[104-106] Histamine in turn enhances dendritic cell function and cytokine production by T cells.[107-109] Both AD patients and mice exhibit higher serum IgE levels.[2,110,111] Studies have shown that most herbal medicines that inhibit AD development lower serum IgE levels. For example, Topical herbal medicines such as silymarin and aloperine also reduce serum IgE levels in NC/Nga AD model.[52] Some herbal medicines lower both total serum IgE and allergen specific IgE.[53,81] Mice pre-fed with paramylon, an extract from *Euglena gracilis* Z, for 1 week before induction of AD significantly reduced serum IgE levels in NC/Nga mice.[51] Finally, oral ginseng extract lowered serum IgE levels more than did cyclosporin A.[29]

Yet, other herbal medicines inhibit the development of AD without altering serum IgE levels,[30,44,112,113] and one study even showed that topical *Rehmannia glutinosa* extract increased serum IgE levels.[62] Together, these results suggest that the effects of herbal medicines on serum IgE levels vary among specific ingredients. The effects of herbal

medicines on IgE levels are summarized in Table 3.

Other Pathogenic Mechanisms Impacted by Herbal Medicines

Colonization of *S. aureus* is another common and provocative feature of AD.[115] Lee, et al[28] reported that oral *Rumex japonicus houtt* extract, beginning 3 days before TNCB challenges prevented the development of AD, and induced an over 60% reduction in the density of *S. aureus* on the skin. Toll-like receptors, such as TLR-2, 4, and 9 not only are involved in the pathogenesis of AD,[116-119] but also protect against *S. aureus* infection.[120-122] Oral administrations of *Actinidia arguta* extract at dose of 100 mg·kg^{-1}·day^{-1} for 7 weeks during TNCB challenges remarkably increased the expression levels of mRNA for TLR-2,4,9 in skin.[35] During the development of cutaneous inflammation, migration of inflammatory cells into the skin is mediated by adhesion molecules, such as intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule 1 (VCAM-1).[123-125] The cutaneous mRNA levels of ICAM-1 and VCAM-1 are significantly decreased by topical herbal extract treatment for 23 days.[55,62] However, topical *Drynaria fortune* extract treatment for the same period of time does not alter the cutaneous mRNA levels of ICAM-1 and VCAM-1.[71] These studies indicate that herbal medicines that prevent the development of AD also regulate cutaneous innate immune response and cell migration.

Concluding Remarks

Before or during the hapten or allergen challenge status, either systemic or topical herbal medicines can inhibit the development of AD. These AD preventive herbs improve stratum corneum function, AD severity score and scratching via divergent mechanisms including improving epidermal permeability barrier function, lowering IgE levels, inhibiting inflammatory cell infiltration, cytokine expression and immune defense depending on the type of herbal ingredients utilized. The effect of herbs in preventing AD development is comparable or superior to conventional immune modulators, antihistamine agents and glucocorticoids, but with fewer adverse effects. Herbal medicines could be optional alternatives for preventing the development of AD.

Conflict of Interest

Authors have no conflict of interest.

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Table 3.　Influence of Herbal Medicines on Cytokine and Chemokine Expression during the Development of AD in Murine Models

Herbal extracts[△]	Cytokines and Chemokines (protein)	Cytokines and Chemokines (mRNA)	IgE	Histamine
1	*TARC↓	N/D	↓	↓
2	N/D	IL-4↓, TNF-α↓, IFN-γ↓	↓	N/D
3	IL-4(-), IL-13(-), IFN-γ(-), Botaxin(-), MIP-1(-)	IL-4(-), IFN-γ↓	↓	N/D
5	IL-4↓, IFN-γ↑	IL-4↓, TNF-α↓, IFN-γ↓	↓	↓
7	IFN-γ↓, IL-4(-)	N/D	(-)	N/D
8	IL-4↓, TARC↓	N/D	↓	↓
9	IL-4↓, IL-5↓, IL-10↓, IL-13, IFN-γ↑, IL-12↑	IL-4↓, IFN-γ↑	↓	N/D
10	IL-4↓, IFN-γ(-)	N/D	↓	N/D
13	TNF-α↓, TSLP↓, IL-4(-), IL-17(-), and IFN-γ(-)	TNF-α(-), TSLP↓	↓	N/D
14	IFN-γ↓, IL-4(-)	N/D	(-)	N/D
15	N/D	IL-4(-), IFN-γ↑	↓	N/D
16	N/D	IL-4↓, IFN-γ(-)	↓	N/D
17	IL-6↓	IL-4(-), IFN-γ↑	N/D	N/D
18	*TARC↓	*TARC↓	↓	N/D
19	TARC↓, IL-10↑	IL-4↓, TNF-α↓	↓	N/D
20	TNF-α↓, IL-4	N/D	↓	↓
21	IL-4↓, IL-18↓, IL-12↓, IFN-γ(-)	N/D	↓	N/D
Oral fermented barley extract[(112)]	IL-4(-), IL-17↓, IFN-γ↓	N/D	(-)	N/D
Oral hesperidin[(114)]	IL-4(-), IL-10(-), IL-17↓, IFN-γ↓	N/D	↓	N/D
22	*IL-4↓, *IFN-γ↓	N/D	↓	N/D
23	*IL-4↓, *IFN-γ↓	N/D	↓	
24	*TARC↓	*TARC↓, *MDC↓	↓	↓
Topical *Bambusae caulis* in Liquamen[(68)]	N/D	IL-4↓, IL-13↓, TNF-α↓, IFN-γ↑	↓	N/D
25	IL-4↓	IL-4↓, TNF-α↓, IFN-γ↑	↓	N/D
26	IL-4↓, IL-13↓, IL-31, TNF-α↓	N/D	↓	↓
27	IL-4↓, *TARC↓	*TARC↓, *MDC↓, *RANTES↓	↓	N/D
28	*TNF-α↓, *IL-4↓, IL-6↓	IL-4↓, IL-6↓, TNF-α↓, TARC↓, RANTES↓, IFN-γ(-)	↓	↓
29	IL-6↓	IL-4↓, IL-6↓, TNF-α↓, IFN-γ(-)	↓	N/D
30	IL-4↓, IL-5↓, MIP-1↓, TNF-α↓, IFN-γ↓, Eotaxin↓	N/D	↓	N/D
31	IL-1β↓, IL-4↓, IL-6↓, IL-10↑, IL-13↓, TNF-α↓, IFN-γ↓	N/D	↓	N/D
32	TNF-α↓, IL-4↓	N/D	↓	↓
33	TARC↓	IL-4↓, IL-5↓, IL-13↓, TNF-α↓, IFN-γ↓	↓	N/D
34	IL-4↓, IL-13↓	IL-4↓, IL-5↓, IL-13↓, IL-17↓, IL-31↓, TNF-α↓, IFN-γ↓	↓	N/D
35	TNF-α↓, TARC↓	IL-4, TNF-α↓, TARC↓, *MDC↓, *RANTES↓	↓	↓
36	*TARC↓, *MDC↓, *RANTES↓	IL-4↓, TNF-α↓, TARC↓, MDC↓, RANTES↓	↑	↓
37	TARC↓	TARC↓, IL-4↓, IL-5↓, IL-13↓, TNF-α↓, IFN-γ↓	↓	N/D

Notes: [△]Numbers and route of administration are from to Table 1. ACD: allergic contact dermatitis; ICD: irritant contact dermatitis; TSLP: thymic stromal lymphopoietin; TARC: thymus and activation-regulated chemokine; MDC: macrophage-derived chemokine; MIP-1: Macrophage inflammatory protein 1; RANTES: regulated upon activation normal T cell expressed and presumably secreted ; (-): no changes, *In vitro* study.

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