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Anti-Inflammatory Herbal Extracts and Their Drug Discovery Perspective in Atopic Dermatitis

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Abstract

Atopic dermatitis (AD) is an allergic disorder characterized by skin inflammation. It is well known that the activation of various inflammatory cells and the generation of inflammatory molecules are closely linked to the development of AD. There is accumulating evidence demonstrating the beneficial effects of herbal extracts (HEs) on the regulation of inflammatory response in both *in vitro* and *in vivo* studies of AD. This review summarizes the anti-atopic effects of HEs and its associated underlying mechanisms, with a brief introduction of *in vitro* and *in vivo* experiment models of AD based on previous and recent studies. Thus, this review confirms the utility of HEs for AD therapy.

Key Words: Herbal extracts, Natural products, Atopic dermatitis, Inflammatory cells, Inflammatory molecules, Keratinocytes

INTRODUCTION

Atopic dermatitis (AD) is a chronic inflammatory skin disorder (CISD) characterized by skin barrier dysfunction and itching (Yang *et al*., 2020). Its prevalence in developing countries has been increasing (Arafune *et al*., 2021). The onset of AD is closely related to allergen exposure and is influenced by genetic and environmental factors (Novak and Leung, 2011). Inflammatory cells, such as keratinocytes, Langerhans cells, macrophages, dendritic cells, T lymphocytes, B lymphocytes, and mast cells, play an important role in AD development by generating inflammatory molecules and influencing the activation of immune cells against the invasion of various antigens when the skin barrier is in a damaged state (Kasraie *et al*., 2013; David Boothe *et al*., 2017).

Keratinocytes are mainly present in the epidermis and play a pivotal role in host defense by detecting pathogens (Chieosilapatham *et al*., 2021). This type of cell is the source of inflammatory cytokines, chemokines, and adhesion molecules such as IL-6, IL-8, CCL5 (known as RANTES), CCL17 (known as TARC), CCL22 (known as MDC), and MCP-1 (known as CCL2), which are involved in the amplification of cutaneous inflammation. Langerhans cells, which are antigen-presenting cells (APCs), differentially express toll-like receptors (TLRs) and play a role in pathogen recognition (Mitsui *et al*., 2004). This type of cell has been known to interact with keratinocytes and T lymphocytes in AD development (Dubrac *et al*., 2010). Macrophages have TLRs, as seen in Langerhans and dendritic cells, and are abundant in AD skin (Kasraie *et al*., 2013). An increase in nitric oxide (NO), PGE2, TNF-α, IL-6, and MCP-1 was reported in experimental models of AD (Lim *et al*., 2014; Choo *et al*., 2019; Park *et al*., 2021), and macrophages are known to be a major source of these molecules. Dendritic cells are known as professional APCs, and their presentation of antigens to naïve T cells leads to T cell activation and antigen-specific adaptive immunity (Novak, 2012; Kumar *et al*., 2019). T helper type 2 (Th2) cells play a crucial role in AD development by generating cytokines, including IL-4, -5, -13, and -31 (Brandt and Sivaprasad, 2011). IL-4/IL-13 promote B cell activation (Nur Husna *et al*., 2022), and IL-5 has a significant role in the maturation and development of eosinophil (Kouro and Takatsu, 2009). B cells differentiate into plasma cells that produce antibodies against secreted Th2 cytokines, including IgM, IgG, IgA, and IgE (Spiegelberg *et al*., 1991; Kader *et al*., 2021). IgE is associated with mast cell and eosinophil activation (Liu *et al*., 2011). Mast cell-secreted histamine is known to

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induce itching in AD (Umehara *et al*., 2021).

Herbal extracts (HEs) have been commonly used in Asia as folk medicines for treating various disorders (Kumar *et al*., 2013; Yamaguchi *et al*., 2015; Guo *et al*., 2017; Zhu *et al*., 2021). The cumulative evidence indicates that HEs as crude extracts of leaves, stems, bark, and roots contain bioactive compounds that have an ameliorative effect in inflammatory disease, with comparatively fewer side effects than other medicines (Chan *et al*., 2008; Nagai and Okunishi, 2009; Yang *et al*., 2017; Lee *et al*., 2019a; Ryu *et al*., 2022). Previous and recent investigations based on *in vitro* and *in vivo* AD models have shown that HEs and their active compounds exert an ameliorative effect on AD development by suppressing immune cell recruitment and immune cell-derived molecules (Nam *et al*., 2011; Wu *et al*., 2011; Choi *et al*., 2014; Chan *et al*., 2015; Lim *et al*., 2016). Interestingly, an insightful review reported that various types of herbal compounds exert effects against AD (Wu *et al*., 2021). Thus, the advantage of HEs could be emphasized in pharmacological therapy for allergic disorders including AD, suggesting that HEs may be novel therapeutics in AD. In this review, we describe the protective effect of HEs at the level of practically usable extracts against AD based on previous and recent investigations conducted on *in vitro* and *in vivo* AD models (Fig. 1).

CELL LINES/PRIMARY CELLS AND STIMULATORS FOR *IN VITRO* AD STUDIES

To investigate the anti-inflammatory effects of HEs, bioactive fractions, or compounds in *in vitro* AD studies, a variety of cell lines or primary culture cells have been used with stimulators as follows. **Keratinocytes:** Human keratinocyte HaCaT cell lines were applied in *in vitro* studies of AD with TNF-α or TNF-α/IFN-γ as the stimulator (Choi *et al*., 2010; Lee *et al*., 2010; Sung *et al*., 2011a; Sung *et al*., 2011b; Choi *et al*., 2012a; Sung *et al*., 2012; Choi *et al*., 2014; Lim *et al*., 2014; Park *et al*., 2015; Yang *et al*., 2015a; Choi *et al*., 2016; Lim *et al*., 2016; Sung *et al*., 2016; Kim *et al*., 2021). **Langerhans cells:** Langerhans cells derived from mice were stimulated with peptidoglycan (PEG) in an AD study (Matsui *et al*., 2010). **Macrophages:** Murine macrophage cell line RAW264.7 was used in *in vitro* models of AD with its stimulator lipopolysaccharide (LPS) (Ha *et al*., 2014; Lim *et al*., 2014; Cho *et al*., 2018; Kim *et al*., 2022). Mouse bone marrow-derived macrophages were used for *in vitro* AD study with LPS stimulation (Lee *et al*., 2022a). **Dendritic cells:** Human monocyte-derived dendritic cells were stimulated with a cytokine cocktail (TNF-α/IL-1β/IL-6/PGE2) in an *in vitro* study of AD (Chan *et al*., 2015). **T lymphocytes:** Human Jurkat T cells were activated with anti-CD3/CD28 or PMA plus A23187 (PMACI) in an *in vitro* study of AD (Lee *et al*., 2022b). **B lymphocytes:** Human U266B1 cells were stimulated with LPS (Hwang *et al*., 2012). Mouse splenic B cells were incubated with stimulator IL-4/LPS in an *in vitro* study of AD (Higuchi *et al*., 2013). **Mast cells:** Human mast cells (HMC-1) and their stimulator PMACI (Oh *et al*., 2012; Cho *et al*., 2017), rat peritoneal mast cells (RPMCs) and their stimulator compound 48/80 (Oh *et al*., 2012), mouse mast cell MC/9 cells and their stimulators compound 48/80 and PMACI (Ha *et al*., 2014; Sung *et al*., 2014), and rat basophilic leukemia mast cell line RBL2H3 and its stimulators DNP-specific BSA, PMA/Ionomycin, A23187, IgE/HAS, PMACI, and C48/80 (Kim *et al*., 2013; Lee *et al*., 2019b; Kim *et al*., 2021; Lee *et al*., 2022c) were applied in *in vitro* studies of AD. Mouse bone-marrow-derived mast cells were incubated with stimulator DNP-specific BSA in an *in vitro* study of AD (Kim *et al*., 2013). **Splenocytes:** Primary splenocytes isolated from mice were used in *in vitro* studies of AD with its stimulators anti-CD3/

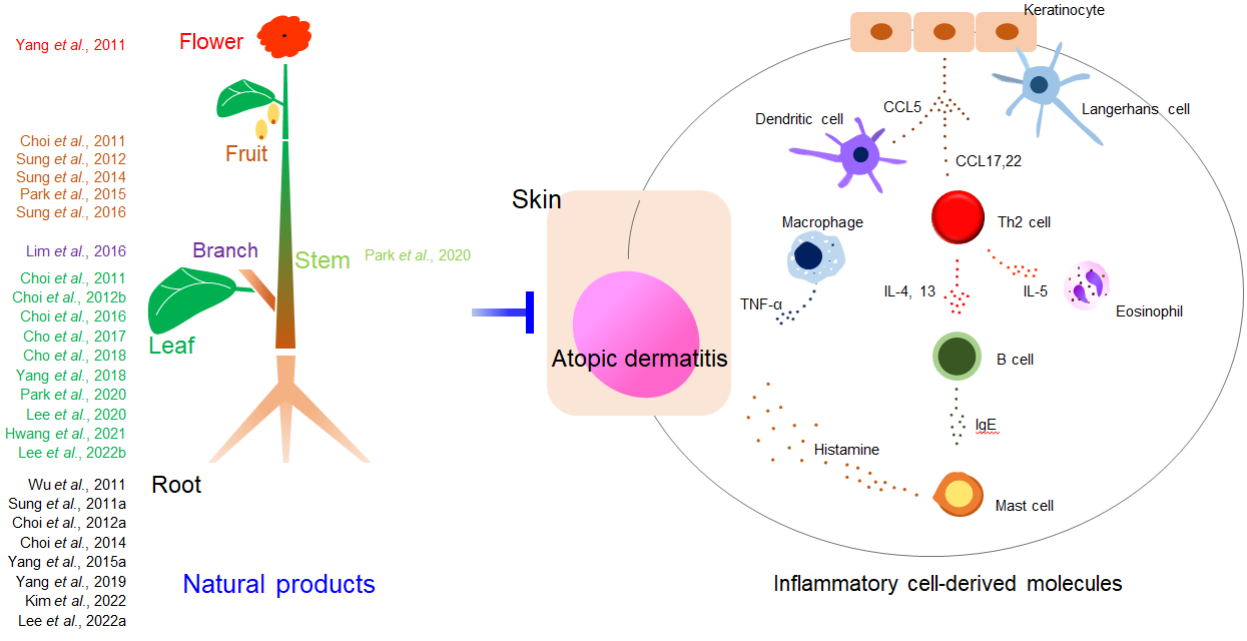

Fig. 1. Anti-AD effects of HEs in AD development. Herbal flower, fruit, branch, stem, leaf, and root extracts ameliorate AD progression by suppressing the generation of inflammatory cell-derived molecules.

Table 1. Anti-AD effects of HEs in *in vitro* models of AD (2010–2022)

HaCaT Cells (Keratinocytes)				
Plant source	POP	Stimulator	Inhibitory effect	Ref., year
Broussonetia kazinoki		TNF-α/IFN-γ	CCL5, 17, 22	Lee *et al*., 2010
Sophora flavescens	Roots	TNF-α/IFN-γ	CCL17, 22, 27	Choi *et al*., 2010
Rehmannia glutinosa		TNF-α/IFN-γ	RANTES, TARC, MDC	Sung *et al*., 2011a
Cinnamomum caccia	Bark	TNF-α/IFN-γ	RANTES, TARC, MDC	Sung *et al*., 2011b
Illicium verum	Fruits	TNF-α/IFN-γ	IL-1β, 6, TARC, MDC, ICAM-1	Sung *et al*., 2012
Platycodi Radix	Roots	TNF-α/IFN-γ	TARC	Choi *et al*., 2012a
Platycodon grandiflorum	Roots	TNF-α/IFN-γ	TARC	Choi *et al*., 2014
Morus alba		TNF-α/IFN-γ	TARC	Lim *et al*., 2014
Sanguisorba officinalis	Roots	TNF-α/IFN-γ	IL-8, RANTES, TARC, MDC	Yang *et al*., 2015a
Xanthii fructus	Fruits	TNF-α/IFN-γ	TARC, MDC	Park *et al*., 2015
Forsythia suspense	Fruits	TNF-α/IFN-γ	RANTES, TARC, MDC	Sung *et al*., 2016
Hovenia dulcis	Branches	TNF-α/IFN-γ	IL-6, TNF-α, TARC, MDC	Lim *et al*., 2016
Moringa oleifera	Leaves	TNF-α/IFN-γ	IL-1β, 6, TNF-α, CCL17	Choi *et al*., 2016
Patrinia scabiosifolia		TNF-α/IFN-γ	IL-6, 8, MCP-1, TARC	Cha *et al*., 2017
Pyrus ussuriensis		TNF-α	IL-1β, 6	Cho *et al*., 2018
Perillae herba	Leaves	TNF-α/IFN-γ	IL-6, 8, RANTES, TARC	Yang *et al*., 2018
Centella asiatica		TNF-α/IFN-γ	IL-6, COX-2	Lee *et al*., 2020
Fritillariae thunbergii		TNF-α/IFN-γ	IL-4, TARC, MDC	Kim *et al*., 2021
Rosa davurica		TNF-α/IFN-γ	NO, PGE2, IL-6,TARC	Hwang *et al*., 2021
Indigo pulverata		TNF-α/IFN-γ	MCP-1, RANTES, TARC, MDC, ICAM1	Min *et al*., 2022

POP (parts of the plant), CCL2 (known as MCP-1), CCL5 (known as RANTES), CCL17 (known as TARC), CCL22 (known as MDC), CCL27 (known as CTACK).

CD28 and ovalbumin (OVA) (Shim and Choung, 2014; Cho *et al*., 2018; Choi *et al*., 2020).

EXPERIMENTAL MOUSE MODELS FOR *IN VIVO* AD STUDIES

In an AD-like phenotype mouse model, the increase in dermatitis severity, scratching, and transepidermal water loss (TEWL) is clear, and this increase is associated with an influx of inflammatory cells, including T and B cells, eosinophil, mast cells, and macrophages as well as the generation of those cell-derived molecules. To evaluate the ameliorative effects of HEs, bioactive fraction, or compounds on AD *in vivo*, different mouse strains have been studied with application of AD inducers as follows. The **NC/Nga mouse** was first introduced as an AD animal model showing spontaneous AD occurrence (Matsuda *et al*., 1997). Researchers have been using this mouse in experimental animal models of AD with various AD inducers, such as 2,4-dinitrochlrobenzene (DNCB) (Yang *et al*., 2011), 2,4-dinitrofluorobenzene (DNFB) (Wu *et al*., 2011), Dermatophagoides farinae (DfE) (Lee *et al*., 2010), and house dust mites (HDM) (Lim *et al*., 2014). The **BALB/c mouse** has been applied in AD studies with various AD inducers, such as DNCB (Hwang *et al*., 2012), DfE/DNCB (Choi *et al*., 2016), oxazolone (Lee *et al*., 2019b), trimellitic anhydride (TMA) (Choi *et al*., 2020), and ovalbumin (OVA) challenge/patch (Kim *et al*., 2021). The **C57BL/6 mouse** has been used for AD research with inducers DNFB (Nam *et al*., 2011) and 2,4,6-trinitrochlorobenzene (TNCB) (Kim *et al*., 2021). The **ICR mouse** has been treated with AD inducers compound 48/80, histamine (Oh *et al*., 2012), and oxazolone (Kim *et al*., 2022). The **SKH-1 hairless mouse** has been utilized as an AD animal model with its AD inducer DNCB (Lee *et al*., 2019b).

ANTI-AD EFFECT OF HEs IN *IN VITRO* AND *IN VIVO* STUDIES

We briefly introduce the HEs showing ameliorative effects against AD based on previous and recent *in vitro* and/or *in vivo* studies from 2010-2022, as summarized in Tables 1-2.

Schefflera leucantha (2010)

Matsui *et al*. (2010) reported that an ethanol leaf extract (ELE) of *S. leucantha* (SL), which is used as a herbal medicine in China, inhibits CCL5 (known as RANTES) secretion/CCL17 (known as TARC) mRNA expression in PEG-stimulated murine Langerhans cells and histamine generation in IgE-stimulated murine mast cells.

Broussonetia kazinoki (2010)

Previous *in vitro* and *in vivo* results have shown that an ethanol heartwood extract (EHE) of *B. kazinoki* (BK) decreases the mRNA expression of CCL5, CCL17, and CCL22 (known as MDC) in TNF-α/IFN-γ-stimulated human keratinocyte HaCaT cells, and topical application of BKEHE ameliorates AD-like skin lesions, mast cell influx, and IgE/IL-4 secretion in HDM-exposed NC/Nga mice (Lee *et al*., 2010).

Sophora flavescens (2010)

The *in vitro* results confirm that PC downregulates the mRNA expression of CCL17, CCL22, and CCL27 (known as CTACK) in TNF-α/IFN-γ-stimulated HaCaT cells (Choi *et al*.,

Table 1-1. Anti-AD effects of HEs in *in vitro* models of AD (2010–2022)

Epidermal Langerhans Cells				
Plant source	POP	Stimulator	Inhibitory effect	Ref., year
Schefflera leucantha		Peptidoglycan	CCL5, 17	Matsui *et al*., 2010
RAW264.7 Cells (Murine Macrophage)				
Plant source	POP	Stimulator	Inhibitory effect	Ref., year
Morus alba		LPS	NO, PGE2	Lim *et al*., 2014
Artemisia capillaris		LPS	NO	Ha *et al*., 2014
Pyrus ussuriensis		LPS	NO	Cho *et al*., 2018
Cynanchi atrati		LPS	IL-1β, 6	Kim *et al*., 2022
Bone Marrow-Derived Macrophage				
Plant source	POP	Stimulator	Inhibitory effect	Ref., year
Paeonia lactiflora	Roots	LPS	IL-6, 10, 12, TNF-α	Lee *et al*., 2022a
THP-1 (Human Monocytes)				
Plant source	POP	Stimulator	Inhibitory effect	Ref., year
Duchesnea chrysantha	Whole	HDM	IL-6, 8, MCP-1	Lee *et al*., 2012
Monocyte-Derived Dendritic Cells				
Plant source	POP	Stimulator	Inhibitory effect	Ref., year
Cortex Moutan	Roots	Cytokine cocktail	IL-10, 12, 23	Chan *et al*., 2015
Jurkat Cells (Human T lymphocytes)				
Plant source	POP	Stimulator	Inhibitory effect	Ref., year
Helianthus annuus	Leaves	PMACI, Anti-CD3/CD28	IL-2	Lee *et al*., 2022b
Mouse Splenic B cells				
Plant source	POP	Stimulator	Inhibitory effect	Ref., year
Garcinia mangostana	Rinds	IL-4/LPS	IgE, IFN-γ	Higuchi *et al*., 2013

2010).

Cordyceps bassiana (2011)

It was previously shown that topical application of the butanol fraction (BF) of *C. bassiana* (CB) fruiting bodies reduces AD symptoms in NC/Nga mice with DNFB-induced AD based on suppression of the dermatitis score, mast cell influx, serum histamine/IgE, and the expression of IL-4/IFN-γ (Wu *et al*., 2011).

Alnus japonica (2011)

Topical application of an ethanol leaf and bark extract (ELBE) of *A. japonica* (AJ) attenuates AD severity in HDM-treated NC/Nga mice by inhibiting eosinophil numbers, plasma IgE, serum IL-4, -5, and -13, and mRNA/protein expression of iNOS/COX-2 (Choi *et al*., 2011).

Rehmannia glutinosa (2011)

The ameliorative effects of ethanol root extract (ERE) of *R. glutinosa* (RG) on AD were evaluated in both *in vitro* and *in vivo* (Sung *et al*., 2011a). In that study, RGERE effectively reduced secretion of TNF-α/IFN-γ-induced RANTES, TARC, and MDC in HaCaT cells. In addition, it inhibited increased ear thickness, mRNA expression of cytokines (IL-4 and TNF-α)/chemokines (RANTES, TARC, and MDC)/adhesion molecules (ICAM-1 and VCAM-1), and serum histamine/IgE in DfE-exposed NC/Nga mice.

Cinnamomum caccia (2011)

A previous AD study showed that an ethanol bark extract (EBE) of *C. cassia* (CC) exerts anti-inflammatory effects in TNF-α/IFN-γ-stimulated HaCaT cells by attenuating RANTES, TARC, and MDC secretion (Sung *et al*., 2011b). It also moderately reduced the dermatitis score, serum IgE/TNF-α/histamine, and mRNA expression of molecules (IL-4, TNF-α, and TARC) in the back skin of NC/Nga mice exposed to DfE.

Chelidonium majus (2011)

Researchers have shown the protective effect of ethanol aerial part extract (EAPE) of *C. majus* (CM) in an *in vivo* study of AD (Yang *et al*., 2011), where its administration (oral or topical) led to downregulation of scratching behavior and serum TNF-α/IL-4/IgE in NC/Nga mice of DNCB-induced AD.

Table 1-2. Anti-AD effects of HEs in *in vitro* models of AD (2010–2022)

HMC-1 (Human Mast Cells)				
Plant source	POP	Stimulator	Inhibitory effect	Ref., year
Betula platyphylla	Roots	PMACI	IL-6, 8, TNF-α	Oh *et al*., 2012
Diospyros lotus	Leaves	PMACI	IL-6, TNF-α	Cho *et al*., 2017
MC/9 (Murine Mast Cells)				
Plant source	POP	Stimulator	Inhibitory effect	Ref., year
Gardenia jasminoides	Fruits	C48/80	Histamine	Sung *et al*., 2014
Artemisia capillaris		PMACI	Histamine	Ha *et al*., 2014
RBL2H3 (Rat Mast Cells)				
Plant source	POP	Stimulator	Inhibitory effect	Ref., year
Morus bombycis	Stems	DNP-specific BSA	IL-4, TNF-α	Kim *et al*., 2013
Quercus acutissima		PMA/Ionomycin	IL-4	Lee *et al*., 2019b
Fritillariae Thunbergii		A23187	IL-4	Kim *et al*., 2021
Grewia tomentosa		PMACI, C48/80	β-hexosaminidase	Lee *et al*., 2022c
RPMC (Rat Mast Cells)				
Plant source	POP	Stimulator	Inhibitory effect	Ref., year
Betula platyphylla		C48/80	Histamine	Oh *et al*., 2012
Mouse Bone Marrow-Derived Mast Cells				
Plant source	POP	Stimulator	Inhibitory effect	Ref., year
Morus bombycis		DNP-specific BSA	β-hexosaminidase	Kim *et al*., 2013
Mouse Splenocytes				
Plant source	POP	Stimulator	Inhibitory effect	Ref., year
Pyrus ussuriensis	Leaves	Anti-CD3/CD28	IL-4, 13	Cho *et al*., 2018
Rosae multiflorae		Ovalbumin	IL-2, 4, 5, 13, IFN-γ	Choi *et al*., 2020

***Terminalia chebula* (2011)**

The experimental results from Nam *et al*. (2011) confirmed that an aqueous seed extract (ASE) of *T. chebula* (TC) mitigates AD symptoms *in vivo*. In that study, the topical application of TCASE inhibited ear swelling, eosinophil recruitment, and MMP-9/IL-31-positive cells in DNFB-exposed C57BL/6 mice.

***Illicium verum* (2012)**

Sung *et al*. (2012a) have shown the *in vitro* anti-atopic effect of ethanol fruit extract (EFE) of *I. verum* (IV) and its underlying mechanisms. In that study, IVEFE suppresses the mRNA and protein expression of cytokines/chemokines/adhesion molecules (IL-1β, IL-6, TARC, MDC, and ICAM-1) and the activation of NF-κB/STAT1/MAPK (ERK and p38)/Akt in TNF-α/IFN-γ-stimulated HaCaT cells.

***Betula platyphylla* (2012)**

The modulating effect of *B. platyphylla* (BP) ERE on AD symptoms has been previously confirmed *in vitro* and *in vivo* (Oh *et al*., 2012). In the *in vitro* experiments, pretreatment with BPERE (1 mg/mL) remarkably reduced the secretion of histamine in compound 48/80-stimulated rat peritoneal mast cells (RPMCs); 1 mg/mL BPERE also notably suppressed the generation of TNF-α/IL-6/IL-8, nuclear translocation of NF-κB, and the activation of caspase-1 in PMACI-stimulated human mast cell line HMC-1. In the *in vivo* experiments, oral administration of BPERE (400 mg/kg) was found to contribute to the suppression of scratching behaviors in ICR mice treated with compound 48/80 or histamine. It also exerted a regulatory effect on increased serum IgE in DNCB-exposed BALB/c mice.

***Psidium guajava* (2012)**

The findings of a study from Choi *et al*. (2012b) showed that the water extract (WE) of leaves of *P. guajava* (PG) has an anti-AD effect on NC/Nga mice with DNCB-induced AD, reducing dermatitis severity, serum IgE/TARC, and ear mRNA expression of TNF-α/IFN-γ/Th2 cytokines (IL-4, -5, and -13).

***Chrysanthemum boreale* (2012)**

The ameliorative effect of *C. boreale* (CB) flowers was examined in an experimental animal model of AD. The experimental results indicated its regulatory effect on itching behaviors and serum IgE in DNCB-treated NC/Nga mice (Yang *et al*., 2012).

Platycodi Radix (2012)

Choi *et al*. (2012a) evaluated the anti-inflammatory ability

Table 2. Anti-AD effects of HEs in *in vivo* models of AD (2010–2022)

Nc/Nga mouse				
Plant source	POP	Stimulator	Inhibitory effect	Ref., year
Broussonetia kazinoki		HDM	IL-4, IgE	Lee *et al*., 2010
Alnus japonica	Leaves	HDM	IL-4, 5, 13, IgE	Choi *et al*., 2011
Morus alba		HDM	IgE, Histamine	Lim *et al*., 2014
Cordyceps bassiana	Fruits	DNFB	IL-4, IgE, Histamine, IFN-γ	Wu *et al*., 2011
Rehmannia glutinosa	Roots	DfE	IL-4, TNF-α, IgE, RANTES, TARC, MDC	Sung *et al*., 2011a
Cinnamomum cassia		DfE	IL-4, TNF-α, IgE, TARC, Histamine	Sung *et al*., 2011b
Gardenia jasminoides		DfE	IL-4, 6, TNF-α, Histamine	Sung *et al*., 2014
Artemisia capillaris		DfE	IgE, Histamine	Ha *et al*., 2014
Forsythia suspense		DfE	IL-4, TNF-α, IgE, RANTES, TARC, MDC	Sung *et al*., 2016
Chelidonium majus		DNCB	IL-4, TNF-α, IgE	Yang *et al*., 2011
Psidium guajava	Leaves	DNCB	IL-4, 5, 13, TNF-α, IgE, TARC, IFN-γ	Choi *et al*., 2012b
Chrysanthemum boreale	Flowers	DNCB	IgE	Yang *et al*., 2012
Platycodi Radix	Roots	DNCB	IL-4, TNF-α, IgE, TARC	Choi *et al*., 2012a
Duchesnea chrysantha		DNCB	IgE	Lee *et al*., 2012
Platycodon grandiflorum		DNCB	IL-4, 5, 13, TNF-α, IgE, RANTEX, TARC	Choi *et al*., 2014
Solanum tuberosum		DNCB	IgE, IgG1	Shim and Choung, 2014
Hovenia dulcis		DNCB	IL-1β, IL-4, 5, 12, TNF-α, IgE, CCL5, 11, 17	Lim *et al*., 2016
Patrinia scabiosifolia		DNCB	IgE	Cha *et al*., 2017
Pyrus ussuriensis		DNCB	IgE	Cho *et al*., 2018
Pinus densiflora	Bark	DNCB	IL-4, 13, 17A, 31, TNF-α, IgE, IgG1	Lee *et al*., 2018
Spirodela polyrhiza		DNCB	IL-6, IL-31, IgE	Lee *et al*., 2021
Indigo Pulverata Levis		DNCB	TNF-α, IL-6, 13, IgE	Min *et al*., 2022

of Changkil (CK), which is an aqueous root extract (ARE) of P. Radix (PR), in an experimental model of AD; 50 and 100 μg/mL CK exerted significant inhibition on mRNA/protein expression of TARC in TNF-α/IFN-γ-stimulated HaCaT cells. In addition, topical application of CK ameliorated the severity of dermatitis and ear thickness. It also inhibited the generation of serum IgE/TARC, reduction of serum IL-10, and upregulation of ear TNF-α/IL-4 in NC/Nga mice treated with DNCB.

Duchesnea chrysantha (2012)

An *in vitro* study by Lee *et al*. (2012) showed that ethanol whole plant extract (EWPE) of D. chrysantha (DC) has an anti-inflammatory effect in HDM-stimulated human monocytic cell line THP-1, downregulating the release of IL-6, IL-8, and MCP-1 (known as CCL-2). In addition, its anti-inflammatory ability was confirmed in both DNCB-painted NC/Nga mice, showing its regulatory ability on skin dermatitis/serum IgE, and splenocytes from DNCB-painted mice, showing its inhibitory ability on IL-5, IL-13, MCP-1, and eotaxin.

Garcinia mangostana (2013)

Ethanol rind extract (10 μg/mL) of *G. mangostana* (GM) significantly downregulates IL-4/LPS-induced IgE in splenic B cells from NC/Tnd mice and the mRNA expression of IFN-γ in pokeweed mitogen (PWM)-stimulated lymphocytes (Higuchi *et al*., 2013). Its oral administration also reduces the severity of dermatitis, plasma IgE generation, eosinophil/mast cell influx, and mRNA expression of IL-4, IFN-γ, MDC and eotaxin-2 in NC/Tnd mice, a model for human AD.

Morus bombycis (2013)

The anti-AD effect of a methanol stem extract (MSE) of *M. bombycis* (MB) was reported in an *in vitro* study (Kim *et al*., 2013). In that study, MBMSE reduced the release of β-hexosaminidase in antigen (AG)-stimulated mast cells, such as rat basophilic leukemia mast cell line RBL-2H3 and bone marrow mononuclear cells (BMMCs). In particular, 100 μg/mL MBMSE remarkably suppressed the mRNA and protein of TNF-α/IL-4 and the activation of Syk, AKT, and MAPK (ERK, p38, and JNK) in AG-stimulated RBL-2H3 cells.

Schizonepeta tenuifolia (2013)

The *in vivo* results from Choi *et al*. (2013) showed that treatment with *S. tenuifolia* (ST) extract exerts a protective effect on skin dermatitis, serum IgE/TNF-α/IL-6 and dorsal skin NF-κB/MAPK activation in BALB/c mice treated with DNCB.

Gardenia jasminoides (2014)

The experimental results from Sung *et al*. (2014) confirmed that pretreatment with 400 μg/mL EFE of *G. jasminoides* (GJ) inhibits 48/80-induced histamine in the MC/9 murine mast cell line. It was also revealed that the GJEFE active compound, 100 μM geniposide, suppressed histamine release in 48/80-stimulated MC/9 cells (Sung *et al*., 2014). In the *in vivo* study, the topical application of 400 μg/mL GJEFE significantly reduced epidermal thickening, mast cell influx, serum IL-4/histamine, ear IL-4, IL-6, and TNF-α mRNA in NC/Nga mice of DfE-induced AD.

Platycodon grandiflorum (2014)

Saponin fraction (SF) from ARE of *P. grandiflorum* (PG) (1 and 2 μg/mL) and its active compound platycodin D (1 and 2 μM) dose-dependently attenuate the mRNA/protein expression of TARC and the activation of NF-κB/STAT1 in TNF-α/

Table 2-1. Anti-AD effects of HEs in *in vivo* models of AD (2010–2022)

BALB/c mouse				
Plant source	POP	Stimulator	Inhibitory effect	Ref., year
Betula platyphylla		DNCB	IgE	Oh *et al*., 2012
Schizonepeta tenuifolia		DNCB	IL-6, TNF-α, IgE	Choi *et al*., 2013
Chamaecyparis obtuse		DNCB	IL-1β, IL-6, IgE	Yang *et al*., 2015b
Artemisia argyi		DNCB	IL-1β, IL-4, 6, IgE, Histamine, IFN-γ	Han *et al*., 2016
Angelicae dahuricae		DNCB	IL-4, 6, 10, 12, TNF-α, IgE	Ku *et al*., 2017
Combretum quadrangulare	Leaves	DNCB	IL-6, 13	Park *et al*., 2020
Centella asiatica	Leaves	DNCB	IL-4, 5, 6, 10, TNF-α	Lee *et al*., 2020
Rosa davurica	Leaves	DNCB	IL-6, IgE	Hwang *et al*., 2021
Indigo Pulverata Levis		DNCB	IL-6, 13, TNF-α, IgE	Min *et al*., 2022
Paeonia lactiflora		DNCB	IL-6, 12, 17A, TNF-α, IgE	Lee *et al*., 2022a
Helianthus annuus		DNCB	IgE	Lee *et al*., 2022b
Moringa oleifera		DfE/DNFB	IL-4, 5, 10, 17, 22, TNF-α, IgE, IFN-γ	Choi *et al*., 2016
Quercus acutissima		Oxazolone	IL-1β, IL-4, 33, TNF-α	Lee *et al*., 2019b
Rosae multiflorae		TMA	IL-1β, IL-4, TNF-α	Choi *et al*., 2020
Styphnolobium japonicum	Seeds	Ovalbumin	IgE	Kim and Lee, 2021
C57BL/6 mouse				
Plant source	POP	Stimulator	Inhibitory effect	Ref., year
Terminalia chebula	Seeds	DNFB	IL-31, MMP-9	Nam *et al*., 2011
ICR mouse				
Plant source	POP	Stimulator	Inhibitory effect	Ref., year
Cynanchi atrati	Roots	Oxazolone	IL-6, TNF-α	Kim *et al*., 2022

IFN-γ-stimulated HaCaT cells (Choi *et al*., 2014). Moreover, SF and platycodin D induce HO-1 upregulation and Nrf2 activation in HaCaT cells, while 2 mg/kg oral administration of SF alleviates the dermatitis score, ear swelling, mast cell influx, serum IgE/TARC, and the mRNA expression of cytokines and chemokines (IL-4, -5, -13, TNF-α, IFN-γ, and TARC) in DNCB-painted NC/Nga mice.

Solanum tuberosum (2014)

Oral administration of *S. tuberosum* (ST) ethanol extract resulted in protective effects with respect to ear swelling/scratching behaviors and an inhibitory effect on serum IgE/IgG1 in DNCB-treated NC/Nga mice (Shim and Choung, 2014). The experimental results also showed that splenocytes isolated from NC/Nga mice administered with ST extract suppress IL-4, -12, -13, and IFN-γ stimulation.

Morus alba (2014)

Lim *et al*. (2014) examined whether a *M. alba* (MA) ethanol extract could regulate AD development through *in vitro* and *in vivo* studies. Their results indicated that 100 μg/mL MA ethanol extract significantly suppresses LPS-induced NO/PGE2 generation in mouse macrophage RAW264.7 cells and TNF-α/IFN-γ-induced TARC production in HaCaT cells. Furthermore, its anti-AD effect was confirmed in NC/Nga mice treated with HDM, showing an ameliorating effect on skin dermatitis and plasma IgE/histamine.

Artemisia capillaris (2014)

A. capillaries (AC) ethanol extract was confirmed to suppress the generation of NO in LPS-stimulated RAW264.7 cells and the secretion of histamine in PMACI-stimulated MC/9 cells (Ha *et al*., 2014). Topical administration of AC was shown to ameliorate the dermatitis scores and plasma histamine/IgE in DfE-sensitized Nc/Nga mice.

Sanguisorba officinalis (2015)

The anti-inflammatory effects of *S. officinalis* (SO) ERE were reported in an *in vitro* study by Yang *et al*. (2015a). In that study, 50 and 100 μg/mL SOERE significantly decreased the mRNA/protein expression of chemokines (RANTES, TARC, MDC, and IL-8) in TNF-α/IFN-γ-stimulated HaCaT cells. Moreover, its regulatory effect on TNF-α/IFN-γ-induced STAT1 and NF-κB activation was notable in HaCaT cells.

Cortex Moutan (2015)

An *in vitro* study by Chan *et al*. (2015) showed the anti-AD effect of gallic acid (GA), the active component of Cortex Moutan (CM), which is known as the dried root cortex (DRC) of Paeonia suffruticosa Andrews. The experimental results revealed that 200 μg/mL GA significantly inhibits the expression of surface makers (CD40, CD80, CD83, CD86, CD11c, and HLA-DR) in cytokine cocktail-stimulated monocyte-derived dendritic cells. CA also inhibits the generation of IL-10, IL-12p40, and IL-23 in activated dendritic cells.

Xanthii fructus (2015)

The ethanol extract of X. fructus (XF), the dried fruit (DF) of Xanthium strumarium L., has regulatory effects on the production of cytokines and the activation of transcription factors in

activated epithermal keratinocytes (Park *et al*., 2015). In brief, treatment with XF ethanol extract (10 μg/mL) significantly inhibited TNF-α/IFN-γ-induced upregulation of TARC and MDC mRNA/protein expression in HaCaT cells. It also suppressed the activation of NF-κB, STAT1, and p38 activation in TNF-α/IFN-γ-stimulated HaCaT cells.

***Chamaecyparis obtusa* (2015)**

The experimental results from Yang *et al*. (2015b) confirm that the volatile organic compounds (VOC) of *C. obtusa* (CO) have anti-AD effects in BALB/c mice of DNCB-induced AD by modulating skin dermatitis, serum IgE, and skin mRNA of IL-1β and IL-6.

***Forsythia suspensa* (2016)**

Sung *et al*. (2016) demonstrated the protective effect of *F. suspense* (FS) EFE on AD development both *in vitro* and *in vivo*. In the *in vitro* experiments, 200 and 400 μg/mL FSEFE had the ability to inhibit the generation of RANTES, TARC, and MDC in TNF-α/IFN-γ-stimulated HaCaT cells. In addition, forsythiaside, phillyrin, pinoresinol, and phylligenin, which are the active compounds of FSEFE, had an inhibitory effect on TNF-α/IFN-γ-induced RANTES, TARC, and MDC in HaCaT cells. In the *in vivo* experiments, FSEFE significantly suppressed the dermatitis score, ear thickness, eosinophil/mast cell influx in back skin, serum TNF-α/histamine/IgE, and ear mRNA of molecules (IL-4, TNF-α, RANTES, TARC, MDC, ICAM-1, and VCAM-1) in a NC/Nga mouse model of DfE-induced AD.

***Hovenia dulcis* (2016)**

It was previously examined whether an ethanol branch extract (EBRE) of *H. dulcis* (HD) and its active compound methyl vanillate (MV) have a modulatory effect on AD development via *in vitro* and *in vivo* studies (Lim *et al*., 2016). The experimental results showed that HDEBRE (5 and 10 μg/mL) and MV (5 and 10 μM) exert a suppressive effect on the mRNA expression of cytokines/chemokines (TNF-α, IL-6, TARC, and MDC) and activation of MAPK (ERK, JNK, and p38) in TNF-α/IFN-γ-stimulated HaCaT cells. Furthermore, oral administration of HDEBRE effectively ameliorated skin dermatitis, mast cell influx, increased serum IgE, and upregulation of skin mRNA of cytokines/chemokines (IL-1β, -4, -5, -12; IFN-γ; CCL5, 11, 17) and GATA3 in a DNCB-painted NC/Nga mouse model.

***Moringa oleifera* (2016)**

M. oleifera (MO) ELE suppresses the mRNA expression of cytokines/chemokines (TNF-α, IL-6, IL-1β, and CCL17) and the activation of MAPK (ERK and JNK) in TNF-α/IFN-γ-stimulated HaCaT cells (Choi *et al*., 2016). Furthermore, its protective effect on AD was confirmed in BALB/c mice of DfE/DNCB-induced AD, showing inhibitory ability on skin dermatitis, mast cell recruitment, plasma IgE/IgG2a, and ear mRNA of various factors (TNF-α; IL-4, -5, -10, -17, -22, -31, -32; IFN-γ; CD206; RORγt; and TSLP).

***Artemisia argyi* (2016)**

Oral administration of *A. argyi* (AA) ethanol extract has a regulatory effect on serum histamine/IgE/IL-1β/IL-4/IL-6/IFN-γ, lymph nodes mRNA of IL-1β/IL-4/IL-6/IL-13/IFN-γ/GM-CSF, and activation of Lyn, Syk, MAPK (ERK, JNK, and p38), PI3K, AKT, and IκBα in lymph nodes of DNCB-induced AD like BALB/c mice (Han *et al*., 2016).

***Diospyros lotus* (2017)**

In a previous report on experimental models of AD, it was reported that the *D. lotus* (DL) ELE has ameliorative effects (Cho *et al*., 2017). In that study, the inhibitory effect of DLELE had an on the generation of TNF-α and IL-6 in PMACI-stimulated HMC-1 cells. In a hairless mouse model of DNFB/HDM-induced AD, oral administration of 20 mg/kg DLELE effectively reduced skin dermatitis, mast cell influx in ear, and serum IL-4/IgE.

***Angelicae dahuricae* (2017)**

A. dahuricae (AD) is known as Chinese Angelica and also as Baig-Ji in Korea. WE of AD has an ameliorative effect on DNCB-induced AD in BALB/c mice, suppressing the increases in levels of mast cells/CD4+ cells; immune cells (neutrophils, eosinophils, and monocytes); IgE; IL-4, -6, -10, and -12; and TNF-α (Ku *et al*., 2017).

***Patrinia scabiosifolia* (2017)**

P. scabiosifolia (PS) has been used as traditional medicine in inflammatory disease in East Asia, including in Korea, and its reductive effect was confirmed not only in TNF-α/IFN-γ-induced IL-6/IL-8/MCP-1/TARC *in vitro* (HaCaT cells) but also in DNCB-induced IgE *in vivo* (NC/Nga mice) (Cha *et al*., 2017).

***Pyrus ussuriensis* (2018)**

It has been examined whether *P. ussuriensis* (PU) ELE can alleviate AD-like symptoms (Cho *et al*., 2018). The *in vitro* experimental results revealed that PUELE has an inhibitory ability on the generation of NO in LPS-stimulated RAW264.7 cells and the secretion of IL-1β/IL-6 in TNF-α-stimulated HaCaT cells. The results also indicated that 8 μg/mL PUELE significantly decreases the anti-CD3/anti-CD28-induced production of IL-4 and IL-13 in splenocytes isolated from C57BL/6 mice. Furthermore, rutin, a major constituent of PUELE, significantly inhibits IL-6 production in TNF-α-stimulated HaCaT cells. In an *in vivo* model, PUELE suppresses the severity of skin dermatitis, scratching tendency, TEWL, and serum IgE in an experimental NC/Nga mouse model of DNCB-induced AD.

Perillae Herba (2018)

ELE of P. Herba (PH), which is distributed in Asia, has been reported to exert an inhibitory ability in TNF-α/IFN-γ-induced TARC/RANTES/IL-6/IL-8 secretion and MAPK activation in HaCaT cells (Yang *et al*., 2018).

***Pinus densiflora* (2018)**

It was previously reported that methanol bark extract (MBE) of *P. densiflora* (PD), which is known as Korean red pine, has an anti-AD effect on DNCB-exposed Nc/Nga mice by mitigating AD-like skin lesions, scratching behavior, serum IgG1, and dorsal skin mRNA of IL-4/IL-13/IL-17A/IL-31/TNF-α (Lee *et al*., 2018).

***Quercus acutissima* (2019)**

A recent study confirmed the protective effect of *Q. acutissima* (QA) ethanol shell extract (ESE) using AD-like experimental models (Lee *et al*., 2019b). The *in vitro* results indicated that pretreatment with QAESE and its active compounds

(gallic acid and ellagic acid) inhibited the mRNA expression of IL-4 in PMA/Ionomycin-stimulated RBL-2H3 cells. In addition, QAESE, gallic acid, and ellagic acid decreased the release of β-hexosaminidase in IgE/DNP-BSA-stimulated RBL-2H3 cells. In an experimental BALB/c mouse model of oxazolone-induced AD, QAESE demonstrated a regulatory effect on the mRNA expression of TNFα, IL-1β, IL-4, and IL-33 in mouse ear. Furthermore, QAESE ameliorates not only AD-like skin lesions but also serum IL-4/IgE upregulation in a SKH-1 hairless mouse model of DNCB-induced AD. In these models, QAESE also exerts a suppressive effect on mast cell influx and the mRNA expression of TNFα, IL-1β, IL-4, IL-25, and IL-33 in mouse ear.

***Rumex japonicus* (2019)**

Recently, the anti-AD effect of ERE of *R. japonicus* (RJ) has been reported in both *in vitro* and *in vivo* studies (Yang *et al*., 2019). In that report, 25 and 50 μg/mL RJERE was shown to inhibit ERK, AKT, and IκBα phosphorylation in TNF-α-stimulated HaCaT cells. In addition, 4 and 8 mg/mL RJERE decreased DNCB-induced upregulation of ear thickness and spleen weight.

***Rosae multiflorae* (2020)**

Choi *et al*. (2020) recently demonstrated the anti-AD effect of *R. multiflorae* (RM) extract both *in vitro* and *in vivo*. In the *in vitro* experiments, RM extract (200 and 400 μg/mL) attenuated the secretion of cytokines (IL-2, -4, -5, and -13 and IFN-γ) and the activation of STAT6 in OVA-stimulated splenocytes isolated from BALB/c mouse. In addition, RM extract exerted an inhibitory effect on CD3/CD28-induced IL-2 in CD4+ T cells isolated from splenocytes of BALB/c. In the *in vivo* experiments, oral administration of 400 mg/kg RM extract significantly reduced ear thickness, ear cytokines (IL-1β, IL-4, and TNF-α), and serum IgE in TMA-induced AD-like BALB/c mice. RM extract also demonstrated an inhibitory ability on the mRNA expression of Th2 cytokines in draining lymph nodes in a TMA-induced AD-like mouse model.

***Combretum quadrangulare* (2020)**

A recent study reported that an ethanol leaf and stem extract (ELSE) of *C. quadrangulare* (CQ) attenuates serum IgE, blood eosinophil, skin mast cells, and tissue IL-6/IL-13-TARC/TSLP in AD BALB/c mice induced by DNCB (Park *et al*., 2020). CQELSE also inhibited the activation of MAPK (ERK, JNK, and p38) in skin lysate. In particular, 400 mg/kg CQELSE exerted notable *in vivo* anti-AD effects.

***Centella asiatica* (2020)**

C. asiatica (CA), known as a medicinal plant, is distributed in Southeast Asia. A recent finding from Lee *et al*. (2020) showed the anti-AD effect of CA both *in vitro* and *in vivo*. In their study, pretreatment with CAELE dose-dependently reduced the expression of COX-2 and IL-6 in TNF-α/IFN-γ-stimulated HaCaT cells. Treatment with CAELE had an ameliorative effect on the increase in ear thickness, lymph node weight, and ear mast cell/TNF-α/IL-4/IL-5/IL-6/IL-10/iNOS/COX-2/CXCL9 in DNCB-exposed BALB/c mice. CAELE also decreased the DNCB-induced upregulation of TNF-α/COX-2/MAC-1/IL-6 expression and p38 activation.

***Fritillariae thunbergii* (2021)**

A recent study confirmed the protective effect of a *F. thunbergii* (FT) chloroform fraction of ethanol extract (CFEE) on AD based on both *in vitro* and *in vivo* studies (Kim *et al*., 2021). In that study, 50 μg/mL FTCFEE notably downregulated the generation of TARC/MDC/IL-4 and upregulated the mRNA expression of FLG/INV/AQP-3 in TNF-α/IFN-γ-stimulated HaCaT cells, with an inhibitory ability on MAPK activation as well as β-hexosaminidase activity, IL-4 production, and ERK/p38 MAPK activation in A23187-stimulated RBL2H3 cells. The *in vivo* results showed that the topical application of FTCFEE (100 mg/mL) reduced increased levels of ear thickness, scratching behaviors, and SCORing Atopic Dermatitis (SCORAD) index in a BALB/c mouse model of DNCB-induced AD. In addition, the inhibitory effect of FTCFEE on the influx of mast cells, CD4+ T cells, and CD8+ T cells was confirmed by histopathological analysis.

***Styphnolobium japonicum* (2021)**

The anti-AD effect of sophoricoside isolated from an ethanol seed extract of *S. japonicum* (SJ) was recently examined in experimental models of AD (Kim and Lee, 2021). *In vitro* results showed that sophoricoside attenuated IL-5/IL-13 bioactivity in a murine pre-B cell line, BaF- B03 cells. Their results also indicated that sophoricoside could inhibit naïve CD4+ T cells (isolated from spleens and lymph nodes of C57BL/6 mice) and differentiate various Th cell subtypes (Th1, 2, and 17) by downregulating the mRNA expression of transcription factors such as T-bet. Furthermore, *in vivo* results indicated that topical application of 30 mg/kg sophoricoside notably inhibited serum IgE, mast cell influx, and dermal thickness in a BALB/c mouse model of OVA challenge and patch-induced AD. Sophoricoside also reduced AD symptoms in a C57BL/6 mouse model of TNCB-induced AD by ameliorating skin dermatitis and mast cell recruitment.

***Rosa davurica* (2021)**

R. davurica (RD) has various biological properties (e.g., antioxidant and anti-inflammatory) and is known to be distributed in China, Japan, and Korea. The experimental results of Hwang *et al*. (2021) confirmed the beneficial effect of RD in an experimental model of AD. In that study, ELE of RD (10, 30, and 100 μg/mL) significantly mitigates TNF/IFN-γ-induced NO/PGE2/TARC/IL-6 generation, iNOS/COX-expression, MAPK activation, and NF-κB activation in HaCaT cells. In DNCB-induced AD BALB/c mice, topical administration of RDELE inhibited the DNCB-induced upregulation of skin/ear thickness, lymph node/spleen size, blood leukocytes, and serum IgE/IL-6/ALT/AST/CREA/BUN (Hwang *et al*., 2021).

***Spirodela polyrhiza* (2021)**

Ethanol extract of *S. polyrhiza* (SP) decreases mast cell influx, IgE, IL-6, and IL-31 in DNCB-exposed Nc/Nga mice (Lee *et al*., 2021). This anti-AD effect is further enhanced by combination with Olea europaea leaf extract in treatment.

***Cynanchi atrati* (2022)**

Recent *in vitro* results from Kim *et al*. (2022) confirmed that pretreatment with 10 μg/mL ERE of *C. atrati* (CA) decreases mRNA expression of IL-6/IL-1β and the activation of NF-κB in LPS-stimulated RAW264.7 cells. In that study, CAERE inhibits the mRNA and protein expression of regulator of calcineurin

1 (RCAN1), a known NF-κB inhibitor, in RAW264.7 cells. Furthermore, it was found that sinapic acid (SA), a phenolic constituent of CAERE, suppresses the mRNA expression of IL-6/IL-1β and the activation of IκB in LPS-stimulated RAW264.7 cells. SA also upregulates the mRNA expression of RCAN1 in RAW264.7 cells. In an *in vivo* study, the topical administration of 10 μg/mL CAERE on ear tissues exerts an ameliorative effect on skin inflammation in an ICR mouse model of oxazolone-induced AD by decreasing ear thickness and the mRNA expression of IL-6/TNF-α.

***Grewia tomentosa* (2022)**

Recently, Lee *et al*. (2022c) demonstrated the anti-AD effect of *G. tomentosa* (GT), which is distributed in Asia, both *in vitro* and *in vivo*. In that study, the EAPE of GT significantly reduced IgE/HAS-induced β-hexosaminidase release, PMACI-induced β-hexosaminidase, and C48/80-induced β-hexosaminidase release in RBL-2H3 cells. In addition, GTEAPE (50 and 100 μg/mL) attenuated IgE/HAS-induced molecules (IL-1β, -4, -5, -6, -13; TNF-α; MCP-1; TSLP; and TGF-β1) and activation of Syk/PLCγ1/PKCδ/PI3K/AKT/p65/p38/JNK/ERK. In an experimental mouse model of AD induced by anti-DNP IgE/DNP-HAS, the oral administration of GTEAPE ameliorated dermatitis score, ear thickness, serum IgE, ear IL-1β/IL-4/IL-5/IL-6/TNF-α, and MAPK/NF-κB activation.

***Indigo Pulverata Levis* (2022)**

Min *et al*. (2022) demonstrated the anti-inflammatory effect of *I. Pulverata Levis* (IPL), known as Chung-Dae in AD study. In the *in vitro* experiments, WE of IP was shown to suppress the expression of RANTES/TARC/MDC/MCP-1/MIP-3α/ICAM1 and the nuclear translocation of NF-κB in TNF-α/IFN-γ-stimulated HaCaT cells. In the *in vivo* experiments, the oral administration of IPWE suppressed DNCB-induced spleen hypertrophy, dermatitis, eosinophil/mast cell recruitment, serum IgE/TNF-α, tissue TNF-α/IL-6/IL-13, and activation of ERK/p38/NF-κB.

***Paeonia lactiflora* (2022)**

The ameliorative effect of water root extract (WRE) of *P. lactiflora* (PL) in an experimental model of AD was recently reported (Lee *et al*., 2022a). The experimental results indicate that PLWRE has an anti-inflammatory effect in LPS-stimulated bone marrow-derived macrophages by suppressing inflammatory molecules (TNF-α; IL-6, -10, -12; iNOS; and COX-2) and in DNCB-induced AD BALB/c mice by ameliorating serum cytokines (TNF-α, IL-6, and IL-12)/IgE, skin dermatitis, and tissue IL-6/IL-12/IL-17A.

***Helianthus annuus* (2022)**

It was recently reported that ELE of *H. annuus* (HA) mitigates IL-2 generation following anti-CD3/CD28 or PMACI stimulation in human Jurkat T cells. In addition, HAELE suppresses anti-CD3/CD28-induced TAK, IκBα, MAPK activation, and nuclear translocation of NF-κB. In the *in vivo* experiments, oral gavage of HAELE was found to mitigate increases in the levels of ear thickness, serum IgE, and lymph node size in DNCB-treated BALB/c mice (Lee *et al*., 2022b).

CONCLUSION AND PERSPECTIVES

Based on previous and current experimental results, we have summarized and described the beneficial effects of HEs beginning with a brief introduction of experimental models of AD. Thus, this review confirms the beneficial properties of HEs and their usefulness in AD therapy. This review also facilitates comprehensive understanding regarding the establishment of AD experimental models by detailing summarized information on the *in vitro* and *in vivo* models used in the study of AD. In AD research using HEs, further mechanistic studies and confirmation of safety will facilitate the development of AD drugs and adjuvants for prevention and treatment.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

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