Allergy Inhibition Using Naturally Occurring Compounds Targeting Thymic Stromal Lymphopoietin Pathways: a Comprehensive Review

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Abstract

Naturally occurring compounds have widely been applied to treat diverse pharmacological effects, including asthma, allergic diseases, antioxidants, inflammation, antibiotics, and cancer. Recent research has revealed the essential role of the thymic stromal lymphopoietin (TSLP) in regulating inflammatory responses at mucosal barriers and maintaining immune homeostasis. Asthma, inflammation, and chronic obstructive pulmonary disease are allergic disorders in which TSLP plays a significant role. Although TSLP's role in type 2 immune responses has undergone comprehensive investigation, its involvement in inflammatory diseases and cancer has also been found to be expanding. However, investigating how to block the TSLP pathway using natural products has been limited. This paper summarizes the roles of various medicinal plants and their chemical components that effectively inhibit the TSLP pathway. In addition, we also highlight the contributions of several plant-derived compounds to treat allergic diseases via targeting TSLP. This review intends to offer innovative concepts to scientists investigating the use of naturally produced compounds and extracts for the treatment of allergic illnesses.

Key Words: Allergic disease, Thymic stromal lymphopoietin, Medicinal plant, Naturally occurring compound

INTRODUCTION

Allergic diseases (ADs) represent one of the most common diseases prevalent in numerous parts of the world (Weiss and Sullivan, 2001; Comeau and Ziegler, 2010; Wu *et al*., 2021). Increasing prevalence of these diseases is seen as a worldwide concern leading to significant rise in healthcare spending. According to the World Health Organization (WHO), ADs are the fourth leading chronic disease, with 20 to 30% of the people worldwide currently affected, which will steadily rise to 50% by 2050 (Papadopoulos *et al*., 2012; Wu *et al*., 2021). The quality of life of the affected individuals is severely reduced by chronic eczematous lesions, pruritus, sleep loss, food limitations, and psychosocial affections, even if it is a serious condition with a milder severe form. Furthermore, ADs are also related to the development and malignant progression of many cancers (El-Zein *et al*., 2014), inflammatory (Barnes 2000), asthma (Eguiluz-Gracia *et al*., 2018), rheumatologic (Murdaca *et al*.,

2019), neurological diseases (Tzeng *et al*., 2018), and cardiovascular disorders (Silverberg *et al*., 2018).

Thymic stromal lymphopoietin (TSLP) belongs to the interleukin 2 (IL-2) family and is central in developing atopic diseases such as atopic dermatitis, allergic rhinitis, and asthma. TSLP works via a heterodimeric receptor complex composed of the thymic stromal lymphopoietin receptor CRLF2 and the IL-7Rα chain. Upon binding, STAT5 is phosphorylated, leading to the expression of downstream transcription factors. TSLP-activated dendritic cell (DCs) cause vigorous multiplication of the allogeneic CD4+ T cells, which later differentiate into T helper 2 (Th2) cells and release allergy-promoting cytokines, such as IL-4, IL-5, IL-13, and TNF-, activating B and mast cells as well as other leukocytes. In the presence of IL-4 and TSLP, naive CD4+ T cells differentiate into IL-4+ and IL-4- Th2 cells. Following such an occurrence, the IL-4-negative population evolves to form a distinct subgroup of IL-13+, IL-5+, and IL-9+ T cells. High TSLP levels in lymph nodes induced the formation

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of a population of IL-4- and IL-13⁺ T cells *in vivo*. Many studies have emphasized that aberrant TSLP signaling is closely associated with allergic inflammation, including asthma, allergic rhino conjunctivitis, atopic dermatitis, anaphylaxis, and urticaria (Akdis, 2012). Indeed, growing bodies of experimental and clinical evidence suggest that high TSLP expression is associated with allergic diseases in humans and mice.

Moreover, another study has shown that inhibiting the TSLP receptor in a primate animal model can lead to decreased allergic inflammation (Cheng *et al*., 2013). However, despite the urgency to investigate anti-allergic medications, there have been relatively few studies on naturally existing substances that specifically modulate the TSLP signaling pathways. Thus, inhibiting the display and secretion for targeting TSLP, IL-25, and IL-33 by phytochemicals is a feasible preventive or therapeutic approach that may assist in treating allergic inflammation, atopic dermatitis, asthma, and other allergic states.

Natural compounds have remained instrumental in drug discovery, encompassing various applications such as anti-allergic, anti-inflammatory, antioxidant, antibiotic, anti-bacterial, and even anti-cancer properties (Newman, 2021). Approximately 60% of newly approved small molecule drugs by the Food and Drug Administration (FDA) in the last three decades are believed to have originated from or are connected to natural products (Patridge *et al*., 2016). Significantly, several methodologies have been used to investigate their pharmacological effects, leading to notable advancements in the field of pharmaceutical research (Atanasov *et al*., 2021; Wainwright *et al*., 2022). Multiple allergy medications, such as antihistamines, corticosteroids, anti-inflammatory medications, and mast cell blockers, effectively alleviate symptoms. However, these treatments have side effects and certain limitations when used for prolonged durations (Bantz *et al*., 2014). Although traditional herbal medicines and their phytochemicals have long been used to treat ADs, little is known about the potential of inhibiting the TSLP pathway using natural compounds for treating the disease (Adhikary *et al*., 2021). In our continuing efforts to study the potential anti-allergic effects of naturally occurring compounds (Park *et al*., 2017; Nguyen *et al*., 2018; Park *et al*., 2019b; Vinh *et al*., 2019a, 2019b; Nguyen *et al*., 2020; Shin *et al*., 2021), the current review is the first comprehensive report on the possible natural compounds inhibiting the TSLP pathway. Furthermore, it offers a scientific basis for further investigating the mechanisms underlying anti-allergic properties and their potential application in related diseases.

INHIBITION OF TSLP IN ALLERGIC DISEASES USING MEDICINAL PLANTS AS TARGETED THERAPIES

For ages, herbal therapy has been used to heal and treat various illnesses. Their wide availability, affordability, and lack of side effects compared to synthetic pharmaceuticals have led to the worldwide wise utility of such herbal medicines. The WHO estimates that around 60% of people worldwide and about 80% of those living in underdeveloped nations rely on herbal medicines for their primary healthcare needs (Newman, 2021). TSLP, a cytokine that participates in the immune responses, crucially regulates allergic conditions and asthma (Comeau and Ziegler, 2010). It is primarily produced by epithelial cells, such as those lining the respiratory and gastroin-

testinal tracts. It acts as an early warning signal in response to environmental triggers, such as allergens. The mechanism of action of TSLP in allergy involves activating various immune cells that promote allergic inflammation. Upon exposure to allergens such as pollen, dust mites, or certain dietary proteins, epithelial cells in the airways or gut secrete TSLP, which subsequently engages with dendritic cells and antigen-presenting cells, playing a vital role in the initiation and control of immunological responses (Adhikary *et al*., 2021). TSLP activates DCs by binding to specific receptors on their surface, leading to their maturation and migration to nearby lymph nodes. In the lymph nodes, the DCs present the allergenic proteins to the naive T cells, initiating an allergic immune response. Upon interaction with TSLP-activated DCs naive T cells differentiate into Th2 cells, a specific subset of T helper cells that release cytokines such as IL-4, IL-5, and IL-13 (Fig. 1) (Shen *et al*., 2012). These cytokines promote the recruitment and activation of other immune cells, such as eosinophils, mast cells, and basophils, involved in allergic inflammation. Eosinophils release inflammatory mediators and promote tissue damage. Mast cells and basophils release histamine, leukotrienes, and other chemicals that cause the symptoms associated with allergic reactions, including itching, swelling, mucus production, and bronchoconstriction. Additionally, TSLP can directly act on other cell types, such as B cells, which produce antibodies, and epithelial cells, further amplifying the allergic response (Yoou *et al*., 2016a). Thus, TSLP secretion by epithelial cells in response to allergens leads to the activation of DCs, differentiation of Th2 cells, and subsequent release of inflammatory cytokines, contributing to the allergic immune response and the development of allergic inflammation in tissues such as the airways or gut. Gaining insight into the processes of TSLP and its significance in allergic illnesses is crucial for the development of novel therapeutic strategies to address allergies and asthma. Researchers are exploring the potential of targeting TSLP or its receptors to modulate allergic responses and alleviate symptoms associated with allergic diseases. The ability of the medicinal extracts to treat AD has been delineated in this review.

Alpinia intermedia (AI)

The perennial plant *Alpinia intermedia* (AI), traditionally used as folk medicine in Japan, ameliorated the severity of AD both *in vitro* and *in vivo*. *In vitro* study, AI extract inhibited TSLP expression and mast cell degranulation. *In vivo*, topical application of AI extract to the mice skin significantly reduced scratching behavior and improved skin barrier function. The addition of the extracts to cell cultures resulted in a reduction of TSLP mRNA expression in PAM212 keratinocytes, decreased degranulation in bone marrow-derived cultured mast cells and neurite outgrowth in PC12 cells. Thus, it indicates that the extract of this plant enhances skin condition by suppressing various inflammatory responses, which may serve as a therapeutic intervention for patients with atopic dermatitis (Amagai *et al*., 2017).

Artemisia scoparia (AS)

Artemisia scoparia (AS) has been historically used in treating inflammation. It exerts anti-inflammatory effects by reduction of TSLP and interleukin production via suppressing caspase-1 activity *in vitro*. AS also inhibited MAPK and NF-κB signaling pathway to reduce cytokine production (Nam *et al*.,
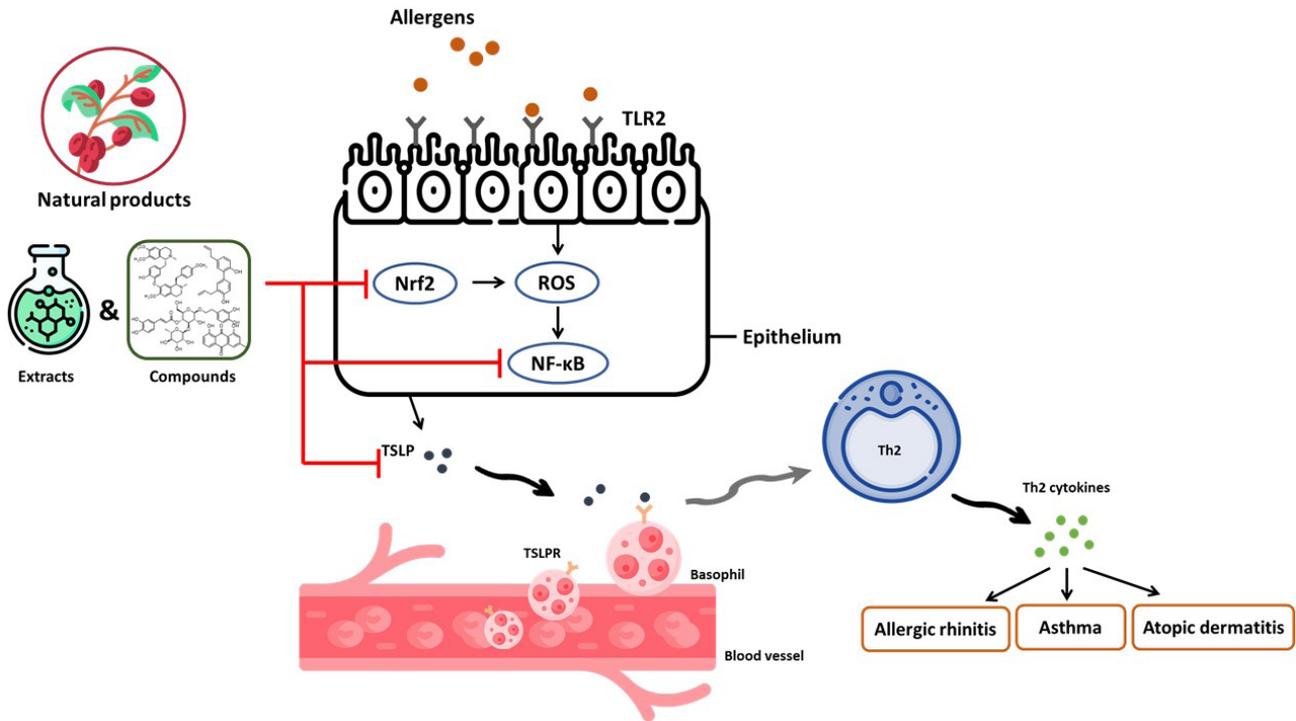
Fig. 1. The diagram illustrates the mechanism of action of phytochemicals in allergic disorders. NRF2: Nuclear factor erythroid-2-related factor 2, ROS: Reactive oxygen species, NF-kB: nuclear factor kappa-light-chain-enhancer of activated B cells, TSLP: Thymic stromal lymphopoietin, TLR2: Toll-like receptor 2, Th2: T helper 2 cell.

2018). In an *in vivo* study, AS significantly reduced the expression of histamine and cytokines, alleviated clinical symptoms of DNFB-induced skin lesions and associated scratching behaviors, diminished the infiltration of inflammatory cells in skin lesions, and lowered inflammatory cytokines within these lesions (Ryu *et al*., 2018).

Brassica oleracea (BO)

Brassica oleracea (BO) refers to diverse crop plants from the Brassicaceae family, such as cabbage or broccoli. The water extract of *Brassica oleracea* significantly reduced the secretion of TSLP and caspase-1 activity *in vitro* by using phorbol 12-myristate 13-acetate and A23187 (PMACI)-stimulated human mast cells (HMC-1 cells). BO also substantially inhibited the levels of inflammatory cytokines, which is strongly regulated by its main bioactive compound sulforaphane (Jeon *et al*., 2020).

Combretum quadrangulare (CQ)

Combretum quadrangulare (CQ), a small tree of the family Combretaceae distributed in southeastern Asia. The ethanol extract of CQ substantially suppressed the mRNA expression of cytokines in BALB/c mice with DNCB-induced atopic dermatitis-like skin lesions by suppressing MAPK signaling. CQ also reduced serum IgE levels and inhibited mast cell infiltration. Moreover, it significantly increased the expression of filaggrin, so restoring epidermal thickness and easing the clinical symptoms of AD (Park *et al*., 2020).

Fructus cnidii (FC)

Fructus cnidii (FC), a traditional Chinese medicine called

'she-chuang-zi', have reported to show anti-allergic activity. Ethyl acetate fraction of FC was found to successfully alleviate symptoms similar to AD in *in vivo* research. In addition to suppressing the quantity of cytokines and serum immunoglobulins, it prevented mast cells from diffusing into the bloodstream. Furthermore, scratching behavior and skin thickness were also alleviated. So, FC might be potent treatment for AD and other inflammatory disease (Chen *et al*., 2020a).

Gardenia jasminoide (GJ)

Gardenia jasminoides (GJ), an evergreen flowering plant called gardenia or cape jasmine, alleviated AD-like skin lesions, ear swelling and scratching behavior by its topical application onto mice. The GJ extract not only decreased the levels of serum IgE and other cytokines, but it also prevented the invasion of inflammatory cells when it was administered. And it increased skin barrier protein expression in mice. Additionally, its major components geniposidic acid and gardenoside have been reported to inhibit the production of chemokines in HaCaT cells (Park *et al*., 2019d).

Morinda citrifolia (MO)

Morinda citrifolia (MO), commonly referred to as Noni, demonstrated the ability to suppress histamine release and various chemokine levels associated with AD *in vitro*. In an *in vivo* experiment, MO reduced Th2-mediated cytokine levels in mouse skin lesions and restored the expression of skin barrier proteins, including filaggrin, loricin, and occludin. MO reduced epidermal ear thickness, mast cell infiltration, and cytokine levels *in vivo* (Kim *et al*., 2020).

Panax ginseng (PG)

Panax ginseng (PG), world's most well-known processed ginseng product, showed therapeutic effect in atopic dermatitis. PG extract suppressed the expression of well-known chemoattracts for Th2 cells, MDC (CCL22, Macrophage-derived chemokines) and TARC (CCL17, Thymus and activation-regulated chemokines), by inhibition of MAPK signaling pathway *in vitro* (Park *et al*., 2019c). PG extract reduced itching sensation by suppressing Th2-driven inflammation and reduced cytokine levels like IgE, IL-31, TNF-α and TSLP *in vivo*. Its treatment also recovered ear size and skin moisture. A 2,4,6-trinitro-1-chrolobenzene (TNCB) treated on the ears and backs of NC/Nga mice was used in the study (Lee and Cho, 2017).

Polygonum tinctorium (PT)

Polygonum tinctorium (PT), famous for traditional indigo dye, have shown anti-inflammatory activities. By blocking the caspase-1 signalling pathway, PT reduced inflammatory cytokine expression in AD-like conditions *in vitro* and *in vivo*. In an animal model of allergic rhinitis, the research shows that PT influences the synthesis of many cytokines, including TSLP, IL-32 and many others (Jeong *et al*., 2014). One study demonstrated that oral administration of PT diminished the severity of AD-like lesions in DNFB-induced skin, subsequently leading to reductions in inflammatory mRNA and protein levels, serum IgE, interleukin-4, and caspase-1 expression in mast cells. Topical treatment enhanced clinical symptoms in DNFB-induced AD mice by reducing histamine and IgE levels and inhibiting the synthesis and mRNA expression of TSLP (Han *et al*., 2014a).

Sargassum horneri (SH)

Sargassum horneri (SH) is a widely recognized and edible seaweed renowned for its antioxidant properties. SH extracts exhibited anti-inflammatory effects both *in vitro* and *in vivo*. In TNF-α/IFN-γ-stimulated HaCaT keratinocytes, SH extracts reduced the levels of various cytokines and chemokines (Han *et al*., 2021b). One of the studies examines the anti-inflammatory efficacy of SH in alleviating asthma symptoms aggravated by Particulate Matter in asthmatic mice. SH mitigates PM-induced granulocyte infiltration, inhibits TLR2/4/7 expression, and diminishes MyD88-dependent NF-κB activation. This leads to reduced expression of pro-inflammatory cytokines and chemokines, indicating SH as a viable choice for PM-exacerbated severe asthma (Herath *et al*., 2020).

Solanum tuberosum (ST)

Solanum tuberosum (ST), an herbaceous perennial grown for edible tubers, is a potential treatment for AD. Its ethanol extract has been reported to lower systemic Th2 response, which is induced by Th2 cell cytokines, via inhibition of TSLP production and blocking nuclear translocation of NF-κB p65. Additionally, it restored the protein production of filaggrin in skin lesions analogous to AD *in vivo* using NC/Nga Mice (Yang *et al*., 2015).

Combination of natural products

Cinnamomum cassia and Artemisa annua (CIAR): The combination of two herbal medicines, *Cinnamomum cassia* and *Artemisa annua* extracts (CIAR), effectively reduced the Th2-type cytokine response by suppression of TSLP expression which leads to Th2-type cytokine activation, in *in vivo* experiment, using OVA-Induced Balb/C Mice. In addition, CIAR was able to decrease the number of inflammatory cells in the blood as well as the infiltration of immune cells. It markedly decreased the thickness of the respiratory epithelium, therefore relieving asthma-like symptoms (Bae *et al*., 2022).

Huang-Lian-Jie-Du Decoction (HLJDD): Huang-Lian-Jie-Du Decoction (HLJDD) is a renowned traditional Chinese herbal formula with historical origins dating back to the Tang dynasty. It consists of various plant components in each particular proportions. HLJDD lowered the production of cytokines and inflammatory cell infiltration. It also significantly improving the clinical AD-like symptoms in mice (which were induced by 2,4-dinitrobenzene) with skin lesions by inhibition of NF-κB and MAPK pathways and increasing filaggrin expression (Chen *et al*., 2020b).

Madi-Ryuk (MDR): Madi-Ryuk (MDR) comprises various medicinal herbs, including *Pinus densiflora*, *Carthamus tinctorius*, *Hordeum vulgare*, *Ulmus davidiana*, *Taraxacum coreanum*, *Leonurus japonicas*, *Angelica gigas*, *Achyranthes aspera*, and *Glycyrrhiza uralensis* (Kim *et al*., 2019b). MDR decreased the inflammatory cytokine levels and NO production *in vitro* using human mast cell HMC-1. It also suppressed the release of histamines and TSLP production by inhibition of NF-κB, and MAPK signaling pathways. Furthermore, MDR reduced inflammatory cell infiltration via downregulation of caspase 1 expression *in vivo* (Kim *et al*., 2018).

Yu-Ping-Feng-San (YPFS): Yu-Ping-Feng-San (YPFS), a Chinese herbal decoction also known as *Jade-Screen Powder*, consists of *Radix Astragali*, *Rhizoma Atractylodis Macrocephalae*, and *Radix Saposhnikovia* (Bao *et al*., 2020). Clinically, YPFS is widely used to treat allergic disorders with few adverse reactions. It inhibited overproduction of TSLP and IL-4, 5, 13 both *in vivo* and *ex vivo*. Furthermore, YPFS effectively alleviated AD-like symptoms by upregulation of cell junction proteins including level of desmoglein-1 (DSG1), claudin-1 (CLDN-1) and occludin (OCC) (Zheng *et al*., 2019).

Natural product ointment

Jawoongo: Jawoongo, a traditional herbal medicine containing Lithospermum root and *Angelica gigas*, exhibits anti-inflammatory properties *in vitro* and *in vivo*. In *in vitro* study, it inhibited NO production and suppressed the expression of inflammation-associated molecules. In *in vivo* study, its ointment form reduced skin thickness and mast cell infiltration into mouse skin lesions. Furthermore, the administration of Jawoongo has the ability to suppress the expression of cytokines and the activation of the NF-kB and MAPK pathways in a variety of immune cell types. As a whole, it indicates that Jawoongo has the potential to be an effective candidate medicine for the treatment of AD (Ku *et al*., 2018).

Qingpeng (QP): Qingpeng ointment (QP), a chinese medicine used in treatment of AD, has been known for treating chronic itch. It suppressed scratching behavior by inhibition of MAPK signaling pathway *in vivo* (squaric acid dibutylester (SADBE) in mice). It also downregulated itch-related genes including TRPV4 and TSLP in the epidermis. Additionally, QP therapy decreased Th1/2 cytokine productions, so it might be a good clinical candidate for treatment of AD-like symptoms (Gong *et*

Table 1. Medicinal plants targeting TSLP pathways for allergic disease treatment: a summary

	Extract	Results	In vitro/In vivo	References
1	*Alpinia intermedia*	Suppression of cytokine expression and inflammatory cell infiltration. Alleviation of clinical AD-like symptoms.	*In vitro & in vivo*	Amagai *et al.*, 2017
2	*Artemisia scoparia*	Suppression of cytokine production by blocking caspse-1 signaling pathway. Alleviation of clinical AD-like symptoms.	*In vitro & in vivo*	Nam *et al.*, 2018; Ryu *et al.*, 2018
3	*Brassica oleracea*	Decrease TSLP production by blocking caspase-1 signaling pathway.	*In vitro*	Jeon *et al.*, 2020
4	*Combretum quadrangulare*	Suppression of cytokine expression by inhibition of MAPK signaling pathway. Alleviation of epidermal thickness via skin barrier function regulation.	*In vitro & in vivo*	Park *et al.*, 2020
5	*Fructus cnidii*	Inhibition of Mast cell infiltration. Alleviation of clinical AD-like symptoms.	*In vivo*	Chen *et al.*, 2020a
6	*Gardeia jasminoides*	Decrease serum IgE level and inflammatory cell infiltration. Increase skin barrier protein expression and amelioration of clinical AD-like symptoms.	*In vivo*	Park *et al.*, 2019d
7	*Morinda citrifolia*	Suppression of TSLP expression. Increase skin barrier protein expression and amelioration of clinical AD-like symptoms.	*In vitro*	Oh *et al.*, 2021b
8	*Panax ginseng*	Suppression of cytokine expression by inhibition of MAPK signaling pathway. Alleviation of clinical AD-like symptoms.	*In vitro & in vivo*	Lee and Cho 2017; Park *et al.*, 2019c
9	*Polygonum tinctorium*	Decrease cytokine expression by blocking caspase-1 signaling pathway.	*In vitro & in vivo*	Han *et al.*, 2014a; Jeong *et al.*, 2014
10	*Sargassum horneri*	Reduce cytokine expression and inflammatory response by inhibition of NF-κB pathway.	*In vivo*	Herath *et al.*, 2020
11	*Solanum tuberosum*	Suppression of TSLP production by inhibition of NF-κB pathway.	*In vitro*	Yang *et al.*, 2015
12	CIAR	Suppression of TSLP expression and mast cell infiltration.	*In vitro & in vivo*	Bae *et al.*, 2022
13	Huang-Lian-Jie-Du	Improve clinical AD-like symptoms by inhibition of MAPK and NF-κB signaling pathway.	*In vivo*	Chen *et al.*, 2020b
14	Madi-Ryuk	Inhibition of inflammatory response by blocking caspase-1, MAPK and NF-κB signaling pathway.	*In vitro & in vivo*	Kim *et al.*, 2018; Kim *et al.*, 2019b
15	Yu-Ping-Feng-San	Suppression of cytokine production. Alleviation of clinical AD-like symptoms by upregulation of cell junction proteins.	*In vitro & in vivo*	Zheng *et al.*, 2019; Bao *et al.*, 2020
16	Jawoongo	Suppression of inflammatory response and recovery of epidermal skin thickness.	*In vitro & in vivo*	Ku *et al.*, 2018
17	Qingpeng ointment	Suppression of chronic itch by regulation of itch-related genes and MAPK signaling pathway.	*In vitro & in vivo*	Gong *et al.*, 2019

IgE: Immunoglobulin E, MAPK: Mitogen-activated protein kinase.

al., 2019). Table 1 showed a summary of medicinal plants targeting TSLP pathways for allergic disease.

PHYTOCHEMICALS AS THERAPIES FOR ALLERGIC DISEASES TARGETING TSLP PATHWAYS

Secondary metabolites from medicinal plants, including alkaloids, terpenoids, phenolics, and saponins, have various pharmacological effects. In this review, we describe how natural phytochemical components inhibit TSLP in the context of allergy by targeting the TSLP pathways. The detailed references and natural agents that inhibit TSLP are listed in Table 2.

Alkaloids
Alkaloids are naturally occurring organic compounds characterized by at least one nitrogen atom and basic properties. Here, we emphasize a selection of alkaloids which target TSLP pathways for the treatment of allergic diseases (Fig. 2A).

Berberine
Berberine, a yellow-colored alkaloid effectively suppressed the NF-κB activity induced by phorbol myristate acetate and A23187. In addition, berberine inhibits the activation of caspase-1 in HMC-1 cells. Moreover, it effectively inhibits the production of TSLP in primary mast cells. These findings suggest that berberine has potential therapeutic benefits in treating inflammatory and atopic diseases by targeting TSLP inhibition (Kim *et al*., 2015a)

Neferine
Neferine has been found to have AD related preventive anti-inflammatory activity in *in vitro* and *in vivo* experiment. Neferine suppressed expression of inflammatory cytokines and ameliorated AD-like symptoms via regulation of skin moisturization and MAPK/NF-κB signaling pathway, using human keratinocyte (HaCaT) cells. Additionally, neferine suppressed swelling of spleen, a largest lymphatic organ which can be enlarged by inflammation (Yang *et al*., 2021).

Tryptanthrin
Tryptanthrin, a plant alkaloid with indoloquinazoline moiety, might be a potential drug for mast cell mediated allergic disease. In *in vitro* experiment, Tryptanthrin inhibited mast cell proliferation by downregulating the expression of MDM2, a negative regulator of p53, which is activated by TSLP and induces mast cell tumorigenesis, by using human mast cell line (HMC-1) cells. Also, IL-13, a cytokine which promotes mast cell proliferation were decreased by tryptanthrin. Furthermore, it regulated the TSLP signaling pathway by decreasing the expression of IL-7Rα (IL-7 receptor alpha chain) and TSLPR (Han *et al*., 2016).

Flavonoids
Flavonoids are plant-derived natural compounds showing diverse pharmacological activities, which generally consist of two phenolic rings and one heterocyclic ring. In this work, we suggested a group of flavonoids which is associated with TSLP regulation for the treatment of AD (Fig. 2B).

Acteoside
Acteoside, also called as verbascoside, can be potent therapeutic for AD by regulating mast cell proliferation and apoptosis. MDM2, a negative regulator of p53 target, is activated by TSLP and induces mast cell tumorigenesis. And TSLP also activates STAT5/STAT6 signaling pathway to promote mast cell development. Acteoside suppressed mast cell proliferation by blocking MDM2 and STAT signaling pathway. TSLP-stimulated HMC-1 cells exhibit an upregulation of anti-apoptotic factors and a downregulation of apoptotic factors such as caspase-3. Acteoside induced apoptosis of mast cells by regulation of bcl-2 and caspase-3 (Yoou *et al*., 2015).

Baicalein
Baicalein, an essential compound derived from *Scutellaria baicalensis*, is the first small molecule capable of blocking TSLP signaling. Additionally, *in vivo* and *in vitro* studies have shown that baicalein effectively inhibits TSLP signaling pathway by blocking the interaction of TSLP and its receptor, TSLPR (Zhu *et al*., 2021). Also, baicalein inhibited type 2 immune response by suppression of STAT5, which is activated by TSLP signaling pathway (Park *et al*., 2019a).

Epigallocatechin-3-O-gallate (EGCG)
EGCG, generally referred to as a potent antioxidant, is a primary bioactive constituent found in green tea. Many reports demonstrated its inflammatory activity. In HMC-1 cell line, EGCG suppressed NF-κB activity by inhibiting caspase-1, a special caspase family protein which is responsible for the maturation of IL-1β and IL-18 and activating NF-κB signaling pathway. EGCG decreased the production and mRNA expression of TSLP through blocking NF-κB signaling pathway. So EGCG can be a potential therapeutics for TSLP induced allergic disease (Moon *et al*., 2012a).

Eupatilin
Eupatilin, a lipophilic flavonoid, can be a valuable candidate as an anti-allergic agent. Eupatilin demonstrates beneficial effects in a mouse model of AD-like symptoms induced by oxazolone. It effectively reduced the expression of inflammatory cytokines and recovered skin damage by increasing the production of skin structural proteins (Jung *et al*., 2018).

Fisetin
Fisetin, a bioflananol abundant in fruit and vegetables, has reported to possess anti-inflammatory activity. It suppressed histamine release and expression of inflammatory markers like COX-2 and IL-4 *in vitro*. In *in vivo* study, fisetin alleviated not only LPS-induced inflammation but also the clinical symptoms of AD. Fisetin reduced ear swelling and epidermal thickness in DNFB-treated mice. And it also inhibited infiltration of inflammatory cells into skin lesions and cytokine productions (Kim *et al*., 2014).

Formonectin
Formonectin (FMN), an isoflavone phytoestrogen, exhibits a protective effect in allergic diseases *in vivo* and *in vitro*. FMN inhibits DC activation which leads to T cell differentiation. FMN is associated with the downregulation of TSLP/IL-33 production through GPER (G protein-coupled estrogen receptor) signaling pathway (Yuan *et al*., 2020). It also upregulates the expression of the A20 (TNFAIP3) protein, a regulator of im-

Table 2. Phytochemicals as Therapies for Allergic Diseases Targeting TSLP Pathways

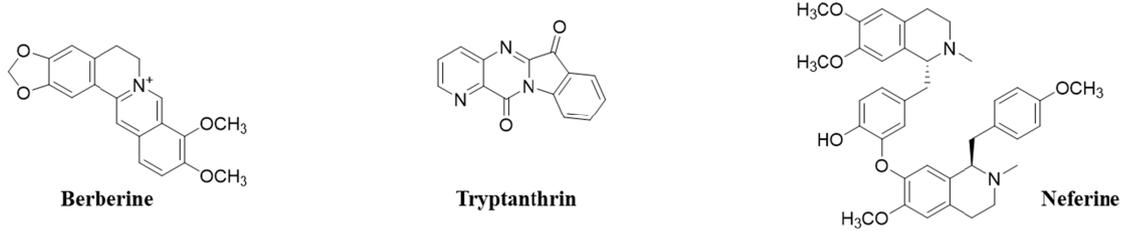|	Compound	Result	Source	In vitro or in vivo	References
	Alkaloids				
1	Berberine	Inhibition of TSLP production via caspase-1/NF-κB signaling pathway.	Berberis vulgaris	In vitro	Kim et al., 2015a
2	Neferine	Suppression of cytokine expression via inhibition of NF-κB signaling pathway. Amelioration of AD-like clinical symptoms.	Nelumbo nucifera	In vitro	Yang et al., 2021
3	Tryptanthrin	Anti-proliferative effect on TSLP-stimulated mast cell proliferation via MDM2/p53 pathway regulation.	Strobilanthes cusia	In vitro	Han et al., 2016
	Flavonoids				
4	Acteoside	Suppression of mast cell proliferation through regulation of MDM2/STAT pathway and apoptotic markers	Verbascum sinuatum L	In vitro	Yoou et al., 2015
5	Baicalein	Inhibition of TSLP production via blocking TSLP and TSLP receptor (TSLPR) interaction Suppression of type 2 immune response via STAT5 signaling pathway.	Scutellaria baicalensis	In vitro & in vivo	Park et al., 2019a; Yoshida et al., 2021; Zhu et al., 2021
6	Epigallocatechin-3-O-gallate	Inhibition of TSLP production via caspase-1/NF-κB signaling pathway.	Camellia sinensis	In vitro	Moon et al., 2012a
7	Eupatilin	Inhibition of inflammatory cytokine expression and recovery of skin barrier proteins.	Artemisia asiatica	In vivo	Jung et al., 2018
8	Fisetin	Attenuation of LPS induced inflammation and AD-like clinical symptoms.	Rhus cotinus	In vivo	Kim et al., 2014
9	Formononetin	Inhibition of DC activation and T cell differentiation. Suppression of TSLP/IL-33 expression via GPER signaling pathway.	Trifolium pratense	In vitro & in vivo	Shen et al., 2014; Zheng et al., 2019; Yuan et al., 2020; Yoshida et al., 2021; Yuan et al., 2021
10	Kaempferol	Inhibition of TSLP production via MAPK and NF-κB signaling pathway.	Ginkgo biloba	In vitro	Nam et al., 2017
11	Naringenin	Inhibition of TSLP production via NF-κB signaling pathway and suppression of mast cell proliferation through regulation of MDM2/STAT pathway.	Citrus reticulata	In vitro & in vivo	Moon et al., 2011; Han et al., 2018
12	Quercetin	Inhibition of cytokine production by MAPK and NF-κB signaling pathway Inhibition of mast cell deregulation and infiltration by PLC-γ signaling pathway.	Camellia sinensis	In vitro & in vivo	Jung et al., 2010; Gupta et al., 2016; Sozmen et al., 2016b; Beken et al., 2020
13	Saponarin	Inhibition of inflammatory cytokine expression via MAPK signaling pathway and maintaining skin moisture.	Hordeum vulgare L	In vivo	Min et al., 2021
14	Calycosin	Recovery of epithelial tight junction by inhibition of HIF1-α. Inhibition of TSLP/IL-33 production via TLR4 mediated NF-κB signaling pathway.	Astragalus propinquus	In vitro & in vivo	Shen et al., 2014; Tao et al., 2017; Jia et al., 2018; Yuan et al., 2020

Table 2. Continued 1

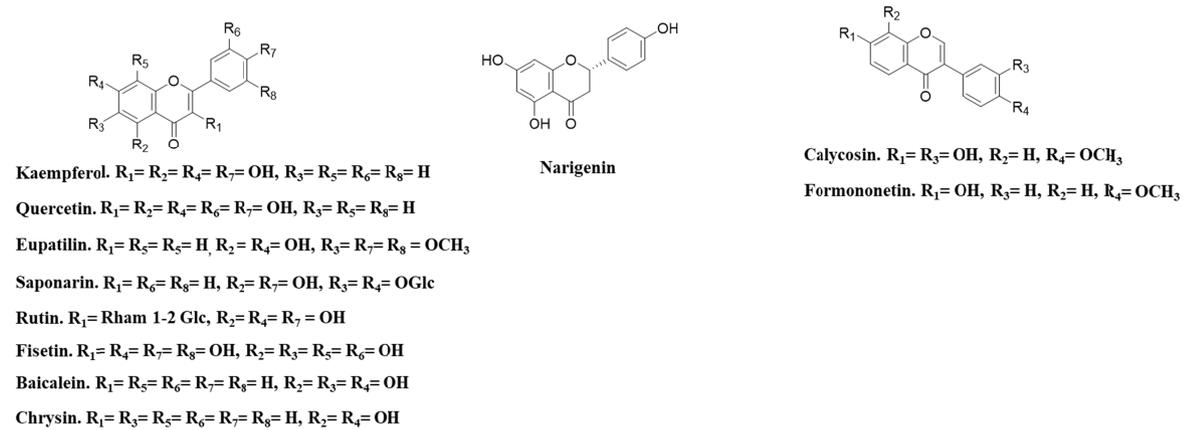|	Compound	Result	Source	In vitro or in vivo	References
	Phenols				
15	Catechin	Attenuation of nasal allergic reaction via modulation of T helper cell differentiation.	*Camellia sinensis*	In vitro & in vivo	Pan et al., 2018a
16	Chrysin	Inhibition of inflammatory cytokine production by blocking NF-κβ signaling pathway. Inhibition of inflammatory cytokine expression via MAPK and NF-κβ/EGR-1 signaling pathway	*Passiflora caerulea*	In vitro & in vivo	Yeo et al., 2021a
17	Chrysophanol	Suppression of cytokine expression via caspase-1/NF-κβ and MAPK signaling pathway. Inhibition of mast cell proliferation by regulation of MDM2/p53 and apoptosis axis.	*Rheum rhabarbarum*	In vitro & in vivo	Jeong et al., 2018a; Han et al., 2019; Kim et al., 2019a
18	Cinifugin	Suppression of cytokine expression and recovery of tight junction deficiency.	*Saposhnikovia divaricata*	In vitro & in vivo	Wang et al., 2017
19	Curcumin	Decrease of TSLP production via caspase-1/NF-κβ and STAT6/GATA3 signaling pathway.	*Curcuma longa*	In vitro & in vivo	Moon et al., 2013
20	Eckol	Suppression of chemokine and cytokine production via NF-κβ and MAPK signaling pathway.	*Ecklonia cava*	In vitro	Cho et al., 2020
21	Ferulic acid	Decrease of chemokine production and suppression of immune cell infiltration.	*Ferula communis*	In vitro & in vivo	Brugiolo et al., 2017a
22	Licochalcone A	Suppression of TSLP and cytokine production by decrease the DNA-binding activity of NF-κβ.	*Glycyrrhiza glabra*	In vitro	Kim et al., 2015c
23	Manoalide	Suppression of cytokine expression via blocking NF-κβ and MAPK signaling pathway	*Luffariella variabilis*	In vitro	Yeom et al., 2021
24	Resveratrol	Suppression of IL-25, IL-33, TSLP expression and recovery of epidermis irregularity.	*Veratrum grandiflorum*	In vivo	Sozmen et al., 2016a
25	Rosmarinic acid	Inhibition of TSLP-induced mast cell proliferation by regulation of MDM2/pSTAT6. Blocking TSLP signaling pathway.	*Rosmarinus officinalis L.*	In vitro & in vivo	Yoou et al., 2016b
26	Tannic acid	Decrease of TSLP and cytokine expressions via caspase-1/NF-κβ and alleviation of clinical AD-like symptoms.	*Caesalpinia spinosa*	In vitro & in vivo	Jung et al., 2010; Kim et al., 2018
27	Vanillic acid	Inhibition of allergic symptoms via blocking NF-κβ and MAPK signaling pathway.	*Angelica Sinensis*	In vitro	Jeong et al., 2018b
	Lignans				
28	(+)-galbelgin	Effective against pSTAT5 and TSLP/TSLPR interactions in both *in vitro* assays (STAT5 test and ELISA assay), the remaining two also	*Machilus thunbergia*	In vitro	Shin et al., 2021
29	Machilin A		*Machilus thunbergia*		Shin et al., 2021
30	Meso-dihydroguaiaretic acid		*Machilus thunbergia*		Shin et al., 2021

Table 2. Continued 2

	Compound	Result	Source	In vitro or in vivo	References
	Terpenoids				
31	Astragaloside IV	Improve allergic symptoms by suppression of pro-allergic cytokine expression.	*Astragalus membranaceus var mongholicus*	*In vitro & in vivo*	Zhang *et al.*, 2015; Bao *et al.*, 2016a
32	Atractylenolide III (ATL-III)	Inhibition of mast cell proliferation and decrease the production of TSLP-induced pro-inflammatory cytokines.	*Atractylodes japonica*	*In vitro*	Yoou *et al.*, 2017
33	Atractylone	Suppression of mast cell activation and chemokine production. Alleviation of clinical allergic symptoms *in vivo*	*Atractylodes macrocephala*	*In vitro & in vivo*	Kim *et al.*, 2016
	β-sitosterol	Inhibition of TSLP production by Ca²⁺/caspase-1/NF-kβ pathway.	*Sambucus chinensis*	*In vitro & in vivo*	Han *et al.*, 2014b
35	Deacetylasperulosidic acid	Inhibition of cytokine production via blocking NF-kβ and MAPK signaling pathway and restoring clinical AD-like symptoms.	*Morinda citrifolia*	*In vitro*	Oh *et al.*, 2021a Oh *et al.*, 2021b
36	Ginsenoside Rh2	Inhibition of TSLP expression and ameliorated AD-like skin symptoms by NF-kβ pathway.	*Panax ginseng*	*In vitro & in vivo*	Ko *et al.*, 2019
37	Ursolic acid	Decrease TSLP expression by intracellular Ca²⁺ level regulation and NF-kβ signaling pathway.	*Camellia sinensis*	*In vitro*	Moon *et al.*, 2019
38	(-)-loliolide	Suppression of cytokines expression by downregulation of NF-kβ and MAPK pathway and upregulation of Nrf2-/HO-1 signaling pathway.	*Fumaria officinalis L.*	*In vitro & iin vivo*	Han *et al.*, 2021a

STAT5: Signal transducer and activator of transcription 5, LPS: Lipopolysaccharide, MDM2: mouse double minute 2, PLC-r: phospholipase C gamma, HIF1-a: Hypoxia-Inducible Factor 1-alpha, GATA3: GATA-binding protein 3, EGR-1: early growth response 1, HO-1: Heme oxygenase-1.

(A)

Berberine

Tryptanthrin

Neferine

(B)

Kaempferol. R$_1$= R$_2$= R$_4$= R$_7$= OH, R$_3$= R$_5$= R$_6$= R$_8$= H

Quercetin. R$_1$= R$_2$= R$_4$= R$_6$= R$_7$= OH, R$_3$= R$_5$= R$_8$= H

Eupatilin. R$_1$= R$_5$= R$_5$= H, R$_2$= R$_4$= OH, R$_3$= R$_7$= R$_8$ = OCH$_3$

Saponarin. R$_1$= R$_6$= R$_8$= H, R$_2$= R$_7$= OH, R$_3$= R$_4$= OGlc

Rutin. R$_1$= Rham 1-2 Glc, R$_2$= R$_4$= R$_7$ = OH

Fisetin. R$_1$= R$_4$= R$_7$= R$_8$= OH, R$_2$= R$_3$= R$_5$= R$_6$= OH

Baicalein. R$_1$= R$_5$= R$_6$= R$_7$= R$_8$= H, R$_2$= R$_3$= R$_4$= OH

Chrysin. R$_1$= R$_3$= R$_5$= R$_6$= R$_7$= R$_8$= H, R$_2$= R$_4$= OH

Narigenin

Calycosin. R$_1$= R$_3$= OH, R$_2$= H, R$_4$= OCH$_3$

Formononetin. R$_1$= OH, R$_3$= H, R$_2$= H, R$_4$= OCH$_3$

(C)

Eckol

Chrysophanol

Licochalcone A

Cimifugin

Tannic acid

Curcumin

Resveratrol

Honokiol

Catechin

Chrysin

Acteoside

Bisphenol A

Ferulic acid

Vanilic acid

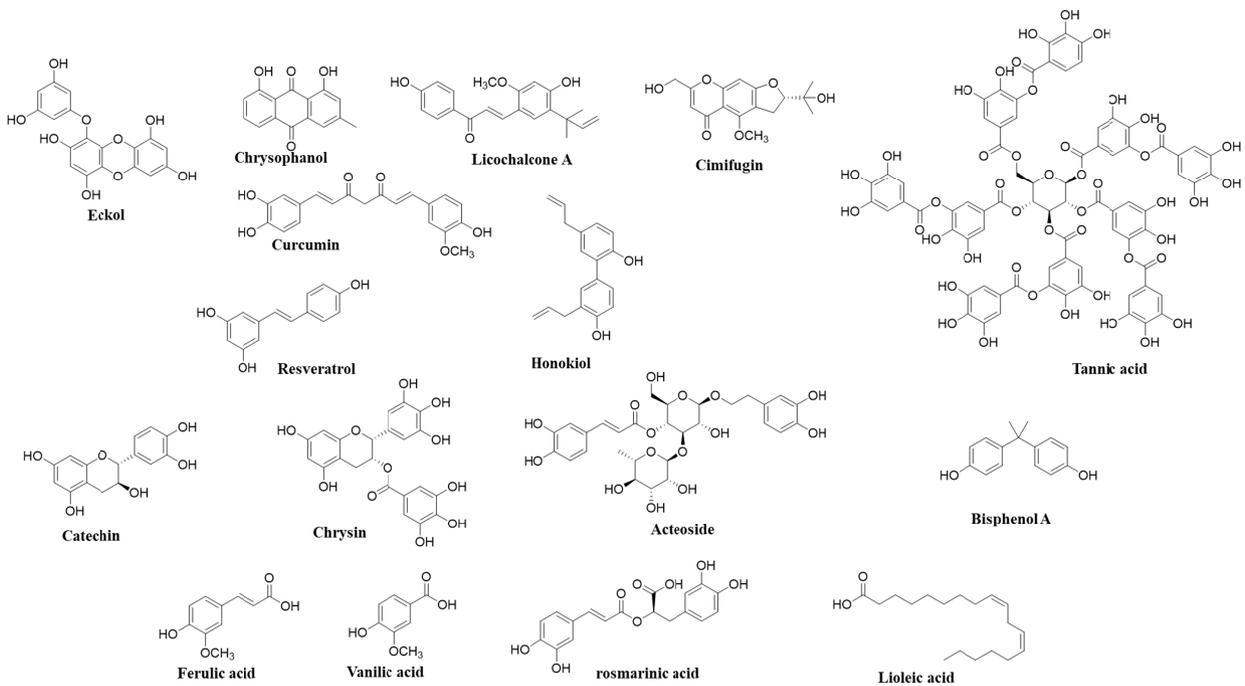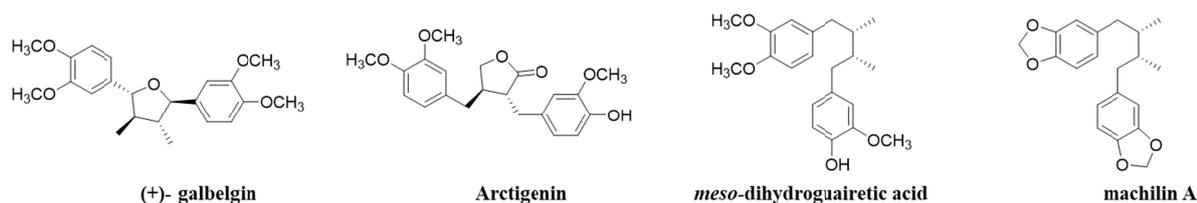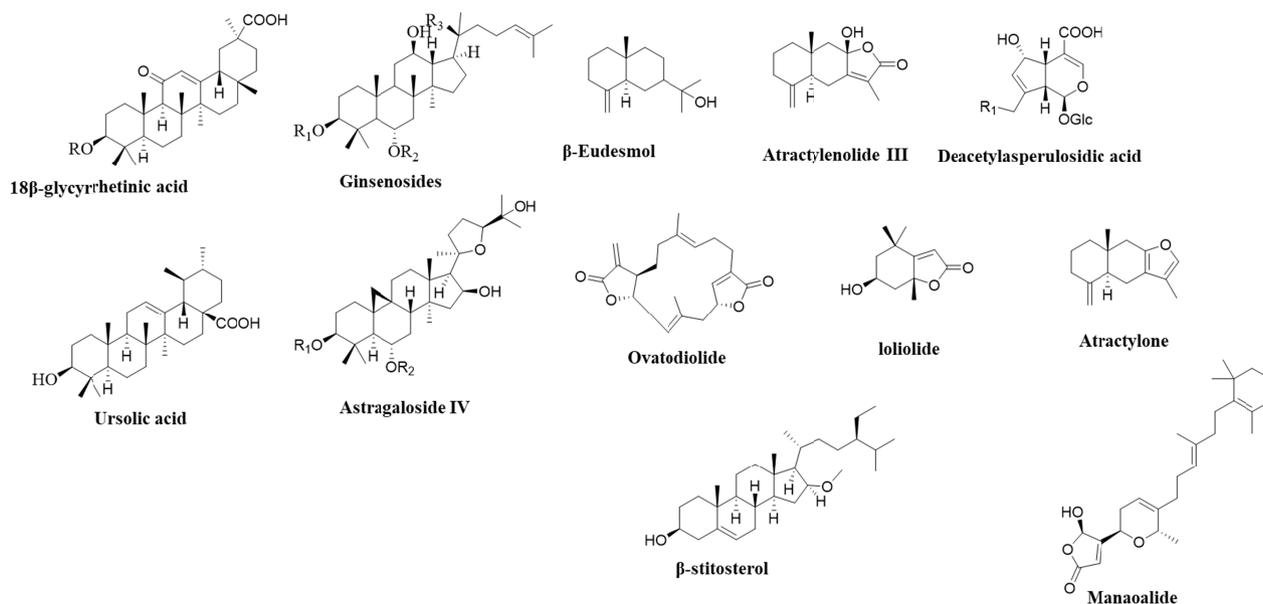rosmarinic acid

Lioleic acid

Fig. 2. Compounds with anti-allergic activity targeting TSLP pathways. (A) Alkaloids; (B) Flavonoids; (C) Phenolics; (D) Lignans; (E) Terpenoids and their derivatives.

(D)

(+)- galbelgin   Arctigenin   *meso*-dihydroguairetic acid   machilin A

(E)

18β-glycyrrhetinic acid   Ginsenosides   β-Eudesmol   Atractylenolide III   Deacetylasperulosidic acid

Ursolic acid   Astragaloside IV   Ovatodiolide   loliolide   Atractylone

β-stitosterol   Manaoalide

Fig. 2. Continued.

mune cell function in airway allergic disease. A fluorescein iso-thiocyanate (FITC)-induced mouse model and Human kerati-nocytes (HaCaT) cells were used in such experiment (Yuan *et al.*, 2021).

Kaempferol

Kaempferol is a natural flavonol having antioxidant and anti-inflammatory effects. *In vitro*, Kaempferol suppressed the production of proinflammatory cytokines by inhibition of MAPK and NF-κB signaling pathway. It also had a cytoprotective ef-fect by suppression of the LPS (lipopolysaccharide)-induced production of inflammatory mediators. Additionally, kaempfer-ol inhibited the differentiation of monocytes into macrophage-like cells. A human monocyte cell line THP-1 was used in this experiment (Nam *et al.*, 2017).

Naringenin

A flavonoid aglycone abundant in grapefruit, naringenin, exhibits a significant inhibitory effect on TSLP production via NF-kβ activity downregulation (Moon *et al.*, 2011). It also sup-pressed cell proliferation and induce apoptosis in mast cells by reducing the protein level of MDM2 and pSTAT6, while up-

regulating cleaved poly ADP-ribose polymerase (PARP) and p53 levels in TSLP-induced HMC-1 cell. As a result, narin-genin inhibited the cytokine production and inflammation (Han *et al.*, 2018).

Quercetin

Quercetin, a famous antioxidant, showed wound healing effect in inflamed state. Quercetin suppressed cytokine pro-duction by MAPK and NF-κB pathway *in vitro* by using Im-mortalized human HaCaT keratinocytes (Beken *et al.*, 2020), and also decreased IgE and cytokine levels *in vivo* (Sozmen *et al.*, 2016b). It inhibited inflammatory cell infiltration and also regulated mast cell degranulation by PLC-γ2 pathway (Gupta *et al.*, 2016). Quercetin provides a notable option to treat air-way inflammation.

Saponarin

Saponarin, a flavone glycoside mainly obtained from bar-ley, significantly inhibits inflammatory and allergic responses in various cell lines (RAW 264.7, RBL-2H3, and HaCaT Cells). It showed inhibitory activity on cytokine production through MAPK signaling pathway. It suppressed the expression of in-

flammatory mediators like COX-2 and suppressed chemokine expressions. It also protects skin by maintaining moisture and physicochemical barriers by upregulation of hyaluronan synthase-3 (HAS3), aquaporin 3 (AQP3) (Min *et al*., 2021).

Phenols

Phenolic compounds, natural bioactive substances synthesized through shikimic acid and phenylpropanoid pathway, are found abundantly in fruits and vegetables. Here, we highlighted several phenolics, which have been reported as inhibitors of TSLP derived from medicinal plants (Fig. 2C).

Calycosin

Calycosin is a phytoestrogen, supposed to have a potential therapeutic candidate for AD. It improved epithelial tight junction by inhibiting the expression of HIF1-α, increasing epithelial permeability and upregulated under allergic condition *in vivo* and *in vitro* (Jia *et al*., 2018). It also reduced the production of TSLP and IL-33 by inhibiting the TLR4 mediated NF-κB signaling pathway. *In vivo*, mice were just sensitized with FITC (fluorescein isothiocyanate), and immortalized human keratinocytes (HaCaT cells) were used *in vitro* (Tao *et al*., 2017).

Catechin

Catechin, famous for its anti-inflammatory activity, might be a good treatment for nasal allergy. Catechin decreased TSLP production by blocking phosphorylation of NF-κB p65 signaling pathway *in vitro*. In *in vivo* experiment, catechin reduced clinical symptoms of nasal allergy in allergic rhinitis mouse model. The counting of sneezing and nose rubbing behavior was decreased. Additionally catechin reduced cytokine levels in the serum and modulated the balance between T helper type 2 and T helper type 1 cells (Pan *et al*., 2018b).

Chrysin

A 5,7-dihydroxyflavone, chrysin is reported to decrease the production of inflammatory cytokines via MAPK and NF-κB signaling pathways in *in vivo* and *in vitro* experiment using HaCaT keratinocytes. Especially, chrysin inhibited ERK1/2 and JNK1/2-mediated EGR-1 (early growth response 1) expression, a transcription factor which induces TSLP production under inflamed state (Yeo *et al*., 2021a).

Chrysophanol

Chrysophanol, a unique anthraquinone isolated from fungi, is reported to exert various biological activities. Chrysophanol inhibited various cytokines expressions by inhibiting caspase-1, NF-κB and MAPK signaling pathway *in vitro* (Jeong *et al*., 2018a). It also prevented and the production of TSLP by blocking TSLP and TSLPR interaction (Kim *et al*., 2019a). In *in vivo* study, it alleviated clinical allergic symptoms while inhibiting the proliferation of mast cells via regulation of MDM2/p53 and caspase-3/Bax/Bcl-2 signaling pathway (Han *et al*., 2019)

Cimifugin

Cimifugin, an effective compound found in *Saposhnikovia divaricate*, is used as medicine for anti-inflammatory disease. In mice atopic dermatitis model, it alleviated AD symptoms via regulating tight junction deficiency by increasing tight junction gap protein expression. Also *in vitro* study, tight junction protein expressions like CLDN-1 and OCC were increased by cimifugin. Also, TSLP and Th2 cytokine production was suppressed. This process attenuates the development of allergic inflammation, so cimifugin might have potential of targeting primary cytokines and TJs for therapeutic intentions. FITC mice and immortalized human epidermal (HaCaT) cells were used in this study (Wang *et al*., 2017).

Curcumin

Curcumin, a main constituent from tumeric, is known as a strong anti-inflammatory agent. Curcumin reduced LPS-induced NO production *in vitro* (Ben *et al*., 2011). It suppressed the expression of TSLP and Th2-cytokines via downregulation of caspase-1/NF-κB and STAT6/GATA3 signaling pathway *in vivo* and *in vitro*. In mice, inflammatory cell infiltration was decreased, and redox imbalance was restored under airway inflamed state (Sharma *et al*., 2019).

Eckol

Eckol, one of phlrotannins isolated from marine brown algae *Ecklonia cava* (EC), has potential for drugs of AD. It was reported that eckol from EC inhibited the activation of MAPKs and NF-κB signaling pathway by hindering the TNF-α/IFN-γ-mediated nuclear translocation of NF-κB p65 in HaCaT cells. It also inhibited MAPK signaling pathway, which consequently suppressed mRNA expression of proinflammatory cytokines and chemokine production (Cho *et al*., 2020).

Ferulic acid

Ferulic acid (FA) inhibits an allergic Th2 response by effectively decreasing key features of allergic markers *in vivo* (Brugiolo *et al*., 2017b). FA decreased inflammatory cytokines and chemokines via inhibition of NF-κB signaling pathway. Also, it suppressed Th2 immune response and regulated the filaggrin upregulation (Zhuo *et al*., 2020, Brugiolo *et al*., 2017b). Additionally, FA mitigates allergic symptoms by decreasing infiltration of inflammatory cells and restoring the balance of Th2 cell proliferation. For the *in vivo*, ovalbumin- (OVA-) induced Th2-mediated allergic mice was used, and for the *in vitro* antigen-presenting dendritic cells (DCs) was used in this study (Lee *et al*., 2015).

Licochalcone A

Licochalcone A is a chaloconid, a natural phenol exhibiting anti-inflammatory activity *in vitro*. Licochalcone A suppressed the expression and production of TSLP and various proinflammatory mediators. It showed the inhibitory effect on IKK activity, and also inhibited NF-κB nuclear translocation and DNA-binding activity by using BEAS 2B cells and primary bronchial epithelial cells. So Licochalcone A could be a prominent option for treatment of asthma (Kim *et al*., 2015b).

Manoalide

Manoalide, a marine sesterterpenoid famous for a calcium channel blocker, has been known for its anti-cancer and super oxide scavenging activity. In HMC-1 cells, it prevented the secretion of various inflammatory cytokines without cytotoxic effects by inhibiting caspase-1 activity. Furthermore, manoalide treatment effectively inhibited mast cell stimulation by blocking NF-κB and MAPK signaling pathway. So it seems that manoalide can be potential candidate for allergic disease treatment (Yeom *et al*., 2021).

Resveratrol

Resveratrol, a stilbenoid antioxidant, demonstrates well known anti-inflammation activity. In *in vivo* experiment, resveratrol mitigated inflammation severity by decreasing expression of keratinocyte derived cytokines in AD-like skin lesions. Also, resveratrol ameliorated thickening and irregularity of mice epidermis skin via controlling keratinocyte derived apoptosis (Sozmen *et al*., 2016a).

Rosmarinic acid (RA)

Rosmarinic acid (RA) effectively reduced TSLP-induced mast cell proliferation by decreasing the expression of MDM 2 and pSTAT6 *in vitro*. RA also modulated mast cell apoptosis via regulating apoptotic marker expression, inducing PARP cleavage by p53 and caspase 3 activation and reducing procaspase-3 and Bcl-2, and *in vivo* experiment, it inhibited inflammatory molecules production through TSLP signaling pathway (Yoou *et al*., 2016b).

Tannic acid

Tannic acid (TA), a polyphenol natural product with bitter taste, effectively suppressed TSLP and various inflammatory cytokine expressions by inhibition of caspase-1, NF-κB and MAPK signaling pathways *in vitro* (Jung *et al*., 2010). TA also might be associated with VEGF signaling pathway, a regulator of permeability of epithelial cells and overexpressed in AD-like symptoms. In *in vivo* experiment, TA decreased clinical AD-like symptoms (Kim *et al*., 2018).

Vanillic acid

Vanillic acid, a benzoic acid derivative widely used as flavoring agent, ameliorated allergic response by controlling MAPK and NF-κB signaling pathway. MAPK signaling pathway has been established an important role in controlling inflammatory gene expression. In HMC-1 cells, VA reduced the levels of TSLP and proinflammatory cytokines via inhibition of MAPK signaling pathway. Furthermore, vanillic acid significantly inhibited development of allergic response by blocking caspase-1 and NF-κB signaling pathway (Jeong *et al*., 2018b).

Lignans

Lignans are known for their antioxidant and potential health-promoting properties. Lignans also inhibit the TLSP. Three lignans, specifically (+)-galbelgin, meso-dihydroguairetic acid, and machilin A, (Fig. 2D) isolated from *Machilus thunbergia*, function as antiallergic bioactive substances. All three compounds shown significant inhibitory effect against pSTAT5 and TSLP/TSLPR interactions in both *in vitro* assays (STAT5 test and ELISA assay) and in silico assays. (+)-galbelgin and meso-dihydroguairetic acid exhibited potent pSTAT5 inhibitory actions of 54.5% and 64.1%, respectively, in HMC-1 cells stimulated with hTSLP. Furhtermore, (+)-galbelgin displayed over 20% inhibition of hTSLP–hTSLPR interaction at 0.3 mM. Taken togther, these lignins acts as a strong TLSP Inhibitors (Shin *et al*., 2021)

Terpenoids

Terpenoids is natural compounds synthesized from five-carbon isoprene building blocks, and they exhibit diverse biological activities. In this study, we highlighted several derivatives of terpenoids acting as inhibitors of TSLP derived from medicinal herbs (Fig. 2E).

Astragaloside IV

Astragaloside IV (AS-IV) is a tetracyclic triterpene glycoside mainly found in *Astragalus membranaceus*, showing preventive effect for treatment of allergic disease. In an *in vitro* study, AS-IV significantly mitigated the allergic inflammation by reducing pro-allergic cytokine production (Bao *et al*., 2016b). *In vivo*, AS-IV administration during the early stages alleviated inflammatory response by reducing ear swelling and suppression of Th2 cytokine expressions, by using human peritoneal mesothelial cells (HMrSV5) (Zhang *et al*., 2015).

Atractylenolide III

A sesquiterpenoid widely used as anti-cancer agent, atractylenolide III (ATL-III) decreased TSLP-stimulated cytokine production. ATL-III suppressed the TSLP-induced proliferation of mast cells by regulation of MDM and pSTAT6 signaling pathway. Moreover, ATL-III induce mast cell apoptosis by decreasing Bcl-2 and increasing procaspase-3 expression (Yoou *et al*., 2017).

Atractylone

Atractylone (Atr), a sesquiterpenoid known as effective antioxidant, is reported to alleviate clinical allergic symptoms *in vitro* and *in vivo*. Atr effectively suppressed mast cell activation by blocking caspase-1, MAPK, NF-κB signaling pathway *in vitro*. In mice, Atr reduced histamine release and expression of allergic markers inducing itching nose. Furthermore, Atr mitigate the infiltration of inflammatory cells into nasal mucosa tissues with inhibition of caspase-1 pathway (Kim *et al*., 2016).

β -Sitosterol

β-sitosterol (BS) is one of phytosterols, known for its antioxidant and anti-inflammatory activity. BS inhibited TSLP production by inhibition of Ca^{2+}/ caspase-1 and NF-κB pathway *in vitro*. In mice, expression of inflammation-related markers and caspase-1 activity was suppressed by BS administration. It also inhibited the infiltration of inflammatory cells into skin lesions and alleviated the scratching behavior (Han *et al*., 2014b).

Deacetylasperulosidic acid

Deacetylasperulosidic acid (DAA), a monoterpene glycoside mainly found in *Morinda citrifolia*, exerts antioxidant activity. In *in vitro* study, DAA inhibited the production of cytokines via MAPK and NF-κB signaling pathways. It also decreased histamine release by inhibiting IκBα decomposition (Choi *et al*., 2016; Kim *et al*., 2020; Oh *et al*., 2021b). Additionally, DAA relieved clinical AD-like symptoms by controlling immune balance and recovering skin barrier function *in vivo* in 2,4-Dinitrochlorobenzene-Induced atopic dermatitis NC/Nga Mice (Oh *et al*., 2021a).

Ginsenoside Rh2

Ginsenoside Rh2 (Rh2), a triterpenoid saponin exerts anti-inflammatory activity. In an *in vivo* and *in vitro* study, Rh2 showed the strongest inhibitory activity on TSLP expression when compared to other ginsenoside compounds. In mice experiment, Rh2 ameliorated AD-like skin symptoms by inhibition of the NF-κB pathway and inflammatory cell infiltration. Additionally, Rh2 suppressed the differentiation of naïve CD4^{+} T cells into T helper type 2 cells (Ko *et al*., 2019).
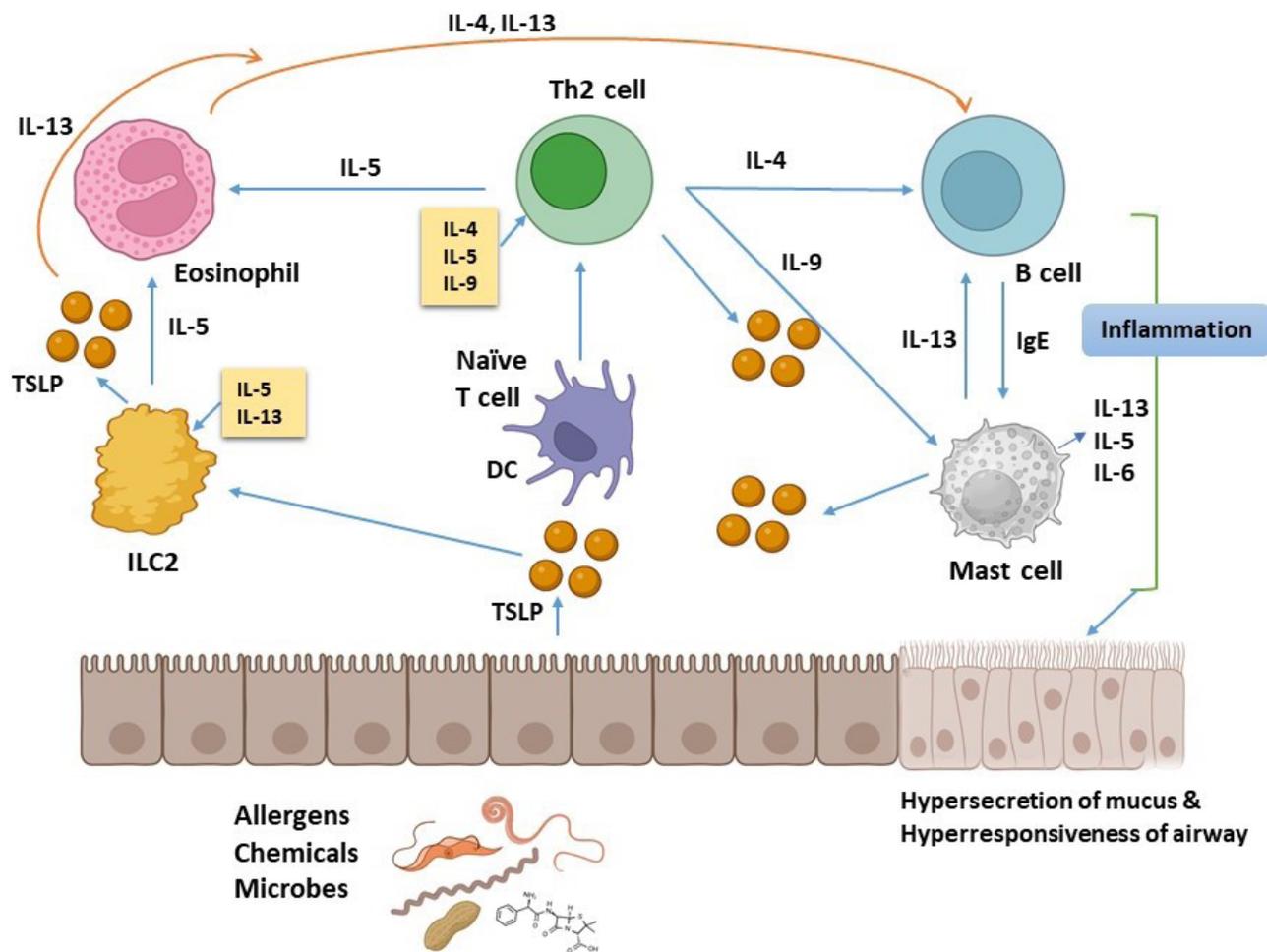
Fig. 3. TSLP promotes Th2-driven immunity, amplifying allergic responses and contributing to asthma progression, modified from (Ebina-Shibuya and Leonard, 2023). DC: Dendritic cell, TSLP: Thymic stromal lymphopoietin, ILC2: Group 2 innate lymphoid cells.

Ursolic acid

Ursolic acid (UA) is a natural triterpene showing a preventive effect for AD treatment in *in vitro* study. UA inhibited mast cell activation by regulation of intracellular Ca^{2+} concentrations, which activates caspase-1, a trigger of NF-κB signaling pathway. Consequently, UA suppressed TSLP expression and production by inhibition of Ca^{2+}/caspase-1/NF-κB axis (Moon *et al*., 2019).

(-)-Loliolide

(−)-Loliolide (LO), a monoterpene lactone possessing various beneficial bioactivities, effectively reduced the expression of initial cytokines such as IL-25, IL-33, and TSLP, which lead to chemokine production. LO is supposed to have cytoprotective role under inflamed condition by inhibiting MAPK and NF-κB signaling pathways while activating the Nrf2/HO-1 signaling pathway, in IFN-γ/TNF-α-Stimulated HaCaT Keratinocytes (Han *et al*., 2021a).

CONCLUSIONS AND PROSPECTS

The current clinical and basic studies emphasize the benefits of using naturally occurring substances with fewer or no adverse effects (Newman, 2021). This review summarizes the naturally occurring compounds that inhibit allergy associated with TSLP pathways. In conclusion, we hypothesize that the TSLP inhibitors can be potential novel targets with a definite advantage in drug development for treating allergic diseases. Moreover, TSLP stimulates immune cells such as dendritic cells to release inflammatory cytokines, thereby contributing to increased airway inflammation. Furthermore, TSLP facilitates the proliferation of immune cells, especially Th2 cells, pivotal in the progression of asthma. By influencing the respiratory mucosa, TSLP heightens sensitivity and establishes an environment conducive to inflammation, thereby contributing to the pathogenesis of asthma (Fig. 3).

This review extensively draws data cellular and animal experiments to evaluate the efficacy of medicinal plants and naturally occurring compounds that inhibit allergy via targeting the TSLP pathway. In general, using traditional medicinal plants to treat allergies is interesting, resulting in the devel-
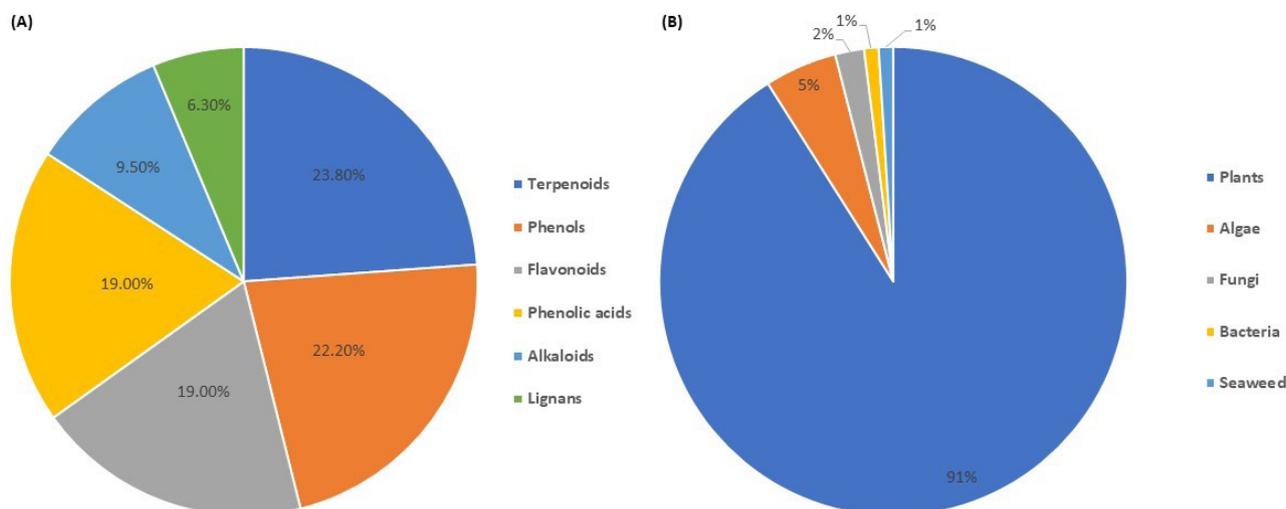
(A)

(B)

Fig. 4. Distribution of (A) Phytochemicals; (B) Natural Products Extracts with Anti-Allergic Activity via Targeting TSLP Pathways.

opment of conventional medicinal plant mixture-based medicines for controlling allergic diseases, e.g., YPFS, Madi-Ryuk, and HLJDD (Table 1). Apart from studies of plant extracts' anti-allergic effects, natural compounds' anti-allergic effects are investigated, with the main classes being terpenoids, flavonoids, alkaloids, phenol, phenolic acids, and ligands (Fig. 4A). The extracts and compounds exhibit sound anti-allergic effects by targeting TSLP pathways *in vitro* and/or *in vivo* studies, warranting further investigations in preclinical and clinical trials.

Plants are the main sources of investigations as they produce anti-allergic substances that target TSLP pathways, with 78 genera belonging to 50 families (accounting for 91%). However, only a few investigations have been performed to date that evaluate the roles of anti-allergic effects via targeting TSLP pathways from other sources, i.e., fungi, bacteria, algae, and seaweeds (Fig. 4B). This observation implies that there may still be anti-allergic agents targeting TSLP pathways from other potential sources that have not been explored. Marine-derived natural products are a prolific source of potential anti-allergic compounds with diverse structures (Kim *et al.*, 2011; Xie *et al.*, 2017). Investigation of anti-allergic compounds targeting TSLP pathways from the marine environment may be a potential source for anti-allergy agents.

This review reveals that several plant extracts, such as KRG, *Astragali Radix*, and *Polygonum tinctorium*, and their mixtures (traditional medicine formula) exhibit allergy inhibitory effects via targeting TSLP pathways under *in vitro* and/ or *in vivo* studies (Table 1). However, the critical components responsible for their anti-allergic effects have not yet been studied. Discovering the potential main components may help develop anti-allergy drugs. Also, several natural products derived from plants (Table 2) have anti-allergic effects and should be considered for further studies *in vivo*, preclinical, and clinical trials. Furthermore, synthesis and semisynthesis of anti-allergic agents based on lead compounds from natural sources should be attempted to develop anti-allergic agents.

Natural bioactive compounds from plants have traditionally been utilised to combat various diseases, and contemporary techniques are now being employed to address the challenge

Table 3. Docking scores of natural product compounds (**1-46**) targeting TSLP pathways with anti-allergic activity are presented. The structure of human TSLP bound to TSLPR and IL-7Ralpha (PDB-ID: 5J11) was provided by the Research Collaboratory for Structural Bioinformatics Protein Data Bank (RCSB PDB). The protein structure was minimized using the OPLS4 force field until the average root-mean-square deviation (RMSD) of the heavy atoms reached 0.3 Å. This was accomplished using the protein preparation tool in Maestro v12.4. The 2D structures of the ligands were transformed into 3D structures using the LigPrep tool. This process aimed to obtain geometry-optimized structures at pH 7.0 ± 2.0 while considering the chirality of the ligand based on its 3D structure. The concluding stage of LigPrep involved energy minimization of the 3D conformers through the utilization of the OPLS4 method. Docking and calculations were performed using the standard precision (SP) mode of the Glide software

Com-pounds	Docking scores	Com-pounds	Docking scores	Com-pounds	Docking scores
1	−6.566	16	−6.249	31	−5.431
2	−6.047	17	−5.932	32	−7.375
3	−7.590	18	−6.551	33	−4.551
4	−6.821	19	−7.215	34	−6.117
5	−6.782	20	-	35	−4.182
6	−7.366	21	−5.427	36	−4.552
7	−8.068	22	−6.783	37	−5.417
8	−6.004	23-1	−4.910	38	−4.468
9	−8.256	23-2	−5.301	39	−4.021
10	−7.589	24	−5.043	40	−6.559
11	−6.165	25	−5.402	41	−5.463
12	−6.429	26	−5.435	42	−6.417
13	−6.624	27	−5.493	43	−3.954
14	−6.028	28	−6.688	44	−5.412
15	−6.096	29	−5.163	45	−3.464
		30	−6.000	46	−4.807

(-) NT.

of combating life-threatening illnesses using these sources. Virtual screening techniques have significantly improved the capacity to utilise computational methods for discovering pharmacological candidates. Recently, the development of herbal products has been gaining popularity. We previously

identified that lignans isolated from *M. thunbergia* significantly inhibit STAT5 phosphorylation and the interaction between TSLP and TSLPR, as determined by ELISA (Shin *et al.*, 2021). Additionally, the protein with PDB-ID: 5J11 provides the structure of human TSLP in complex with TSLPR and IL-7Ralpha (Shin *et al.*, 2021). These studies confirm the importance of treating allergic diseases, which can be applied in future experiments. Virtual screening can validate the interaction of bioactive compounds with human TSLP in complex with TSLPR and IL-7Ralpha. Thus, in our efforts to evaluate the potential of TSLP inhibitors in this review, we conducted molecular docking to assess 47 natural compounds as ligands for human TSLP in complex with TSLPR and IL-7Ralpha. Based on the docking calculations, compounds (**1-47**) exhibited binding energies ranging from − 3.464, and − 8.256 kcal/mol, respectively (Table 3). Therefore, the binding energies of the compounds could aid in understanding the potential for discovering pharmacological candidates that inhibit the TSLP pathway.

In summary, numerous phytochemicals obtained from natural sources offer significant benefits compared to synthetic drugs, primarily due to their biocompatibility and reduced likelihood of toxic side effects. Furthermore, these natural bioactive compounds demonstrate significant efficacy by targeting multiple pathways and are also effective in modulating complex biological processes such as TSLP. Additionally, these natural bioactive compounds are linked to minimal side effects, as they are primarily compatible with the body's environment. The characteristics of phytochemicals position them as promising options for creating therapies focused on regulating TSLP and alleviating allergic reactions. This review outlines the extracts and naturally occurring compounds recognized for their ability to inhibit allergies linked to TSLP pathways, suggesting their promising role in advancing drug development for allergic disease treatment.

CONFLICT OF INTEREST

The authors declare that there are no conflicts of interest.

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REFERENCES

Adhikary, P. P., Tan, Z., Page, B. D. and Hedtrich, S. (2021) TSLP as druggable target–a silver-lining for atopic diseases? *Pharmacol. Ther.* **217**, 107648.

Akdis, C. A. (2012) Therapies for allergic inflammation: refining strategies to induce tolerance. *Nat. Med.* **18**, 736-749.

Amagai, Y., Katsuta, C., Nomura, Y., Oida, K., Matsuda, K., Jang, H., Ahn, G., Hamasaki, T., Matsuda, H. and Tanaka, A. (2017) Amelioration of atopic-like skin conditions in NC/Tnd mice by topical application with distilled Alpinia intermedia Gagnep extracts. *J. Dermatol.* **44**, 1238-1247.

Atanasov, A. G., Zotchev, S. B., Dirsch, V. M. and Supuran, C. T. (2021) Natural products in drug discovery: advances and opportunities. *Nat. Rev. Drug Discov.* **20**, 200-216.

Bae, C., Kim, J., Park, S., Shim, J. and Lee, J. (2022) A herbal concoction of Cinnamomum cassia and Artemisa annua extracts ameliorates allergic rhinitis in OVA-induced Balb/C mice by inhibiting Th2 signaling. *Appl. Sci.* **12**, 340.

Bantz, S. K., Zhu, Z. and Zheng, T. (2014) The atopic march: progression from atopic dermatitis to allergic rhinitis and asthma. *J. Clin. Cell. Immunol.* **5**, 2.

Ben, P., Liu, J., Lu, C., Xu, Y., Xin, Y., Fu, J., Huang H, Zhang Z, Gao Y, Luo L. and Yin Z (2011) Curcumin promotes degradation of inducible nitric oxide synthase and suppresses its enzyme activity in RAW 264.7 cells. *Int. Immunopharmacol.* **11**, 179-186.

Bao, K. F., Yu, X., Wei, X., Gui, L. L., Liu, H. L., Wang, X. Y., Tao, Y., Jiang, G. R. and Hong, M. (2016a) Astragaloside IV ameliorates allergic inflammation by inhibiting key initiating factors in the initial stage of sensitization. *Sci. Rep.* **6**, 38241.

Bao, K., Yuan, W., Zhou, Y., Chen, Y., Yu, X., Wang, X., Jia, Z., Yu, X., Wang, X. and Yao, L. (2020) A Chinese prescription Yu-Ping-Feng-San administered in remission restores bronchial epithelial barrier to inhibit house dust mite-induced asthma recurrence. *Front. Pharmacol.* **10**, 1698.

Barnes, P. J. (2000) New directions in allergic diseases: mechanism-based anti-inflammatory therapies. *J. Allergy Clin. Immunol.* **106**, 5-16.

Beken, B., Serttas, R., Yazicioglu, M., Turkekul, K. and Erdogan, S. (2020) Quercetin improves inflammation, oxidative stress, and impaired wound healing in atopic dermatitis model of human keratinocytes. *Pediatr. Allergy Immunol.* **33**, 69-79.

Brugiolo, A. S. S., Gouveia, A. C. C., De Souza Alves, C. C., E Silva, F. M. D. C., De Oliveira, É. E. and Ferreira, A. P. (2017) Ferulic acid supresses Th2 immune response and prevents remodeling in ovalbumin-induced pulmonary allergy associated with inhibition of epithelial-derived cytokines. *Pulm. Pharmacol. Ther.* **45**, 202-209.

Chen, B. R., Hsu, K. T., Li, T. L., Chan, Y. L. and Wu, C. J. (2021) Topical application of fucoidan derived from Cladosiphon okamuranus alleviates atopic dermatitis symptoms through immunomodulation. *Int. Immunopharmacol.* **101**, 108362.

Chen, X., Zhu, C., Zhang, Y., Yang, N., Shi, H., Yang, W., Yang, Y., Liang, J., Chen, L. and Zeng, X. (2020a) Antipruritic effect of ethyl acetate extract from fructus cnidii in mice with 2, 4-dinitrofluorobenzene-induced atopic dermatitis. *Evid. Based Complement. Alternat. Med.* **2020**, 6981386.

Chen, Y., Xian, Y. F., Loo, S., Lai, Z., Chan, W. Y., Liu, L. and Lin, Z. X. (2020b) Huang-Lian-Jie-Du extract ameliorates atopic dermatitis-like skin lesions induced by 2, 4-dinitrobenzene in mice via suppression of MAPKs and NF-κB pathways. *J. Ethnopharmacol.* **249**, 112367.

Cheng, D. T., Ma, C., Niewoehner, J., Dahl, M., Tsai, A., Zhang, J., Gonsiorek, W., Apparsundaram, S., Pashine, A., Ravindran, P., Jung, J., Hang, J., Allard, J., Bitter, H., Tribouley, C., Narula, S., Wilson, S. and Fuentes, M. E. (2013) Thymic stromal lymphopoietin receptor blockade reducesallergic inflammation in a cynomolgus monkey model ofasthma. *J. Allergy Clin. Immunol. In Pract.* **132**, 455-462.

Cho, K., Park, S. S. and Choi, H. (2021) Improvement of Bronchial immune hypersensitivity reaction using extracts from Chrysanthemum morifolium ramatuelle and Scutellaria baicalensis georgi. *Evid. Based Complement. Alternat. Med.* **2021**, 3173823

Cho, S. H., Kim, H. S., Lee, W., Han, E. J., Kim, S. Y., Fernando, I. S., Ahn, G. and Kim, K. N. (2020) Eckol from Ecklonia cava ameliorates TNF-α/IFN-γ-induced inflammatory responses via regulating MAPKs and NF-κB signaling pathway in HaCaT cells. *Int. Immunopharmacol.* **82**, 106146.

Choi, E. J., Debnath, T., Tang, Y., Ryu, Y. B., Moon, S. H. and Kim, E. K. (2016) Topical application of Moringa oleifera leaf extract ameliorates experimentally induced atopic dermatitis by the regulation of Th1/Th2/Th17 balance. *Biomed. Pharmacother.* **84**, 870-877.

Comeau, M. and Ziegler, S. (2010) The influence of TSLP on the al-

lergic response. *Mucosal Immunol.* **3**, 138-147.

Ebina-Shibuya, R. and Leonard, W. J. (2023) Role of thymic stromal lymphopoietin in allergy and beyond. *Nat. Rev. Immunol.* **23**, 24-37.

Eguiluz-Gracia, I., Tay, T. R., Hew, M., Escribese, M. M., Barber, D., O'hehir, R. E. and Torres, M. J. (2018) Recent developments and highlights in biomarkers in allergic diseases and asthma. *Allergy* **73**, 2290-2305.

El-Zein, M., Parent, M. E., Siemiatycki, J. and Rousseau, M. C. (2014) History of allergic diseases and lung cancer risk. *Ann. Allergy Asthma Immunol.* **112**, 230-236.

Gong, X., Xiong, H., Liu, S., Liu, Y., Yin, L., Tu, C., Wang, H., Zhao, Z., Chen, W. and Mei, Z. (2019) Qingpeng ointment ameliorates inflammatory responses and dysregulation of itch-related molecules for its antipruritic effects in experimental allergic contact dermatitis. *Front. Pharmacol.* **10**, 354.

Gupta, K., Kumar, S., Gupta, R. K., Sharma, A., Verma, A. K., Stalin, K., Chaudhari, B. P., Das, M., Singh, S. P. and Dwivedi, P. D. (2016) Reversion of asthmatic complications and mast cell signalling pathways in BALB/c mice model using quercetin nanocrystals. *J. Biomed. Nanotech.* **12**, 717-731.

Han, E. J., Fernando, I. P. S., Kim, H. S., Lee, D. S., Kim, A., Je, J. G., Seo, M. J., Jee, Y. H., Jeon, Y. J. and Kim, S. Y. (2021a) (−)-Loliolide isolated from Sargassum horneri suppressed oxidative stress and inflammation by activating Nrf2/HO-1 signaling in IFN-γ/TNF-α-stimulated HaCaT keratinocytes. *Antioxidants* **10**, 856.

Han, E. J., Kim, H. S., Jung, K., Sanjeewa, K. K. A., Herath, K. H. I. N. M., Lee, W., Jee, Y., Jeon, Y. J., Lee, J. and Kim, T. (2021b) Sargassum horneri ethanol extract ameliorates TNF-α/IFN-γ-induced inflammation in human keratinocytes and TPA-induced ear edema in mice. *Food Biosci.* **39**, 100831.

Han, N. R., Kang, S. W., Moon, P. D., Jang, J. B., Kim, H. M. and Jeong, H. J. (2014a) Genuine traditional Korean medicine, Naju Jjok (Chung-Dae, Polygonum tinctorium) improves 2, 4-dinitrofluorobenzene-induced atopic dermatitis-like lesional skin. *Phytomedicine* **21**, 453-460.

Han, N. R., Kim, H. M. and Jeong, H. J. (2014b) The β-sitosterol attenuates atopic dermatitis-like skin lesions through down-regulation of TSLP. *Exp. Biol. Med.* **239**, 454-464.

Han, N. R., Kim, H. M. and Jeong, H. J. (2016) Tryptanthrin reduces mast cell proliferation promoted by TSLP through modulation of MDM2 and p53. *Biomed. Pharmacother.* **79**, 71-77.

Han, N. R., Kim, H. Y., Kang, S., Kim, M. H., Yoon, K. W., Moon, P. D., Kim, H. M. and Jeong, H. J. (2019) Chrysophanol, an anthraquinone from AST2017-01, possesses the anti-proliferative effect through increasing p53 protein levels in human mast cells. *Inflamm. Res.* **68**, 569-579.

Han, N. R., Ko, S. G., Moon, P. D. and Park, H. J. (2021c) Ginsenoside Rg3 attenuates skin disorders via down-regulation of MDM2/HIF1α signaling pathway. *J. Ginseng Res.* **45**, 610-616.

Han, N. R., Moon, P. D., Ryu, K. J., Kim, N. R., Kim, H. M. and Jeong, H. J. (2018) Inhibitory effect of naringenin via IL-13 level regulation on thymic stromal lymphopoietin-induced inflammatory reactions. *Clin. Exp. Pharmacol.* **45**, 362-369.

Herath, K. H. I. N. M., Mihindukulasooriya, S. P., Kim, H. J., Kim, A., Kim, H. J., Jeon, Y. J. and Jee, Y. (2020) Oral administration of polyphenol-rich Sargassum horneri suppresses particulate matter exacerbated airway inflammation in murine allergic asthma: Relevance to the TLR mediated NF-κB pathway inhibition. *J. Funct. Foods* **71**, 103991.

Shin, H., Han, Y. K., Byun, Y., Jeon, Y. H. and Lee, K. Y. (2021) Lignans from Machilus thunbergii as thymic stromal lymphopoietin inhibitors. *Molecules* **26**, 4804.

Jeon, M., Lee, J., Lee, H. K., Cho, S., Lim, J. H., Choi, Y., Pak, S. and Jeong, H. J. (2020) Sulforaphane mitigates mast cell-mediated allergic inflammatory reactions in in silico simulation and *in vitro* models. *Int. Immunopharmacol.* **42**, 74-83.

Jeong, H. J., Kim, H. Y. and Kim, H. M. (2018a) Molecular mechanisms of anti-inflammatory effect of chrysophanol, an active component of AST2017-01 on atopic dermatitis *in vitro* models. *Int. Immunopharmacol.* **54**, 238-244.

Jeong, H. J., Nam, S. Y., Kim, H. Y., Jin, M. H., Kim, M. H., Roh, S. S.

and Kim, H. M. (2018b) Anti-allergic inflammatory effect of vanillic acid through regulating thymic stromal lymphopoietin secretion from activated mast cells. *Nat. Prod. Res.* **32**, 2945-2949.

Jeong, H. J., Oh, H. A., Lee, B. J. and Kim, H. M. (2014) Inhibition of IL-32 and TSLP production through the attenuation of caspase-1 activation in an animal model of allergic rhinitis by Naju Jjok (Polygonum tinctorium). *Int. J. Mol. Med.* **33**, 142-150.

Jeong, H. J., Yoou, M. S., Han, N. R., Hwang, S. Y., Yoon, K. W. and Kim, H. M. (2018c) The new therapeutic herbal drug HM 0601 and its bioactive compound rutin exert potent antiproliferative activities in mast cells. *Fundam. Clin. Pharmacol.* **32**, 279-287.

Ji, J., Gui, Y., Wang, Y., Hou, Y., Chen, K., Xi, K., Chen, X., Liu, X. and Zhang, X. (2019) The inhibition of 18β-sodium glycyrrhetinic acid on thymic stromal lymphopoietin expression in the nasal mucosa of allergic rhinitis rats. *Chinese J. Otorhinolaryngol. Head and Neck Surgery* **54**, 456-463.

Jia, Z., Wang, X., Wang, X., Wei, P., Li, L., Wu, P. and Hong, M. (2018) Calycosin alleviates allergic contact dermatitis by repairing epithelial tight junctions via down-regulating HIF-1α. *J. Cell. Mol. Med.* **22**, 4507-4521.

Jung, M. K., Hur, D. Y., Song, S. B., Park, Y., Kim, T. S., Bang, S. I., Kim, S., Song, H. K., Park, H. and Cho, D. H. (2010) Tannic acid and quercetin display a therapeutic effect in atopic dermatitis via suppression of angiogenesis and TARC expression in Nc/Nga mice. *J. Invest. Dermatol.* **130**, 1459-1463.

Jung, Y., Kim, J. C., Park, N. J., Bong, S. K., Lee, S., Jegal, H., Jin, L. T., Kim, S. M., Kim, Y. K. and Kim, S. N. (2018) Eupatilin, an activator of PPARα, inhibits the development of oxazolone-induced atopic dermatitis symptoms in Balb/c mice. *Biochem. Biophys. Res. Commun.* **496**, 508-514.

Kim, B. Y., Park, H. R., Jeong, H. G. and Kim, S. W. (2015a) Berberine reduce allergic inflammation in a house dust mite allergic rhinitis mouse model. *Rhinology* **53**, 353-358.

Kim, G. D., Lee, S. E., Park, Y. S., Shin, D. H., Park, G. G. and Park, C. S. (2014) Immunosuppressive effects of fisetin against dinitrofluorobenzene-induced atopic dermatitis-like symptoms in NC/Nga mice. *Food Chem. Toxicol.* **66**, 341-349.

Kim, H. Y., Jee, H., Yeom, J. H., Jeong, H. J. and Kim, H. M. (2019a) The ameliorative effect of AST2017-01 in an ovalbumin-induced allergic rhinitis animal model. *J. Inflamm. Res.* **68**, 387-395.

Kim, H. Y., Kim, J., Jeong, H. J. and Kim, H. M. (2019b) Potential anti-inflammatory effect of Madi-Ryuk and its active ingredient tannic acid on allergic rhinitis. *Mol. Immunol.* **114**, 362-368.

Kim, H. Y., Nam, S. Y., Hwang, S. Y., Kim, H. M. and Jeong, H. J. (2016) Atractylone, an active constituent of KMP6, attenuates allergic inflammation on allergic rhinitis *in vitro* and *in vivo* models. *Mol. Immunol.* **78**, 121-132.

Kim, H. Y., Jeong, H. J., Han, N. R., Jang, J. B. and Kim, H. M. (2018) Madi-Ryuk and its active compound tannic acid suppress allergic inflammatory reactions in activated human mast cell HMC-1. *J. Food Biochem.* **42**, e12664.

Kim, H. Y., Rho, S. H., Lim, J. H., Park, H. J. and Jeong, H. J. (2019c) Protective effect of linoleic acid against inflammatory reactions by mast cell via caspase-1 cascade pathways. *J. Food Biochem.* **43**, e12932.

Kim, S. H., Yang, M., Xu, J. G., Yu, X. and Qian, X. J. (2015b) Role of licochalcone A on thymic stromal lymphopoietin expression: implications for asthma. *Exp. Biol. Med.* **240**, 26-33.

Kim, S. K., Vo, T. S. and Ngo, D. H. (2011) Antiallergic benefit of marine algae in medicinal foods. *Adv. Food Nutr. Res.* **64**, 267-275.

Kim, S. H., Seong, G. S. and Choung, S. Y. (2020) Fermented Morinda citrifolia (Noni) alleviates DNCB-induced atopic dermatitis in NC/Nga mice through modulating immune balance and skin barrier function. *Nutrients* **12**, 249.

Ko, E., Park, S., Lee, J. H., Cui, C. H., Hou, J., Kim, M. H. and Kim, S. C. (2019) Ginsenoside Rh2 ameliorates atopic dermatitis in NC/Nga mice by suppressing NF-kappaB-mediated thymic stromal lymphopoietin expression and T helper type 2 differentiation. *Int. J. Mol. Sci.* **20**, 6111.

Ku, J. M., Hong, S. H., Kim, S. R., Choi, H. S., Kim, H. I., Kim, D. U., Oh, S. M., Seo, H. S., Kim, T. Y. and Shin, Y. C. (2018) The prevention of 2, 4-dinitrochlorobenzene-induced inflammation in atopic

dermatitis-like skin lesions in BALB/c mice by Jawoongo. *BMC Complement. Altern. Med.* **18**, 215.

Lee, C. C., Wang, C., Huang, H., Lin, C., Leu, S. and Lee, Y. (2015) Ferulic acid induces Th1 responses by modulating the function of dendritic cells and ameliorates Th2-mediated allergic airway inflammation in mice. *Evid. Based Complement. Alternat. Med.* **2015**, 678487.

Lee, H. S., Choi, E. J., Choi, H., Lee, K. S., Kim, H. R., Na, B. R., Kwon, M. S., Jeong, G. S., Choi, H. G. and Choi, E. Y. (2015) Oral administration of 4-hydroxy-3-methoxycinnamaldehyde attenuates atopic dermatitis by inhibiting T cell and keratinocyte activation. *PLoS One* **10**, e0144521.

Lee, H. J. and Cho, S. H. (2017) Therapeutic effects of Korean red ginseng extract in a murine model of atopic dermatitis: anti-pruritic and anti-inflammatory mechanism. *J. Korean Med. Sci.* **32**, 679-687.

Li, H., Kong, D., Xu, Y., Li, X., Yao, G., Chen, K., You, Q., Shi, Q., Zhang, L. and Wang, X. (2017) Tripterygium wilfordii inhibits tonsillar IgA production by downregulating IgA class switching in IgA nephropathy. *Oncotarget* **8**, 109027.

Min, S. Y., Park, C. H., Yu, H. W. and Park, Y. J. (2021) Anti-inflammatory and anti-allergic effects of saponarin and its impact on signaling pathways of RAW 264.7, RBL-2H3, and HaCaT cells. *Int. J. Mol. Sci.* **22**, 8431.

Moon, P. D., Choi, I. H. and Kim, H. M. (2011) Naringenin suppresses the production of thymic stromal lymphopoietin through the blockade of RIP2 and caspase-1 signal cascade in mast cells. *Eur. J. Pharmacol.* **671**, 128-132.

Moon, P. D., Choi, I. H. and Kim, H. M. (2012a) Epigallocatechin-3-O-gallate inhibits the production of thymic stromal lymphopoietin by the blockade of caspase-1/NF-κB pathway in mast cells. *Amino Acids* **42**, 2513-2519.

Moon, P. D., Jeong, H. J. and Kim, H. M. (2013) Down-regulation of thymic stromal lymphopoietin by curcumin. *Pharmacol. Rep.* **65**, 525-531.

Moon, P. D. and Kim, H. M (2012b) Suppression of thymic stromal lymphopoietin production by rutin in mast cells. *Food Chem.* **133**, 76-81.

Moon, P. D., Han, N. R., Lee, J. S., Kim, H. M. and Jeong, H. J. (2019) Ursolic acid downregulates thymic stromal lymphopoietin through the blockade of intracellular calcium/caspase-1/NF-κB signaling cascade in HMC-1 cells. *Int. J. Mol. Med.* **43**, 2252-2258.

Murdaca, G., Greco, M., Tonacci, A., Negrini, S., Borro, M., Puppo, F. and Gangemi, S. (2019) IL-33/IL-31 axis in immune-mediated and allergic diseases. *Int. J. Mol. Sci.* **20**, 5856.

Nam, S. Y., Han, N. R., Rah, S. Y., Seo, Y., Kim, H. M. and Jeong, H. J. (2018) Anti-inflammatory effects of Artemisia scoparia and its active constituent, 3, 5-dicaffeoyl-epi-quinic acid against activated mast cells. *Immunopharmacol. Immunotoxicol.* **40**, 52-58.

Nam, S. Y., Jeong, H. J. and Kim, H. M. (2017) Kaempferol impedes IL-32-induced monocyte-macrophage differentiation. *Chem. Biol. Interact.* **274**, 107-115.

Nešić, A., Čavić, M., Popović, M., Zlatanova, M., Pieters, R., Smit, J. and Gavrović-Jankulović, M. (2019) The kiwifruit allergen act d 1 activates NF-κB signaling and affects mRNA expression of TJ proteins and innate pro-allergenic cytokines. *Biomolecules* **9**, 816.

Newman, D. J. (2021) Natural product based antibody drug conjugates: clinical status as of November 9, 2020. *J. Nat. Prod.* **84**, 917-931.

Nguyen, T. M. N., Le, H. S., Le, B. V., Kim, Y. H. and Hwang, I. (2020) Anti-allergic effect of inotodiol, a lanostane triterpenoid from Chaga mushroom, via selective inhibition of mast cell function. *Int. Immunopharmacol.* **81**, 106244.

Nguyen, T. M. N., Lomunova, M., Vu, T. P. D., Le, B. V., Kim, Y. H., Kang, J. S. and Hwang, I. (2018) Anti-allergic effects of the ethanol extract of Syzygium formosum (Wall.) Masam leaves and its immunoregulatory mechanisms. *J. Ethnopharmacol.* **211**, 171-179.

Oh, H. A., Seo, J. Y., Jeong, H. J. and Kim, H. M. (2013) Ginsenoside Rg1 inhibits the TSLP production in allergic rhinitis mice. *Immunopharmacol. Immunotoxicol.* **35**, 678-686.

Oh, J. S., Seong, G. S., Kim, Y. D. and Choung, S. Y. (2021a) Deacetylasperulosidic acid ameliorates pruritus, immune imbalance, and skin barrier dysfunction in 2, 4-dinitrochlorobenzene-induced atopic dermatitis NC/Nga mice. *Int. J. Mol. Sci.* **23**, 226.

Oh, J. S., Seong, G. S., Kim, Y. D. and Choung, S. Y. (2021b) Effects of deacetylasperulosidic acid on atopic dermatitis through modulating immune balance and skin barrier function in HaCaT, HMC-1, and EOL-1 cells. *Molecules* **26**, 3298.

Pan, Z., Zhou, Y., Luo, X., Ruan, Y., Zhou, L., Wang, Q., Yan, Y. J., Lium Q. and Chen, J. (2018a) Against NF-κB/thymic stromal lymphopoietin signaling pathway, catechin alleviates the inflammation in allergic rhinitis. *Int. Immunopharmacol.* **61**, 241-248.

Papadopoulos, N. G., Agache, I., Bavbek, S., Bilo, B. M., Braido, F., Cardona, V., Custovic, A., Demonchy, J., Demoly, P. and Eigenmann, P. (2012) Research needs in allergy: an EAACI position paper, in collaboration with EFA. *Clin. Transl. Allergy* **2**, 21.

Park, B. B., Choi, J. W., Park, D., Choi, D., Paek, J., Kim, H. J., Son, S. Y., Mushtaq, A. U., Shin, H. and Kim, S. H. (2019a) Structure-activity relationships of baicalein and its analogs as novel TSLP inhibitors. *Sci. Rep.* **9**, 8762.

Park, J. H., Ahn, E. K., Ko, H. J., Lee, J. Y., Hwang, S. M., Ko, S. and Oh, J. S. (2019b) Korean red ginseng water extract alleviates atopic dermatitis-like inflammatory responses by negative regulation of mitogen-activated protein kinase signaling pathway *in vivo*. *Biomed. Pharmacother.* **117**, 109066.

Park, J. H., Hwang, M. H., Cho, Y. R., Hong, S. S., Kang, J. S., Kim, W. H., Yang, S. H., Seo, D. W., Oh, J. S. and Ahn, E. K. (2020) Combretum quadrangulare extract attenuates atopic dermatitis-like skin lesions through modulation of MAPK signaling in BALB/c mice. *Molecules* **25**, 2003.

Park, S, Park, Y., Son, S. H., Lee, K., Jung, Y. W., Lee, K. Y., Jeon, Y. H. and Byun, Y. (2017) Synthesis and biological evaluation of peptide-derived TSLP inhibitors. *Bioog. Med. Chem. Lett.* **27**, 4710-4713.

Park, S. H., An, J. E., Jang, S., Kim, J. Y., Lee, J. W. and Kim, H. K. (2019c) Gardenia jasminoides extract without crocin improved atopic dermatitis-like skin lesions via suppression of Th2-related cytokines in Dfe-induced NC/Nga mice. *J. Ethnopharmacol.* **241**, 112015.

Patridge, E., Gareiss, P., Kinch, M. S. and Hoyer, D. (2016) An analysis of FDA-approved drugs: natural products and their derivatives. *Drug Discov. Today* **21**, 204-207.

Rao, Y. K., Chen, Y. C., Fang, S. H., Lai, C. H., Geethangili, M., Lee, C. C. and Tzeng, Y. M. (2013) Ovatodiolide inhibits the maturation of allergen-induced bone marrow-derived dendritic cells and induction of Th2 cell differentiation. *Int. Immunopharmacol.* **17**, 617-624.

Ryu, K., Yoou, M., Seo, Y., Yoon, K., Kim, H. and Jeong, H. (2018) Therapeutic effects of Artemisia scoparia Waldst. et Kitaib in a murine model of atopic dermatitis. *Clin. Exp. Dermatol.* **43**, 798-805.

Sharma, S., Sethi, G. S. and Naura, A. S. (2020) Curcumin ameliorates ovalbumin-induced atopic dermatitis and blocks the progression of atopic march in mice. *Inflammation* **43**, 358-369.

Shen, D., Xie, X., Zhu, Z., Yu, X., Liu, H., Wang, H., Fan, H., Wang, D., Jiang, G. and Hong, M. (2014) Screening active components from Yu-ping-feng-san for regulating initiative key factors in allergic sensitization. *PLoS One* **9**, e107279.

Shi, H., Zhao, L., Guo, X., Fang, R., Zhang, H., Dong, G., Fu, J., Yan, F., Zhang, J. and Ning, Z. (2020) Arctigenin attenuates breast cancer progression through decreasing GM-CSF/TSLP/STAT3/β-catenin signaling. *Int. J. Mol. Sci.* **21**, 6357.

Shin, H., Han, Y. K., Byun, Y., Jeon, Y. H and Lee, K. Y. (2021) Lignans from Machilus thunbergii as thymic stromal lymphopoietin inhibitors. *Molecules* **26**, 4804.

Silverberg, J. I., Gelfand, J. M., Margolis, D. J., Boguniewicz, M., Fonacier, L., Grayson, M. H., Simpson, E. L., Ong, P. Y. and Fuxench, Z. C. C. (2018) Association of atopic dermatitis with allergic, autoimmune, and cardiovascular comorbidities in US adults. *Ann. Allergy Asthma Immunol.* **121**, 604-612.e3.

Sozmen, S. C., Karaman, M., Micili, S. C., Isik, S., Ayyildiz, Z. A., Bagriyanik, A., Uzuner, N. and Karaman, O. (2016a) Resveratrol ameliorates 2, 4-dinitrofluorobenzene-induced atopic dermatitis-like lesions through effects on the epithelium. *PeerJ* **4**, e1889.

Sozmen, S. C., Karaman, M., Micili, S. C., Isik, S., Bagriyanik, A., Ayyildiz, Z. A., Uzuner, N., Anal, O. and Karaman, O. (2016b) Effects of quercetin treatment on epithelium-derived cytokines and epithelial cell apoptosis in allergic airway inflammation mice mod-

el. *Iran. J. Allergy Asthma Immunol.* **15**, 487-497.

Tao, Y., Wang, Y., Wang, X., Wang, C., Bao, K., Ji, L., Jiang, G. and Hong, M. (2017) Calycosin suppresses epithelial derived initiative key factors and maintains epithelial barrier in allergic inflammation via TLR4 mediated NF-κB pathway. *Cell. Physiol. Biochem.* **44**, 1106-1119.

Tzeng, N. S., Chang, H. A., Chung, C. H., Kao, Y. C., Chang, C. C., Yeh, H. W., Chiang, W. S., Chou, Y. C., Chang, S. Y. and Chien, W. C. (2018) Increased risk of psychiatric disorders in allergic diseases: a nationwide, population-based, cohort study. *Front. Psychiatry* **9**, 133.

Vinh, L. B., Jang, H. J., Phong, N. V., Dan, G., Cho, K. W., Kim, Y. H. and Yang, S. Y. (2019a) Bioactive triterpene glycosides from the fruit of Stauntonia hexaphylla and insights into the molecular mechanism of its inflammatory effects. *Bioog. Med. Chem. Lett.* **29**, 2085-2089.

Vinh, L. B., Park, J. U., Duy, L. X., Nguyet, N. T. M., Yang, S. Y., Kim, Y. R. and Kim, Y. H. (2019b) Ginsenosides from Korean red ginseng modulate T cell function via the regulation of NF-AT-mediated IL-2 production. *Food Sci. Biotechnol.* **28**, 237-242.

Wainwright, C., Teixeira, M., Adelson, D., Buenz, E., David, B., Glaser, K., Harata-Lee, Y., Howes, M. J., Izzo, A. and Maffia, P. (2022) Future directions for the discovery of natural product-derived immunomodulating drugs. *Pharmacol. Res.* **177**, 106076.

Wang, X., Jiang, X., Yu, X., Liu, H., Tao, Y., Jiang, G. and Hong, M. (2017) Cimifugin suppresses allergic inflammation by reducing epithelial derived initiative key factors via regulating tight junctions. *J. Cell. Mol. Med.* **21**, 2926-2936.

Weiss, K. B. and Sullivan, S. D. (2001) The health economics of asthma and rhinitis. I. Assessing the economic impact. *J. Allergy Clin. Immunol.* **107**, 3-8.

Wu, S., Pang, Y., He, Y., Zhang, X., Peng, L., Guo, J. and Zeng, J. (2021) A comprehensive review of natural products against atopic dermatitis: flavonoids, alkaloids, terpenes, glycosides and other compounds. *Biomed. Pharmacother.* **140**, 111741.

Xie, C. L., Liu, Q., Xia, J. M., Gao, Y., Yang, Q., Shao, Z. Z., Liu, G. and Yang, X. W. (2017) Anti-allergic compounds from the deep-sea-derived actinomycete Nesterenkonia flava MCCC 1K00610. *Mar. Drugs* **15**, 71.

Yang, C. C., Hung, Y. L., Ko, W. C., Tsai, Y. J., Chang, J. F., Liang, C. W., Chang, D. C. and Hung, C. F. (2021) Effect of neferine on DNCB-induced atopic dermatitis in HaCaT cells and BALB/c mice. *Int. J. Mol. Sci.* **22**, 8237.

Yang, G., Cheon, S. Y., Chung, K. S., Lee, S. J., Hong, C. H., Lee, K. T., Jang, D. S., Jeong, J. C., Kwon, O. K. and Nam, J. H. (2015) Solanum tuberosum L. cv Jayoung epidermis extract inhibits mite antigen-induced atopic dermatitis in NC/Nga mice by regulating the Th1/Th2 balance and expression of filaggrin. *J. Med. Food* **18**, 1013-1021.

Yeo, H., Lee, Y. H., Ahn, S. S., Jung, E., Lim, Y. and Shin, S. Y. (2021) Chrysin inhibits TNFα-induced TSLP expression through downregulation of EGR1 expression in keratinocytes. *Int. J. Mol. Sci.* **22**, 4350.

Yeom, J. H., Kim, H. Y., Lim, J. H., Yoon, K. W., Kim, H. M. and Jeong, H. J. (2021) A calcium channel blocker, manoalide exerts an anti-allergic inflammatory effect through attenuating NF-κB activity. *Immunopharmacol. Immunotoxicol.* **43**, 799-805.

Yoou, M. S., Kim, H. M. and Jeong, H. J. (2015) Acteoside attenuates TSLP-induced mast cell proliferation via down-regulating MDM2. *Int. Immunopharmacol.* **26**, 23-29.

Yoou, M. S., Nam, S. Y., Jin, M. H., Lee, S. Y., Kim, M. S., Roh, S. S., Choi, I. H., Woo, N., Lim, S. and Kim, D. H. (2017) Ameliorative effect of atractylenolide III in the mast cell proliferation induced by TSLP. *Food Chem. Toxicol.* **106**, 78-85.

Yoou, M. S., Park, C. L., Kim, M. H., Kim, H. M. and Jeong, H. J. (2016) Inhibition of MDM2 expression by rosmarinic acid in TSLP-stimulated mast cell. *Eur. J. Pharmacol.* **771**, 191-198.

Yoshida, K., Takabayashi, T., Kaneko, A., Takiyama, M., Sakashita, M., Imoto, Y., Kato, Y., Narita, N. and Fujieda, S. (2021) Baicalin suppresses type 2 immunity through breaking off the interplay between mast cell and airway epithelial cell. *J. Ethnopharmacol.* **267**, 113492.

Yuan, W. Y., Li, L. Q., Chen, Y. Y., Zhou, Y. J., Bao, K. F., Zheng, J., Hua, Y. Q., Jiang, G. R. and Hong, M. (2020) Two flavonoid compounds attenuate allergic asthma by regulating epithelial barrier via G protein-coupled estrogen receptor: probing a possible target for allergic inflammation. *J. Leukoc. Biol.* **108**, 59-71.

Yuan, W., Chen, Y., Zhou, Y., Bao, K., Yu, X., Xu, Y., Zhang, Y., Zheng, J., Jiang, G. and Hong, M. (2021) Formononetin attenuates atopic dermatitis by upregulating A20 expression via activation of G protein-coupled estrogen receptor. *J. Ethnopharmacol.* **266**, 113397.

Zhang, L., Li, Z., He, W., Xu, L., Wang, J., Shi, J. and Sheng, M. (2015) Effects of Astragaloside IV against the TGF-β1-induced epithelial-to-mesenchymal transition in peritoneal mesothelial cells by promoting Smad 7 expression. *Cell. Physiol. Biochem.* **37**, 43-54.

Zheng, J., Wang, X., Tao, Y., Wang, Y., Yu, X., Liu, H., Ji, L., Bao, K., Wang, C. and Jia, Z. (2019) Yu-Ping-Feng-San ameliorates recurrent allergic inflammation of atopic dermatitis by repairing tight junction defects of the epithelial barrier. *Phytomedicine* **54**, 214-223.

Zhou, Z., Shi, T., Hou, J. and Li, M. (2020) Ferulic acid alleviates atopic dermatitis-like symptoms in mice via its potent anti-inflammatory effect. *Immunopharmacol. Immunotoxicol.* **42**, 156-164.

Zhu, Y., Peng, X., Zhang, Y., Lin, J. and Zhao, G. (2021) Baicalein protects against aspergillus fumigatus keratitis by reducing fungal load and inhibiting TSLP-induced inflammatory response. *Investig. Ophthalmol. Vis. Sci.* **62**, 26.