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Native Vietnamese Medicinal Plants with Anti-atopic Dermatitis Activity: A Systematic Review

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Authors' contributions

This work was carried out in collaboration between both authors. Author DHTT designed the study, carried out the literature search, interpreted the data and wrote the first draft of the manuscript. Author HLS managed the conceptualization, supervision and revision of the study. Both authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Aims: Medicinal plants have always been highly valued as an accessible traditional treatment for atopic dermatitis in Vietnam. Accordingly, this review aims to assemble and discuss plants with validated anti-atopic dermatitis potency in the country, putting a great emphasis on the practice of phytomedicines and the development of plant-based products for dermatologic conditions. Existing concerns and future perspectives are included to ensure comprehensiveness of the overview.
Methodology: This review is a systematic compilation of published *in vitro* studies, clinical trials and case studies on the effectiveness of single plant extracts in alleviating atopic dermatitis that can be found in Vietnam.
Results: 39 publications presenting 31 plant species were collected in total. Preparation of plant extracts and route of administration varied slightly between the studies. Root and leaves are plant parts that were most commonly investigated (25.00% and 22.50%). Disease symptoms were mostly induced on NC/Nga mice (61.54%) using sensitizers like 2,4-dinitrochlorobenzene (28.57%), 1-fluoro-2,4-dinitrobenzene (25.71%) and *Dermatophagoides farinae* body extract (28.57%). Effects of plant extracts on epidermal/dermal thickness, IgE serum level, infiltration of

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immune cells and hyperproduction of inflammatory cytokines were intensively investigated in the collected studies.

Conclusion: This review highlights the enormous potential of medicinal plants as an effective and easily accessible alternative therapy against atopic dermatitis. The use of these still needs to be further supported by scientific evidence and controlled by strict regulations to ensure good practice and stable development of phytomedicines.

Keywords: Atopic dermatitis; systematic review; medicinal plants; alternative therapy; Vietnam.

ABBREVIATIONS

DNFB : 1-fluoro-2,4-dinitrobenzene
TNCB : 2,4,6-trinitrochlorobenzene
DNCB : 2,4-dinitrochlorobenzene
ARRIVE : Animal Research: Reporting of in vivo Experiment
AD : Atopic Dermatitis
DLQI : Dermatology Life Quality Index
EASI : Eczema Area and Severity Index
ESR : Erythrocyte Sedimentation Rate
HO-1 : Heme Oxygenase 1
Ig : Immunoglobulin
ICAM : Intercellular Adhesion Molecule
IFN-γ : Interferon-gamma
IL : Interleukin
KGM : Konjac Glucomannan
MAPK : Mitogen-activated Protein Kinases
MCP : Monocyte Chemoattractant Protein
MDC : Monocyte-derived Cells
NF-κB : Nuclear Factor Kappa-light-chain-enhancer of Activated B Cells
PKGM : Pulverized Konjac Glucomannan
RANTES : Regulated on Activation, Normal T Cell Expressed and Secreted
SCORAD : SCORing Atopic Dermatitis
STAT1 : Signal Transducer and Activator of Transcription 1
Th1 : T helper cell 1
Th2 : T helper cell 2
T reg : T regulatory cells
TARC : Thymus and Activation Regulated Chemokine
TEWL : Transdermal Epidermal Water Loss
TGF-β : Transforming Growth Factor Beta
TNF-α : Tumor Necrosis Factor Alpha
VCAM : Vascular Cell Adhesion Molecules

1. INTRODUCTION

1.1 Atopic Dermatitis

Atopic dermatitis (AD) or atopic eczema is a chronic inflammatory disease with high prevalence up to 20% in infants and 3% in adults with the hallmark of intense pruritic skin lesions [1]. AD is characterized by eczematous skin lesions, lichenification, xerosis, cutaneous hyperactivity and hyperkeratosis [2] manifested through acute, subacute and chronic AD [3] and causes serious frustration for patients in daily life due to its relapsing nature and associated risks of inducing atopic march development [2–4]. Predisposing factors of AD include genetic impairments and environmental factors that can provoke skin inflammation such as microorganism, irritants, allergens, climate, and intense psychological interactions [5,6]. The treatments of AD, thus, aim to alleviate pruritus intensity and restore skin barrier's function and integrity that are damaged through prolonged eczematous, xerotic and lichenlified condition. Unfortunately, existing AD managements are bound to certain concerns that could negatively affect patients' adherence to the treatment [7]: The use of corticosteroids as standard disease management associates with phobia of local side effects like skin atrophy, striae, steroid acne or increased hair growth and systemic side effects such as dwarfism, cataract or Cushing's syndrome [8–11]. Topical calcineurins inhibitors can cause immunosuppression or skin irritating effect, when other systemic therapies can lead to adverse events like headache, nausea, renal impairment or hypertension [12]. Considering these solid evidences, a serious demand for discovery and development of complementary approaches to AD has been imposed, promoting the practice of holistic methods and utilization of naturally derived materials to a great extent [13].

1.2 Vietnamese Medicinal Plants

In Vietnam, a tropical country blessed with a sheer abundance of flora, phytomedicines have been utilized and appreciated since antiquity to treat dermatological conditions. Regarding to atopic dermatitis, a great number of unconventional antidotes have been passed around for generations, using extracts from familiar herbs like common purslane, false daisy, candle bush, snake jasmine, and antique spurge to apply on eczema areas, or mixtures of medicinal plants decocted in daily diet. There

are, however, only a relatively small number of plants whose effectiveness is confirmed by scientific methods; and still, they have not yet been assembled or systemized for the sake of good and common practice. The use of medicinal plants in Vietnam is furthermore advocated by the fact that Vietnamese participants had an exceptionally low frequency of using conventional AD managements (moisturizers, topical corticosteroids and systemic antibiotics) compared to counterparts from other Southeast Asian countries [14] while a large portion of participants showed their preference for AD herbal treatments. Another reason why plant extracts and plant-isolated phytocomponents deserve more attention is that they are widely used in over-the-counter products for AD thanks to their significant anti-inflammatory, anti-microbial and wound healing abilities. With aforementioned reasons, this review aims to summarize the literatures on medicinal plants in Vietnam with anti-AD potentials in an effort to define the role of phytomedicines in treatments for AD, as well as to create an archive of investigated plants and their bioactive compounds that will be useful for drugs discovery and development.

2. MATERIALS AND METHODS

Preliminary search for articles was carried out on various databases like PubMED, HerbMed, ResearchGate, Science Direct and Google Scholar using queries such as "atopic dermatitis or eczema or contact dermatitis", "plant extracts or medicinal plants", and "suppress" or its common synonyms (prevent, inhibit, reduce) or related terms (alleviate or attenuate or ameliorate or improve). All pertinent hits went through a blind assessment done by two individuals using criteria as follows:

- Inclusion criteria:
  - Investigations on efficacy of single plant extract.
  - *In vivo* studies or clinical trials.
  - Studies on medicinal plants that exist in Vietnam's territory. Publications from Đỗ Tất Lợi (Những cây thuốc và vị thuốc Việt Nam [14]) and Võ Văn Chi (Từ điển cây thuốc Việt Nam [15]) were regarded as sources of reference.
- Exclusion criteria:
  - Articles examining efficacy of one single compound, and multi-compound or multi-extract preparation.
  - Articles whose full-texts were not available.
  - Articles whose contents were poorly presented.
  - Articles in other languages than English.

This review was synthesized in a narrative format using acceptable search hits, following the Animal Research: Reporting of *in vivo* Experiment (ARRIVE) Guidelines, and enriched with additional relevant information from other materials. No data pooling or meta-analysis were performed since data from obtained studies were not sufficiently homogenous in terms of methods, testing intervals and outcomes. For readability and informativeness, study design, dosage, route of administration, experimental animals, and results extracted from these studies on different medicinal plants were discussed in separated sections while adverse effects, active components or mechanism of action were appended if existent only.

3. RESULTS

A total number of 39 eligible studies referring to 31 medicinal plants were achieved following presented approach. These results were both described in details and assorted into Table 1 where scientific names, vernacular names and reported pharmacological activities of the plants could be acquired.

3.1 *Alisma orientale* (*A. orientale*)

Anti-inflammatory activity of *A. orientale* has been demonstrated in several studies: The plant extract inhibited contact dermatitis in mouse pinnae before sensitization with 2,4-dinitrochlorobenzene(DNCB) [16] and notably suppressed ear swelling occurred in induction phase of picryl chloride-induced contact dermatitis (PC-CD) model in ICR mice [17]. However, it was over a decade after that *A. orientale*'s effect against AD was examined more intensively. Reduction in dermatitis severity score (37.5%) and scratching behavior (32.1%) was noted in 2,4,6-trinitrochlorobenzene (TNCB)-treated NC/Nga mice after oral administration of *A. orientale* extract in 5 weeks (200 mg/kg/d), although there was no decrease in serum Immunoglobulin E(IgE) level. The degree of hyperplasia and immune cells recruitment in inflamed skin sites were only moderately lowered. The content of alisol and its derivatives in *A. orientale* extract was concluded to be attributable for the plant's mitigating effects [18].

Table 1. Collected studies of plants with investigated anti-atopic dermatitis activity

Scientific name	Vernacular name (in Vietnamese and English)	Reported pharmacological/immunologic activities	Active constituents	Reference
Alisma orientalis (Sam.) Juzep. (Alismataceae)	Trạch tả, water plantain	Anti-inflammatory, anti-complement, anti-bacterial, anti-allergic, NO production inhibitory activities, immunosuppressive effects on lymphocytes [18]	Alisons (A, B), alison acetate (A, B), alismol, 13β,17β-epoxy alfisol A, alisol B 23-acetate and alisol C 23-acetate [18]	Rhizome [18]
Aloe vera L. (Asphodelaceae)	Nha đam, aloe	Anti-inflammatory, wound-healing, moisturizing, anti-aging, anti-fungal, anti-bacterial, anti-oxidant, anti-tumor activities, immunomodulatory effects on IL-5, -10 [19,20]	NM	NM [19]; Leaves [20]
Amorphophallus konjac K. Koch (Araceae)	Khoai nưa, konjak	Anti-obesity, anti-hyperglycemic, anti-hypercholesterolemia, anti-inflammatory activities [24]	Oligosaccharides [24]	Corm [24]
Angelica dahurica Fisch. Ex Hoffm. (Apiaceae)	Bạch chỉ, angelica	Anti-inflammatory, anti-oxidant, anti-oxidative, anti-cancer, anti-histamine, cytochrome P450 activities, beta-endorphin inducing agent [31]	Imperatorin and coumarin [31]	Root [31]
Astragalus membranaceus (Fisch.) Bunge (Fabaceae)	Hoàng kỳ, milk vetch, astragalus	Anti-allergic, IL-4 enhancing and IFN-gamma suppressing effects [32,33]	NM	Root [32,33]
Boesenbergia pandurate (Roxb) Schltr.(Zingiberaceae)	Lưỡi cọp, finger root, Chinese ginger	Anti-cancer, anti-oxidant, anti-inflammatory, anti-bacterial, anti-biofilm, anti-obesity and anti-allergic activities, suppressing effects on mast cell cytokines, mediators, and degranulation [35]	Pinostrobin, cardamonin, boesenbergin, 5,7-dihydoxyflavone, 1,8-cineole, hydroxy-panduratin, and panduratin A [35]	Root [35]
Broussonetia kazinoki Sieb. (Moraceae)	Cây dướng, paper mulberry, kozo	Anti-diabetic, anti-acne, anti-hyperglycemic, anti-oxidant, anti-inflammatory, wound-healing activities, inhibitory effects on NO overproduction, melanin synthesis and tyrosinase [36,37]	Broussonols (A, B, C, D, E), broussontines (A, B, W, X, J1) [36]	Heartwood [36]; Leaves [37]

Scientific name	Vernacular name (in Vietnamese and English)	Reported pharmacological/immunologic activities	Active constituents	Reference
Chrysanthemum indicum L. (Asteraceae)	Kim cúc, Indian chrysanthemum	Anti-inflammatory, anti-microbial, anti-oxidant, MAPKs and NF-*κ*B inhibitory activities. Inhibitory effects on NO, PGE2, TNF-*α*, and IL-1β [38]	Kikkanol (A, B, C), eriodictyol 7-O-β-D-glucopyranosiduronic acid, acaciin, and luteolin 7-O-β-D-glucopyranoside [38]	Flower [38]
Cinnamomum cassia L. (Lauraceae)	Quế, Chinese cinnamon, Chinese cassia	Anti-inflammatory, anti-allergic, anti-microbial, anti-fungal, anti-diabetic, anti-pyretic, anti-ulcerogenic activities [39]	NM	Bark [39]
Cudrania tricuspidata Carrière (Moraceae)	Mỏ quạ, cudrang, Chinese mulberry, silkworm thorn	Anti-hypertensive, anti-inflammatory, anti-hypercholesterolemia, hepatoprotective, T-lymphocyte inhibitory activities [48]	Catholic xanthone, cudraflavone B, gericudranin E, gerontoxanthone A and gancaonin A [48]	Fruits [48]
Dictamnus dasycarpus Turcz. (Rutaceae)	Bạch tiên bì, dictamnus, densefruit dittany	Anti-inflammatory, neuroprotective, immunosuppressive, anti-fungal and anti-allergic activities [50]	Alkaloids, limonoids, phenolic glycosides, dictamine, fraxinellone and skimmianine [50]	Bark [50]
Diospyros kaki Thunb. (Ebenaceae)	Cây hồng, persimmon	Hemostasis modulatory, laxative, hypotensive, diuretic, anti-pruritic, anti-histamine activities [52]	Kaempferol, astragalin [52]	Leaves [52]
Eriobotrya japonica (Thunb.) Lindl. (Rosaceae)	Nhót tây, loquat, Chinese plum	Anti-HIV, hypoglycaemic, wound-healing, anti-tussive, anti-diabetic, anti-inflammatory, nephroprotective, NF-kappaB and mast cell activation inhibitory activities [53,54]	Amygdalin, unsaturated fatty acids, hydrocyanic acid, caffein acid, chlorogenic acid, beta-sitosterol and beta-sitosterol glycoside components [53,54]	Seeds [53,54]
Glycyrrhiza glabra L. (Fabaceae)	Cam thảo, licorice, liquorice, sweet wood	Anti-inflammatory, anti-allergic, anti-microbial activities [55]	Soflavenoids, liquiritigenin, disodium glycyrrhetinic acid and glycyrrhizin [55]	Root [55]
Houttuynia cordata Thunb. (Saururaceae)	Diếp cá, fish mint	Anti-leukemic activity, anti-oxidation activity, anti-cancer activities [65]	NM	Leaves [65]
Hypericum perforatum L. (Hypericaceae)	Ban âu, St John's wort	Anti-depressant, anti-microbial, anti-inflammatory activities [66]	Hypericin and phloroglucin [66]	NM [66]

Scientific name	Vernacular name (in Vietnamese and English)	Reported pharmacological/immunologic activities	Active constituents	Reference
Illicium verum Hook.f. (Schisandraceae)	Đại hồi, star anise	Anti-inflammatory, anti-cancer, anti-microbial, anti-oxidant, anti-cancer, analgesic, sedative and convulsive activities, surpassing effects on NO, prostaglandin E2 and cytokines [67]	Anethole, alpha-pinene, limonene, beta-phellandrene, alpha-terpineol, anisaldehyde, farnesol, shikimic acid, and safrole [67]	Fruits [67]
Kochia scoparia (L.) Schrad (Amaranthaceae)	Địa hoả phu, fireweed, burning bush	Anti-ulcer, anti-arthritis, anti-inflammatory, anti-nociceptive, anti-bacterial, gastroprotective, hepatoprotective activities [70]	Momordin Ic [70]	Fruits [70]
Morus alba L. (Moraceae)	Dâu tằm, white mulberry	Anti-diabetic, hypolipidemic, anti-hypertensive, anti-microbial, anti-oxidant, anti-atherosclerotic, anti-cancer, neuroprotective, and anti-ulcer effects [71]	NM	NM [71]
Myristica fragrans Houtt. (Myristicaceae)	Nhục đậu khấu, nutmeg, mace	Carminative, astringent, hypolipidemic, anti-thrombotic, anti-platelet aggregation, anti-fungal, aphrodisiac, anxiogenic, anti-diarrheal, anti-oxidant and anti- inflammatory activities [72]	Macelignan [72]	Seeds [72]
Perilla frutescens (L.) Britton (Lamiales)	Tía tô, perilla, beefsteak plant	Anti-oxidant, anti-allergic, anti-inflammatory, hepatoprotective, anti-bacterial activities [78]	NM	Leaves [78]
Platycodon grandiflorum A. DC. (Campanulaceae)	Cát cánh, platycodon, balloon flower	Anti-oxidant, anti-proliferative, anti-inflammatory, anti-allergic, anti-microbial, anti-diabetic, hepatoprotective, neuroprotective activities [83,84,85]	Platycodins (A, D, D2, and D3), polygalacin D2, platyconic acid A, and platycosides (A, B, C, D, E and F) [83]	Root [83,84], NM [85]
Psidium guajava L. (Myrtaceae)	Ổi, guava	Anti-inflammatory, hypotensive, anti-diabetic, anti-microbial, anti-allergic activities [89]	NM	Leaves [89]
Rehmannia glutinosa (Gaertn.) Steud. (Orobanchaceae)	Địa hoàng, Chinese foxglove, rehmannia	Anti-inflammatory, anti-allergic, hypotension, immune-enhancement activities [91]	Catalpol, aucubin, ajugol and beta-sitosterol [91]	Root [91]
Rhus verniciflua Stokes (Anacardiaceae)	Cây sơn, Japanese lacquer tree, varnish tree	Anti-inflammatory, anti-viral, anti-rheumatic, cathartic, diaphoretic, and sedative activities [95]	Fisetin and quercetin [95]	Bark [95]

Scientific name	Vernacular name (in Vietnamese and English)	Reported pharmacological/immunologic activities	Active constituents	Reference
Saussurea lappa Clarke (Asteraceae)	Mộc hương, costus	Anti-inflammatory, anti-ulcer, anti-viral, analgesic, digestive, aphrodisiac, diuretic, hepatoprotective activities, effects on IL-6 and TNF-alpha [97]	NM	NM [97]
Schizandra chinensis (Turcz.) Baill.(Schisandraceae)	Ngũ vị tử, five-flavored berry	Anti-oxidant, anti-diabetic, anti-inflammatory activity, hepatoprotective, hypotensive, wound-healing activities [98]	NM	NM [98]
Sophora flavescens Aiton (Fabaceae)	Khổ sâm, dã hoè, shrubby sophora	Anti-cancer, anti-oxidative, anti-bacterial, anti-inflammatory and anti-allergic activities [100]	Prenylated, lavandulylated or lavandulyl flavanones, quinolizidine alkaloids and pterocarpanes [100]	Root [100]
Uncaria rhynchophylla (Miq.) Jacks. (Rubiceae)	Câu đằng, cat's claw	Anti-Inflammatory, anti-hypertensive, anti-oxidative, neuroprotective, vasodilatory, Ca2+-blocking inhibitory activities [103]	NM	Root [103]
Vernonia amygdalina Delile (Asteraceae)	Cây lá đắng, bitter leaf	Anti-oxidant, anti-inflammatory and anti-tumor activities [105,106,107]	Luteolin and derivatives, vernoniosides A1, A2, A3, B1, B2, D3 and C, vernodalin, vernodalol, vernolepin, vernomygdin and vernolides [107]	Leaves [105, 106,107]
Vigna angularis (Willd.) Ohwi & H. Ohashi (Fabaceae)	Đậu đỏ, azuki bean	Diuretic, tumour-suppressive, renal-protective, anti-diabetes, anti-oxidative stress and anti-inflammatory activities [108]	NM	Legume [108]

3.2 *Aloe vera* (*A. vera*)

Orally administered *A. vera* extract (0.8 mg/kg) to mice with spontaneously induced AD showed positive effects that were achieved through suppression of IL-5 and IL-10 [19]. However, the increase of serum IgE level in extract-receiving mice contradicted a later study in which 96% gel was used. The gel improved DNCB-induced AD-like symptoms in BALB/C mice as ulceration and hyperkeratosis were lessened while reappearance of skin structures such as hair follicles or sweat glands were noted at the end of this 10-day treatment. It was then proposed that inhibition of T helper cell 2 (Th2) activation was possibly the mechanism behind *A. vera* gel's anti-AD activity via topical route [20].

Additionally, the effectiveness of *A. vera* as a treatment for other types of dermatitis was as well recorded, including seborrheic dermatitis [21] and diaper dermatitis [22]. There is, however a case in which *A. vera* was found to induce contact dermatitis, although the occurrence of allergic reactions linked to this plant is extremely low [23].

3.3 *Amorphophallus konjac* (*A. konjac*)

Konjac glucomannan (KGM) is a dietary fiber derived from tubers of *A. konjac* with evidence-supported therapeutic effect on AD. Ingestion of pulverized KGM (PKGM) dose-dependingly alleviated AD symptoms in NC/Nga mice, including elevated serum IgE, IgG1 level, and pruritic, eczematous skin lesions [24] by suppressing mastocytosis, eosinophilia, as well as overproduction of pro-inflammatory cytokines (IL-4, IL-10, tumor necrosis factor alpha (TNF-α)) and substance P [25]. Moreover, PKGM inhibited lymphadenopathy and autoimmune responses which might involve in AD pathogenesis by restraining the expression of interferon gamma (IFN-γ) and B-cell activating factor [26]. While decreased IgE level was explained by PKGM's ability to suppress IgE class-switching in B cells by attenuating εGT expression [27], a study of Suzuki et al. then challenged this deduction by stating that it was monocytes, rather than B cells, the first target in such mechanism [28]. Superior effect of hydrolyzed KGM to pulverized KGM's was also claimed in the latter study. According to another research, oral intake of ceramide derived from *A. konjac* significantly improved skin condition and reduced Th2-dominating hypersensitivity toward airborne allergens after a 2-week treatment in children with moderate AD (1.8 mg/day) [29]. Investigated ability to fix skin barrier impairment and reduce IL-1 α level of glucosylceramide from the plant photocomposition has also confirmed *A. konjac* as a nutraceutical with noteworthy anti-AD activity [30].

3.4 *Angelicae dahurica* (*A. dahurica*)

Efficacy of *Anglicae dahuricae* Radix ethanol extract in suppressing AD development was investigated topically at dose 10 mg/mouse using *Dermatophagoides farinae* body extract (DFE)-induced AD model in NC/Nga mice. After 4 weeks of treatment, significant reductions in skin severity and dermal/epidermal thickness accompanied by lowered levels of histamine and IgE were recorded in immunized mice. *In vitro* investigations in this study revealed that the extract also markedly suppressed nitric oxide (NO) synthesis, as well as Thymus and Activation Regulated Chemokine (TARC) and monocyte-derived cells (MDC) mRNA expression in a dose-dependent manner. Presence of oxypeucedanin, oxypeucedanin hydrate, byakangelicin, nodakenin, imperatorin, and isoimperatorin in this extract, which could be attributable for its healing efficacy, was confirmed using HPLC [31].

3.5 *Astragalus membranaceus* (*A. membranaceus*)

Oral administration of lyophilized *A. membranaceus* dried root extract (100 mg/kg/day) was demonstrated to be effective in treating1-fluoro-2,4-dinitrobenzene (DNFB)-induced dermatitis in NC/Nga mice [32]. Despite the failure to suppress IL-4 and serum IgE production, it significantly decreased skin lesions and ear swelling that was followed by hyperplasia and cells infiltration. However, the plant extract was seemingly more effective when being used as a topical treatment than oral intake. Application on skin using 1% *A. membranaceous* extract considerably reduced classic AD symptoms and histological features in DNCB-immunized BALB/C mice [33]. In contrast to the result of Lee et al. serum IgE level slightly declined as production of IL-4, -5, -6, and -13 was strongly inhibited, denoting *A. membranaceus*'s inhibitory effect on Th2-mediated pathway in AD development. TNF-α level and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) expression

were also found to decline in extract-treated mice. Such decrease in inflammatory responses might be related to astragaloside IV, a saponin in *A. membranaceus* phytocomponents with the ability to inhibit NF-κB activation pathway and exert anti-inflammatory effect [34].

3.6 *Boesenbergia pandurata* (*B. pandurata*)

Ethanol extract of *B. pandurata* rhizome has proved to be an effective curative agent against dermatitis in a study where it was orally administered to oxazolone-treated hairless mice in 4 weeks. At both of investigated doses (50 mg/kg/day and 150 mg/kg/day), this extract successfully prevented the advance of AD, as shown by less damages in mice skin barrier, milder clinical manifestations, reduced epidermal/dermal thickness and a fewer amount of infiltrated immune cells. These changes were bound to numerous immunologic evidence like declined IgE concentration that occurred while the level of IgG2a was increased. Significant decreases in the amount of various Th2-mediated molecules (IL-5, IL-13, IL-31, chemokine ligands CCL5, CCL11, CCL17, CCL22, and CCL24), as well as suppresses in IL-5, IL-13 and GATA-3 mRNA expression levels were also reported, concomitantly with the increase of T helper cell 1 (Th1)- and regulatory T cell (Treg)-mediated molecules (IL-12, T-bet, IL-10, Transforming Growth Factor beta (TGF-β), and Foxp3) in mouse spleen. *B. pandurata* has possibly reduced inflammatory responses in AD mice via the blockade of NF-κB signaling pathway, as the lowered concentration of NF-κB1 and 2 mRNA indicated [35].

3.7 *Broussonetia kazinoki* (*B. kazinoki*)

The therapeutic effect of heartwood and leaves ethanol extract of *B. kazinoki* was examined using DFE-immunized NC/Nga mice model, both in dose of 10 mg/mouse for 4 weeks [36,37]. Following the treatment with the extract, thickening of dermis/epidermis, hyperkeratosis, hypertrophy, skin severity score and the number of infiltrated mast cells in dorsal skin markedly decreased, and so did IgE and IL-4 levels in the plasma. The extract's ability to interfere in TNF-α /IFN-γ -induced production of AD related chemokines TARC, MDC and Regulated on Activation, Normal T Cell Expressed and Secreted (RANTES) might be the underlying mechanism for its activity.

3.8 *Chrysanthemum indicum* (*C. indicum*)

Anti-dermatitis effect of 1,3-butylene glycol from *C. indicum* flower extract was topically examined in two concentrations (5% and 30%) using NC/Nga mice with DNCB-induced AD [38]. After the treatment of highly concentrated extract, marked improvements in skin conditions were found along with lowered levels of serum immunoglobulins (IgE and IgG1) while histological changes like significantly decreased amounts of eosinophils and mast cells in dermis, hypertrophy, hyperkeratosis, and edema were noted. Serum levels of relevant mediators (IFN-γ and IL-4) were found decreased as well, concomitantly with the suppressed mRNA expression levels of IFN-γ, IL-4 and IL-13. Such evidence together confirmed *C. indium* as an anti-AD agent with restoring ability on Th1/Th2 ratio.

3.9 *Cinnamomum cassia* (*C. cassia*)

The daily topical treatment using *C. cassia* ethanol extract against DFE induced-AD in NC/Nga mice (400 μg/day) significantly improved skin condition with less signs of erythema, dryness, edema, scarring, hyperkeratosis and dermal recruitment of inflammatory cells after 23 days [39]. The extract furthermore suppressed the expression of TNF-α and TARC while inhibiting serum IgE and histamine levels in a dose-dependent manner. The efficacy of extract from *C. cassia* produced by solid-state fermentation with *Phellinus baumii* (af*Cc*/*Pb*) was found to be superior to that of mentioned *C. cassia* extract in a study of Shin et al. [40]. In DNFB-immunized mice treated with af*Cc*/*Pb* for 8 times over duration of 2 weeks (100 g/mL), observable clinical features were less severe while immune responses were reduced up to 40%. It was also reported that af*Cc*/*Pb*'s effectiveness was probably owing to its inhibitory effects on matrix metalloproteinases-2, -9, -10 and IL-4, -32 expressions.

In spite of evidence for *C. cassia*'s potential in treating AD, there are numerous cases in which it played the role of causative factors. Frequent exposure to *C. cassia* as flavoring agent might cause occupational allergic contact dermatitis, especially to people in bakery or confectionery industry while consumers of cinnamon-containing products might encounter stomatitis and perioral dermatitis [41–47]. It was thus remarkable that a safer anti-AD therapy with higher efficacy could be attained using solid-state fermentation with

P. baumii to eliminate *C. cassia*'s allergenic components, according to Shin et al. in the cited study.

3.10 *Cudrania tricuspidata* (*C. tricuspidata*)

Anti-AD activity of *C. tricuspidata* was confirmed using DFE-immunized NC/Nga mice model when oral administration of the plant extract markedly hindered alterations in skin conditions (60 mg/kg) over 50 days of the experiment [48]. Specifically, restoration of biophysical features was reflected through lowered Eczema Area and Severity Index (EASI) values while reductions of dermal/epidermal thickness and number of infiltrated cells showed significant histological improvements in inflamed skin sites. Such changes associated to the reduction of IgE, histamine and TARC mRNA in the plasma that were also accomplished thanks to *C. tricuspidata* extract.

3.11 *Dictamnus dasycarpus* (*D. dasycarpus*)

DNFB-induced dermatitis on BALB/c mice was a common model used to investigate the anti-inflammatory and anti-allergic activity of *D. dasycarpus* extract [49,50]. In both studies of Han et al. and Kim et al., two doses 30 μg/ear and 300 μg/ear were administered topically, when the higher dose was more efficacious in suppressing edema, dermal hyperplasia, spongiosis, IFN-γ/TNF-α levels and intercellular adhesion molecule(ICAM)-1 immune-expression. *In vitro* investigations from those studies revealed the plant's wide range of regulatory effects, including on mast cells degranulation mediated by β-hexosaminidase and histamine, on phosphorylation of p38Mitogen-Activated Protein Kinases(MAPK), NF-κB p65 and Iκ-Bα, not to mention on production of numerous mediators (IL-6, IL-8, monocyte chemoattractant protein (MCP)-1 and RANTES). It was also reported that *D. dasycarpus* possessed anti-pruritic and anti-allergic effects by deactivating release of histamine and serotonin in mast cells, making it a potential antagonizing agent against AD [51].

3.12 *Diospyros kaki* (*D. kaki*)

The extract obtained from steeping dried *D. kaki* leaves in boiling water was added into a moderate fat diet to reach 0.125% concentration and provided to mice with constant dose of 250 mg/kg during 8 weeks of treatment [52]. For extract-receiving mice, impeded AD progression reflected through skin clinical scores, less histopathological findings and lower scratching frequency were reported. Anti-dermatitis activity of this extract was clarified as production of many mediators including IgE, IL-4 and IL-13 were found suppressed, and furthermore supported by its strong anti-histamine and anti-allergic effects that were examined in this study as well. Additionally, the fact that the efficacy of astragalin, which was investigated all along, showed to be more potent than *D. kaki* leaf extract claimed the major role this compound played in skin healing process. Nonetheless, contribution of other constituents such as kaemferol should as well be regarded when the anti-AD activity of *D. kaki* comes into discussion.

3.13 *Eriobotrya japonica* (*E. japonica*)

E. japonica seed ethanol extract was found effective in suppressing immediate and late-phasic hypersensitive responses caused by either oxazolone or DNFB in rats [53]. Ear swelling, TNF-α overproduction and elevated histamine content in inflamed tissues were dramatically suppressed while simultaneously, lower Erythropoietin and myeloperoxidase activity level revealed that oxazolone/DNFB-induced accumulation of eosinophils and neutrophils was restrained by orally administered *E. japonica* extract. β-sitosterol and β-sitosterol glycoside-containing composition of the plant might have been responsible for described medicating effects, as stated by Sun et al.. In a later study, *E. japonica* seed ethanol extract not only exerted the same anti-dermatitis effect on DNFB-sensitized rats, but also correct the Th1/Th2 balance skewed to Th2 by inhibiting IgE and IL-4 overproduction and increasing Th1 cytokine IL-10 [54]. The experimenting period lasted in 8 days and dose of administration was 10 mL/rat. Presented anti-allergic and immunomodulatory activity altogether have well demonstrated *E. japonica*'s curative effect against AD.

3.14 *Glycyrrhiza glabra* (*G. glabra*)

Gel formulations contained 1% and 2% *G. glabra* extract significantly alleviated erythema, oedema and pruritus after a 2-week treatment for patients with mild to moderate AD in a clinical trial [55]. The 2% gel was evidently more potent than 1% gel as it remarkably improved skin conditions after the first week of the treatment. Such healing

effect of *G. glabra* could be explained by its high glycyrrhizinic acid content (20.3% in the extract and 19.6% in the formulation). In fact, glycyrrhizinic acid has been incorporated as a main anti-inflammatory component of several marketed topical products with clinically investigated efficacy against dermatitis [56–60], possibly thanks to its inhibitory effect on 11 β-hydroxysteroid dehydrogenase [61].

There are actually numerous constituents other than glycyrrhizinic acid in the phytocomposition of *G. glabra* that make the plant a promising herbal remedy for AD. For instance, glycyrrhizin had strong anti-allergic activity expressing through the ability to reduce erythema and edema in albumin-sensitized rabbits via inhibition of prostaglandin E2 [62]. Glycyrrihzin, 18β-glycyrrhetinic acid and liquiritigenin individually were able to ease itchiness and lower ovalbumin-induced elevated IgE level [63]. Licochalcone E, a chalconoid among *G. glabra's* components, was also effective in reducing skin inflammation, as it decreased ear thickness and suppressed IL-12p40 expression through NF-κB downregulation in ozoxalone-treated mice [64].

3.15 *Houttuynia cordata* (*H. cordata*)

In order to verify and enhance the efficacy of *H. cordata* extract in managing dermatitis, a study was designed on hairless mice immunized with DNCB for 5 weeks using the plant extract of 2% in PBS, liposomal suspension and cubosomal suspension [65]. AD-like features including skin roughness and increased water loss in epidermis were significantly reduced, especially for cubosomal suspension-receiving group and followed by liposomal suspension-receiving group. The immunoregulatory effects of these extract-containing suspensions on IFN-γ, IL-4 and IgE were found in the same order of magnitude. As a result, such evidence did not only imply *H. cordata*'s therapeutic effect, but also proved the superior effectiveness that could be achieved through utilization of lipid nano-carriers. It was accordingly believed that these suspensions have enhanced skin permeation of *H. cordata* extract so that its inhibitory effect against AD could be more fully manifested.

3.16 *Hypericum perforatum (H. perforatum)*

The efficacy of a hypericum cream with high content of hyperforin (1.5%) was evaluated in a randomized, placebo-controlled, double-blind, monocentric study on 21 human subjects suffering from mild to moderate AD [66]. SCORing Atopic Dermatitis (SCORAD) Index of patients who adhered to these twice-a-day treatments and the colonization of *Staphylococcus aureus* in inflamed areas have significantly reduced in cream-receiving group as compared to the placebo group. In spite of several adverse events noted during the trial, the superiority of this specific hypericum cream in treating AD was still approved for its hypericin- and allergens-free properties. The study was however limited due to its small sample size, especially when 3 cases of exclusion have been noted along this 4-week treatment.

3.17 *Illicium verum* (*I. verum*)

I. verum ethanol extract significantly mitigated DFE-induced AD in NC/Nga mice as it was topically applied in an amount of 1000 μg/mouse. Over a treating period of 23 days, classic symptoms including severity score, ear swelling, hyperplasia and dermis recruitment of inflammatory cells were suppressed, accompanied by lowered levels of serum IgE, IL-6, ICAM-1 and histamine [67]. In this study and one another, the plant's *in vitro* immunomodulatory effects related to dermatitis pathogenesis were presented. These included inhibitions on production of related cytokines (IL-4, IL-1β, TNF-α), chemokines (TARC, RANTES, MDC), and vascular cell adhesion molecules (VCAM)-1. *I. verum*'s capability to induce blockade of NF- κ B, signal transducer and activator of transcription 1 (STAT1), ERK/p38 MAPK, and Akt pathways furthermore clarified its Th2-related therapeutic mechanism against AD [68].

3.18 *Kochia scoparia* (*K. scoparia*)

Inhibitory effect against dermatitis of *K. scoparia* fruit extract was investigated along with other allergic reactions on ICR mice in a study of Matsuda et al. [69]. The extract was found to reduce ear swelling slightly in effector phase (500 mg/kg, p.o.), yet exhibited no effect in induction phase of PC-CD-induced dermatitis model. Momordin Ic, a compound derived from *K. scoparia*, showed even stronger ability to suppress ear swelling in this study (50 mg/kg, p.o.). In another study by Choi et al. [70], 1% *K. scoparia* extract was used to treat DNCB-induced dermatitis in BALB/C mice. AD-like symptoms were alleviated as less hyperplasia was found while epidermal and dermal thickness

was markedly reduced (39.2% and 35.6%, respectively). Considerable decreases in the production of pro-inflammatory cytokines (IL-1β, TNF-α) and in the expression of MAPKs ERK1/2, p38, JNK and NF-κB in *K. scoparia*-treated mice was reported as well.

Momordin Ic isolated from *K. scoparia* extract might play a major role in curative effect of the plant in both studies. Its greater ability in reducing ear swelling compared to *K. scoparia* extract's suggested that it was among phytocomponents with strong bioactivity in the first article. As being referred to in the second one, momordin Ic was a pro-apoptotic compound whose mechanism is related to MAPK-mediated iNOs pathways and was effective in reducing inflammatory responses in dermatitis model.

3.19 *Morus alba* (*M. alba*)

The topical treatment for AD induced by DFE in NC/Nga mice using *M. alba* ethanol extract in an amount of 10mg/mouse showed strong potency. At the end of 4 experimenting weeks, both skin severity reflected through EASI scores and histological evidence like hyperplasia, keratosis, or infiltration of immune cells were found to be significantly subdued [71]. The extract was also accountable for lowered histamine and IgE levels found in mice plasma, as well as for noteworthy decreases in nitrite, prostaglandin E2 and TARC production that was examined *in vitro* in this same study.

3.20 *Myristica fragrans* (*M. fragrans*)

Orally administered *M. fragrans* extract greatly reduced total serum IgE level in DFE-treated NC/Nga mice (50 and 100 mg/kg/day), along with other AD-like symptoms such as increased transdermal epidermal water loss (TEWL), erythema, epidermal thickness and dermal infiltration of inflammatory cells. Throughout 6 weeks of the investigation, the extract exerted suppressing effect on the expression of IL-4 and IFN-γ in axillary lymph nodes, as well as IL-13 and TNF-α mRNA in skin lesions. Furthermore, it was capable of balancing Th1/Th2 ratio by inhibiting DFE-induced downregulation of T-box transcription factor and upregulation of GATA-3. *M. fragrans* was then suggested as a potential AD treatment with nutritional values [72].

Chung et al.'s work in fact agreed with a previous study in which anti-AD activity of macelignan in *M. fragrans* was predicted. This compound contributed to *M. fragrans*'s curing effect probably by its ability to suppress mRNA levels of pro-inflammatory cytokines including IL-4, IL-13 and TNF-α [73]. Adversely, *M. fragrans* oil was found in two pharmaceutical products in Belgium that caused contact dermatitis, though it was not declared that the oil single-handedly or directly induced allergic response [74]. Nonetheless, *M. fragrans* was listed among other contact dermatitis-inducing spices, as eugenol and solid triglycerides of myristinic acid content in the plant composition were considered to be culpable [75].

3.21 *Perilla frutescens (P. frutescens)*

Aqueous extract of *P. frutescens* has proved its potency in suppressing allergic and inflammatory responses by preventing ear swelling in sensitization phase of oxazolone-induced dermatitis model in ICR mice (400μL/mouse, p.o) [76]. This outcome could hypothetically be explained by interference of the extract in Langerhans cells migration during hypersensitization owing to its inhibitory effect on TNF-α production [77]. In another study using C57BL/6 mice with DNFB-induced AD, orally administered *P. frutescens*'s extract has dramatically reduced mice ear epidermis thickness (35%), presence of eosinophils in local skin tissues (73.7%), and other dermatitis features such as scarring and eczema at the concentration of 100 μg/mL [78]. The extract also restrained the overexpression of matrix metallopeptidase-9 and IL-31 while balanced out distorted ratio of Th1/Th2 through augmentation of T-bet activity. In addition, the suppressing effect of *P. frutescens* oils on DNFB-induced ear swelling was claimed, although it was not of great significance [79].

P. frutescens, a promising anti-AD herb around the kitchen, should be used via ingestion for its activity to exert however. In other words, repetitive contact with the plant materials may in fact lead to dermatitis in many cases [80,81]. The content of perillaldehyde in *P. frutescense* extract was to be blamed for its reported toxicity [82].

3.22 *Platycodon grandiflorum* (*P. grandiflorum*)

Consecutively published researches on the use of *P. grandiflorum* parts have yielded remarkable outcomes. These include dramatic decreases in DNCB-induced dermatitis-like skin perturbation, elevated IgE level in serum and recruitment of

inflammatory cells in NC/Nga mice after oral administration of the plant root extract at varied doses (300 and 500 mg/kg/day [83]; 100 mg/kg/day [84]). Suppression of various Th2 cytokines and chemokines from both study (IL-1, -4, -6, -13, TNF-α, IFN-γ, and TARC), as well as increased level of Th1 IL-10 in the second one were reported. In another study by Kim et al., the downregulation of Th2 IL-4, -5 and IgG1 together with upregulation of Th1 IL-12p40, IFN-γ and IgG2a were found to accompany the improvements of DNFB-aggravated skin [85]. Correspondingly, these studies have provided concrete evidence for the plant's ability to correct Th1/Th2 balance skewed to Th2 upon AD development. In a similar fashion, the protective activity of *Lactobacillus planetarium*-fermented *P. grandiflorum* against DNFB-induced dermatitis NC/Nga mice with optimal potency at dose 50 mg/kg/day was reported [86]. Root-derived saponins, especially platycodin D, were identified both *in vivo* and *in vitro* as bioactive components responsible for the plant's potent healing effect [87,88]. They might have exerted such activities via induction of hemeoxygenase-1 expression, simultaneously with inhibition on NF-κB and STAT1.

3.23 *Psidium guajava* (*P. guajava*)

Topically applied *P. guajava*-containing cream considerably reduced AD clinical severity score and hypersensitive responses to DNCB including elevated dermis/epidermis thickness and infiltration of inflammatory cells in NC/Nga mice [89]. Along with these improvements were dose-dependent reductions in the levels of serum IgE, TARC, and a wide range of involved cytokines (IL4, -5, -13, TNF-$\alpha$and IFN-γ). Another notable result was the increased production of Treg-mediated IL-10 that was responsible for restoration of skin condition. *P. guajava*'s inhibitory effect on TARC and MDC production via blockade of NF-κB and STAT1 activation, concomitant with Heme oxygenase 1(HO-1) upregulation, might be a plausible explanation for its therapeutic effect [90].

3.24 *Rehmannia glutinosa* (*R. glutinosa*)

R. glutinosa's suppressing effect on progression of DFE-induced AD in NC/Nga was extensively examined in a study by Sung et al. [91]. Clinical manifestations assessed by EASI values and histological features such as dermal/epidermal thickening or inflammatory cells accumulation were significantly assuaged in mice treated topically with plant extract. Hyperexpression of involved cytokines (IL-4, TNF-α), chemokines (TARC, MDC, RANTES) and adhesion molecules (ICAM-1, VCAM-1) was restrained together with histamine level and *in vitro* production of TARC, MDC and RANTES. Nonetheless, elevation of serum IgE level in extract-treated mice was recorded as an unexpected result that can play a part in clarifying *R. glutinosa*'s mechanism of action AD.

3.25 *Rhus verniciflua (R. verniciflua)*

Although systemic and contact dermatitis caused by urushiols produced in *R. verniciflua* has been reported with common occurrence [92–94], the plant still contains components that were effective in treating AD. In a study using C57BL/6 mice with DNFB-induced dermatitis, urushiol-removed *R. verniciflua* extract significantly reduced degrees of skin exacerbation, recruitment of mast cell in inflamed sites and ear swelling accompanied by increased vascular permeability (500 mg/kg) [95]. iNOS expression, cytokines (IL-6, TNF-α) production and macrophage activation via NF-κB pathway were inhibited as well. Such findings were presumably related to the presence of fisetin in *R. verniciflua*'s phytocomposition, as similar immunomodulatory effects of the compound were reported in a previous work of Goh et al. [96].

3.26 *Saussurea lappa* (*S. lappa*)

In vitro ability to inhibit the production and mRNA expression of TARC, MDC, RANTES, and IL-8 of *S. lappa* extract gave a hint about its anti-AD potential that was confirmed in the same study [97]. DFE-induced disturbances in skin barrier such as hyperplasia, keratosis or recruitment of immune cells and clinical severity presented by EASI values were lowered in NC/Nga mice fed with the extract. *S. lappa* also acted as a hindrance to the production of histamine, TARC and IgE in these mice, which in turn revealed a plausible mechanism behind the plant's healing capability.

3.27 *Schizandra chinensis* (*S. chinensis*)

NC/Nga mice subjected to repetitive exposure of DNCB with aggravated skin condition, hyperplasia, and intense pruritus from degranulation of infiltrated mast cell have achieved significant recoveries after the topical treatment with *S. chinensis* extract (1%) [98]. As

similar to IgE and IgM concentration in the blood, histamine level along with expression of histamine receptors H1R, H3R and H4R were markedly reduced. Hyperexpression of IL-4, IL-5 and FcεRIβ were found to decrease as well. Likewise, clinical and histopathological manifestations in DNFB-immunized mice were alleviated by topically applied *S. chinensis* fruit extract in a more recent study [99]. Such healing effect might be owing to suppressed production of TNF-α, IFN-γ, IL-6 andMCP-1 that held crucial roles in elicitation of inflammatory responses.

3.28 *Sophora flavescens* (*S. flavescens*)

Topically administered *S. flavescens* extract (10 mg/mL) significantly assuaged immunological responses to DNFB in BALB/c mice including ear swelling, edema, hyperplasia, spongiosis, and infiltration of mononuclear cells [100]. *In vitro* suppressing effects of the extract on mast cell activity and the release of its mediators - histamines and β -hexosaminidase - were reported along. *S. flavescens*'s healing capability was also justified in a former study. Specifically, clinical manifestations of AD, dermal leukocytes infiltration and elevated serum IgE level caused by DFE in NC/Nga mice were was notably lowered after topical treatment with the plant extract [101]. These studies together demonstrated *S. flavescens*' wide range of immunomodulatory ability as the overproduction of IgE, Th cytokines (TNF-α and IFN-γ) and chemokines (TARC/CCL17, MDC/CCL22, and CTACK/CCL27) were well restrained. Prenylated chalcone present in the plant's component with *in vitro* inhibitory ability on chemokines expression via a HO-1-involved pathway might have great contribution to the potency of *S. flavescens* [102].

3.29 *Uncariae rhynchophylla* (*U. rhynchophylla*)

U. rhynchophylla extract administered via oral route was markedly effective in reducing AD-like skin lesions and ear edema resulted from topical sensitization with DNFB in NC/Nga mice [103]. Histological examination of inflamed skin showed notable reductions in dermal/epidermal thickness and recruitment of inflammatory cells. However, these alterations did not associate with either IgE serum level or IL-4 production since no change in these two parameters was found. The efficacy of *U. rhynchophylla* was hence assumed to arise from modulatory effect on Th1 immune responses via inhibition of IFN-γproduction [104].

3.30 *Vernonia amygdalina* (*V. amygdalina*)

In vivo anti-AD activity of *V. amygdalina* aqueous and methanol extract was evaluated on TNCB-treated NC/Nga mice [105]. Both the extracts showed strong prophylactic and curative effects against observable clinical features such as scratching behavior, eczematous skin, ear thickening and filtration of inflammatory cells into ear dermis, as well as upregulation of serum IgE, cytokines (IFN-γ, TNF- α, IL-5) and chemokines (MCP-1, eotaxin). Such anti-allergic effect might relate to ERK pathway of which *V. amygdalina* was previously reported as an inhibitor. Also described in this study was the case of a 17-year-old patient who reported complete disappearance of itchiness in the second week and lowered EASI score on day 21 of the topical treatment with *V. amygdalina*. Furthermore, the plant extract also demonstrated healing effect in the case of chronic, severe and recalcitrant AD of a 5-year-old Congolese patient [106]. The patient reported an appreciable decrease in EASI and Dermatology Life Quality Index (DLQI) after a 3-week adherence to topical application of 10% leaf extract twice a day. At day 40 of the treatment, hematologic and immunologic assays showed lowered level of leukocytes, erythrocyte sedimentation rate (ESR), white blood cells, total IgG, as well as serum total IgE. In another preliminary clinical trial, 25 school children diagnosed with mild to moderate AD were randomly assigned to 4 groups of different treatment including *V. amygdalina*water extract (Vamex1), *V. amygdalina* alcohol extract (Vamex2), dexamethasone and vaseline [107]. After a 3-weeks interval, 69% children in Vamex1 and 71 % in Vamex2 group were completely cleared of AD symptoms while at the end of the trial, significant decreases in pruritus, serum IgE level and ESR were noted.

In all cited studies, the efficacy of *V. amygdalina* extracts in suppressing AD was only slightly inferior to that of positive controls while no adverse effects were reported in all cases. Although these were strong evidence for the plant's safety and efficacy, small sample size of the studies however made it insufficient to confirm *V. amygdalina*'s anti-AD activity in human. Still, its effectiveness could be explained by a wide range of bioactive compounds with anti-inflammatory and anti-allergic activity, especially vernondalin, a terpenoids found in *V. amygdalina* leaf extract [105].

3.31 *Vigna angularis* (*V. angularis*)

The prophylactic and therapeutic effects of red bean (*V. angularis*) on AD was investigated by feeding NC/Nga mice with plant extract daily for 2 weeks prior to the induction using DNCB [108]. Similar to severity of eczematous skin, histopathological features including dermal/epidermal hyperplasia, hyperkeratosis and recruitment of polymorphonuclear cells and mast cells were lessened, showing significant improvements in extract-receiving mice. Furthermore, mRNA expression levels of IL-4, IFN-γ and TNF-α in splenocytes was markedly reduced along with peripheral eosinophils ratio and serum IgE concentration. The treatment in dose of 250 mg/kg was superior to 50 mg/kg as it generated statistically significant results. Specific plant components with anti-AD activity, however, have not yet been figured out since the investigated extract was comprised of great portions of carbohydrate (37.09%) and crude fat (38.06%) with high polyphenols content. In a more recent study, oleanolic acid acetate isolated from *V. angularis* was found to be effective in suppressing development of DFE/DNCB-induced AD and DNFB-induced CD in BALB/c mice [104]. The compound possessed a wide range of immunomodulatory activity demonstrated by reductions in IgE, DFE-specific IgE, and IgG2a levels, as well as in expression of chemokine TARC and numerous cytokines (thymic stromal lymphopoietin, IFN-γ, TNF-α, IL-1β, -4, -5, -6, -10, -17, -22, -31) via MAPKs and NF-κB pathways.

4. DISCUSSION

AD is a multifactorial dermatologic condition with high prevalence characterized by appearance of eczematous skin and intense pruritus [1]. Current AD managements such as emollients, corticosteroids, calcineurin inhibitors, antibiotics, antihistamines or phototherapies, in spite of their potency, are chained to serious concerns of drugs addition, adverse effects and high cost that make it unfavorable for patients to sufficiently comply with in the long term. It was furthermore reported that the popularity of these conventional managements was not widespread among Vietnamese respondents as only a small proportion of respondents used topical corticosteroids (11% to 25%) and systemic antibiotics (11%) for severe AD [109]. Surprisingly, the practice of complementary and alternative therapies for the disease was preferred by a comparably high portion of participants from Vietnam and Japan (both 27%) [109,110]. The exploitation of phytomedicines is not limited to direct topical or oral uses as medicines only: Plant extracts are still one among the main ingredients of well-known commercialized AD products, e.g. *Aloe barbadensis*, *Butyrospermum parkii* and *Vitis vinifera*, and so are numerous compounds isolated from plants such as bisabolol from German chamomile, glycyrrhetinic acid and licochalcone A from licorice [111]. Thereupon, a retrospective review where medicinal plants with anti-AD activity in Vietnam are assembled is of great importance. It is then especially useful for the purpose of providing detailed insights into current phytotherapy approaches whose development would create substantial impacts on the managements of AD.

In this review, a systematic search was performed and a total of 39 studies on 31 medicinal plants with validated anti-AD activity in Vietnam were compiled and reported with additional relevant details. Procured studies fall into 3 categories including research article (87.5%), clinical trial (7.5%) and case study (5.0%). Root and leaves are the most frequently employed plant parts that were subjected in 25.0% and 22.5% of obtained studies respectively, followed by barks, suits and seeds, each in 7.5%. Other investigations utilized extract from whole plant or special parts such as rhizome, corm, heartwood, and legume. Most of these herbal remedies were tested as unadulterated extracts (34 studies) while some others were incorporated into different topical carriers such as gel (*A. vera*, *G. glabra*), cream (*H. perforatum*, *P. guajava*) or suspensions (*H. cordata*). Nonetheless, the efficaciousness of such loaded carriers and of these plants alone were scarcely compared and thus, posing certain questions about the actual potency of contained extracts, the contribution of used vehicles in disease improvements and the plausible pharmacological interactions between testing components.

Albeit all extracts were tested on murine models of AD, disease inducers, specific strains of experimental animals, and methods of delivery differ greatly. Disease induction on experimental animals availed common haptens, namely DNCB (28,57%), DNFB (25,71%), DFE (28,57%), etc., to mimic AD-like symptoms including pruritus, development of eczematous skin lesions, epidermal/dermal thickening and infiltration of pro-inflammatory lymphocytes, accompanied by

elevation of serum IgE level and a wide range of Th2 cytokines. The number of articles using NC/Nga mice occupied 61.54% and outweighed those that used other strains such as BALB/C, hairless mice and C57BL/6 for extract evaluation. As an explanation for this particular favor, NC/Nga mice can develop analogous clinical features and histology to those of afflicted patients, including the overproduction of IgE, spontaneously under conventional condition and thus, are very much valued in the delineation of eczema pathophysiology and treatment [112]. All investigated materials followed topical or oral route of administration, both of which either reflect how the plants are traditionally used or suggest a more proper usage for AD treatment. Nevertheless, while the diversity in testing approaches enables researchers to opt for the most suitable method, it also challenged the conduction of data pooling and thus, no meta-analysis was performed in this narrative-style systematic review.

The determination of herbal healing efficacy critically requires in-depth studies on AD cellular and molecular biomarkers. In order to identify AD subtypes of different phases and pathologies, to assess dose-response relationship between therapeutic agents and disease manifestations, as well as to clarify the pathways by which the condition was made to subdue, it is necessary to examine the level of markers such as immunoglobulins, inflammatory cytokines, adhesion molecules, and immune receptors together with corresponding lymphocytes and effector cells [113]. Overall, immune molecules and cells investigated in collected studies made up a greatly extensive list that disabled data compression and comparison; thus, only a few commonly examined markers are presented here as examples. Thickened epidermis and dermis with histopathological findings and infiltration of eosinophils and mast cells are first signs to be sought. The level of serum IgE formerly considered as a factor with pivotal role in AD development was examined in most articles. While most potential extracts successfully restored IgE level upon improving skin condition, some do not. These extracts, including *A. orientale, A. membranaceus* and *U. rhynchophylla*, emphasized that IgE hypersensitivity is not prerequisite for AD development and is only a hallmark of extrinsic type [2]. Inflammatory cytokines are other reliable markers since their production is simple to determine and well correlated to disease severity and extract activity. Assessment of specific cytokines is useful for determining the phase, on which an extract can act upon, as well as its healing pathway and potency [114]. In the acute phase, AD development is primarily driven by Th2-cytokines, notably IL-4, -5 and -13 that are responsible for inflammatory responses and intense pruritus. The shift to chronic phase occurs when naive T cells differentiate into Th1 cells under the influence of IL-12 produced by activated dendritic cells and triggers the secretion of IFN-gamma, which acts along with other Th17/Th22 cytokines and eventually leads to lichenification [114,115]. Additionally, *in vitro* studies were usually conducted to clarify the particular inflammation inhibitory pathways that investigated plant extracts have followed.

Similar to other therapies, there are shortcomings in the usage of phytomedicines that make it sometimes unfavored by dermatologist and physician. They include firstly the safety of herbal medicines, a pivotal aspect often belied by the assumption that natural treatments do little or no harm to health. This is in fact a dangerous misconception as some among reported plants in this review are even notorious for their highly allergenic profiles such as *A. vera*, *C. cassia*, *I. verum* and *R. verniciflua* [116], and a few others would cause severe systemic side effects while being used excessively. Extrinsic factors, e.g misidentification, mislabeling and contamination of plant materials can be also considered as threats other than the plant's toxicity itself. Secondly, the variety of plant components on one hand exerts a wide span of immunoregulatory activities, but riddles the identification of lead compounds on the other hand. This challenges not only the isolation and confirmation of single plant-derived compounds which is potential for drug discovery, but also the adulteration and adjustment to enhance herbal medicine's efficacy in pharmaceutical manufacture. Lastly, more explanatory and pragmatic studies should be conducted to determine whether they can as well work effectively on human. That is to say, when AD animal models are claimed to be highly relevant to human manifestations, the evaluation of these is used merely to underline the potential of plant extracts, but by no mean to draw final conclusions about their effectiveness and safety in real practice.

The assembly of potential Vietnamese medicinal plants that can be served as substitutes for

immunosuppressive agents has highlighted the practice of herbalism among therapeutic approaches for AD. Thereupon, further research to evaluate and optimize the efficacy of herbal medicines on human are absolutely critical to pave the way for the development of new herbal medications. Efficaciousness of composite herbal medicines should be examined to unveil prominent synergistism occurred between various extracts that could be extremely beneficial in the combat against AD. Another important task is to identify the main phytoconstituents responsible for healing effect that can be sufficiently isolated and refined for commercial use. Additionally, the safety of phytomedicines must be ensured by the removal of hazardous components preceded by approved risk assessment processes. Among several options for such task is solid-state fermentation, a “low technology” system with claims of being able to simultaneously boost the phenolics content and bioavailability of plant extracts as reported in the previous section of this review [117,118]. It is finally important to bear in mind that AD is a complicated skin condition whose exact etiology is unknown and thus, integrative therapy of various managements including the treatment with phytomedicines, dietary intervention, indoor environmental control and psychological support definitely deserves special attention.

On top of this, the underachieving status of traditional medicines deployment in Vietnam is a serious concern arose from weak enforcement of an inadequate and outdated legal framework. Given that Vietnam has an approximate amount of 10,000 flora species with about 4,000 plants that can be used for medicinal purposes, it is an alarmingly contradicting fact that 80-85% herbal medicines circulating on national markets originated from China as reported in June 2016 [119]. The number of GACP-complied herbal medicines manufacturers only counted to 7 by January 2016 [120] when that of GMP-complied manufactures added up to merely 174 by December 2015 [121]. Presented situation undoubtedly demands improved legislations specific to quality control, documentation and intellectual property rights of traditional medicines, at best with reference to guidelines of international organizations (WHO [122], IUCN [123], IUPAC [124], etc.), to ultimately facilitate the research and development of natural-derived AD therapeutics.

5. CONCLUSION

The present review features Vietnamese medicinal plants with alleviating effects on AD, thanks to which the role of plant-based treatments for this specific dermatologic condition is once again emphasized. Through collected studies, phytomedicines are proven to possess wide ranges of anti-inflammatory activities via various pathways without exerting severe side effects over experimental periods. This should however reaffirm the need for further study to validate the efficaciousness of discussing plants in practice and the mechanisms behind that could lead to the introduction of novel dermatitis counteragents, which are considered as alternatives and complements to existing managements. Calls for the embracement of Vietnamese rich medicinal source and tight policies on standardization, documentation and preservation are let out additionally to ensure appropriate deployment of anti-AD herbal medicines in the future to come.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Leung DY, Bieber T. Atopic dermatitis. The Lancet. 2003;361:151–160.
2. Novak N, Bieber T, Leung DYM. Immune mechanisms leading to atopic dermatitis. Journal of Allergy and Clinical Immunology. 2013;112(6 Suppl):S128–S139.
3. Garnacho-Saucedo G, Salido-Vallejo R, Moreno-Giménez JC. Atopic dermatitis: Update and proposed management algorithm. Actas Dermo-Sifiliográficas (English Edition). 2013;104:4–16.
4. Zheng T. The atopic March: Progression from atopic dermatitis to allergic rhinitis and asthma. Journal of Clinical & Cellular Immunology. 2014;05:1–16.

5. Meagher LJ, Wines NY, Cooper AJ. Atopic dermatitis: Review of immunopathogenesis and advances in immunosuppressive therapy. Australasian Journal of Dermatology. 2002;43:247–254.
6. Buske-Kirschbaum A, Geiben A, Hellhammer D. Psychobiological aspects of atopic dermatitis: An overview. Psychotherapy and Psychosomatics. 2001; 70:6–16.
7. Lebwohl MG, Del Rosso JQ, Abramovits W. Pathways to managing atopic dermatitis. consensus from the experts. The Journal of Clinical and Aesthetic Dermatology. 2013;6(7 Suppl):S2-S18.
8. Schoepe S, Schäcke H, May E, Asadullah K. Glucocorticoid therapy-induced skin atrophy. Experimental Dermatology. 2006; 15:406–420.
9. Dhar S, Seth J, Parikh D. Systemic side-effects of topical corticosteroids. Indian J Dermatol. 2014;59(5):460.
10. Bode HH. Dwarfism following long-term topical corticosteroid therapy. JAMA. 1980; 244:813–814.
11. Haeck IM, Rouwen TJ, Timmer-de Mik L, de Bruin-Weller MS, Bruijnzeel-Koomen CA. Topical corticosteroids in atopic dermatitis and the risk of glaucoma and cataracts. Journal of the American Academy of Dermatology. 2011;64:275–281.
12. Boguniewicz M, Eichenfield LF, Hultsch T. Current management of atopic dermatitis and interruption of the atopic march. The Journal of Allergy and Clinical Immunology. 2003;112:S140.
13. Boneberger S, Rupec RA, Ruzicka T. Complementary therapy for atopic dermatitis and other allergic skin diseases: Facts and controversies. Clinics in Dermatology. 2010;28:57–61.
14. Do TL. Những cây thuốc và vị thuốc Việt Nam [Glossary of Vietnamese Medicine Plants and Drugs]; 2014.
15. Vo CV. Từ điển cây thuốc Việt Nam [A dictionary of medicinal plants of Vietnam]; 1997.
16. Dai Y, Hang B, Huang Z, Li P. Anti-inflammatory activities and effect of rhizoma Alismatis on immune system. China Journal of Chinese Materia Medica. 1991;16:622.
17. Kubo M, Matsuda H, Tomohiro N, Yoshikawa M. Studies on Alismatis rhizoma. I. Anti-allergic effects of methanol extract and six terpene components from Alismatis rhizoma (dried rhizome of *Alisma orientale*). Biological & Pharmaceutical Bulletin. 1997;20:511–516.
18. Lee JH, Kwon OS, Jin H-G, Woo E-R, Kim Y-S, Kim HP. The rhizomes of Alisma orientale and alisol derivatives inhibit allergic response and experimental atopic dermatitis. Biological & Pharmaceutical Bulletin. 2012;35:1581–1587.
19. Kim J, Lee I seok, Park S, Choue R. Effects of Scutellariae radix and Aloe vera gel extracts on immunoglobulin E and cytokine levels in atopic dermatitis NC/Nga mice. Journal of Ethnopharmacology. 2010;132:529–532.
20. Finberg MJ, Muntingh GL, Rensburg CE. A comparison of the leaf gel extracts of *Aloe ferox* and *Aloe vera* in the topical treatment of atopic dermatitis in Balb/c mice. Inflammopharmacology. 2015;23(6):337-41.
21. Vardy DA, Cohen AD, Tchetov T. A double-blind, placebo-controlled trial of an *Aloe vera* (*A. barbadensis*) emulsion in the treatment of seborrheic dermatitis. Journal of Dermatological Treatment. 1999;10:7–11.
22. Panahi Y, Sharif MR, Sharif A, Beiraghdar F, Zahiri Z, Amirchoopani G, Marzony ET, Sahebkar A. A randomized comparative trial on the therapeutic efficacy of topical *Aloe vera* and *Calendula officinalis* on diaper dermatitis in children. - PubMed - NCBI. The Scientific World Journal. 2012; 2012:1–5.
23. Ferreira M, Teixeira M, Silva E, Selores M. Allergic contact dermatitis to *Aloe vera*. Contact Dermatitis. 2007;57:278–279.
24. Onishi N, Kawamoto S, Nishimura M, Nakano T, Aki T, Shigeta S, Shimizu H, Hashimoto K, Ono K. The ability of konjac-glucomannan to suppress spontaneously occurring dermatitis in NC/Nga mice depends upon the particle size. BioFactors (Oxford, England). 2004;21:163–166.
25. Onishi N, Kawamoto S, Suzuki H, Santo H, Aki T, Shigeta S, Hashimoto K, Hide M, Ono K. Dietary pulverized konjac glucomannan suppresses scratching behavior and skin inflammatory immune responses in NC/Nga mice. International Archives of Allergy and Immunology. 2007; 144:95–104.
26. Onishi N, Kawamoto S, Suzuki H, Hide M, Ono K. Development of autoantibody responses in NC/Nga mice: Its prevention by pulverized konjac glucomannan

feeding. Archives of Dermatological Research. 2007;300:95–99.

27. Oomizu S, Onishi N, Suzuki H, Ueda K, Mochizuki M, Morimoto K, Kawamoto S, Ono K, Kameyoshi Y, Hide M. Oral administration of pulverized Konjac glucomannan prevents the increase of plasma immunoglobulin E and immunoglobulin G levels induced by the injection of syngeneic keratinocyte extracts in BALB/c mice. Clinical and Experimental Allergy: Journal of the British Society for Allergy and Clinical Immunology. 2006;36: 102–110.
28. Suzuki H, Oomizu S, Yanase Y, Onishi N, Uchida K, Mihara S, Ono K, Kameyoshi Y, Hide M. Hydrolyzed Konjac glucomannan suppresses IgE production in mice B cells. International Archives of Allergy and Immunology. 2010;152:122–130.
29. Kimata H. Improvement of atopic dermatitis and reduction of skin allergic responses by oral intake of konjac ceramide. Pediatric Dermatology. 2006;23: 386–389.
30. Uchiyama T, Nakano Y, Ueda O, Mori H. Oral intake of glucosylceramide improves relatively higher level of transepidermal water loss in mice and healthy human subjects. Journal of Health Science. 2008; 54:559–566.
31. Lee H, Lee JK, Ha H, Lee MY, Seo CS, Shin HK. *Angelicae dahuricae* radix inhibits dust mite extract-induced atopic dermatitis-like skin lesions in NC/Nga mice. Evidence-based Complementary and Alternative Medicine: eCAM. 2012;2012:1–7.
32. Lee SJ, Oh SG, Seo SW, Ahn HJ, Geum D, Cho JJ, Park CS. Oral administration of *Astragalus membranaceus* inhibits the development of DNFB-induced dermatitis in NC/Nga mice. Biological & Pharmaceutical Bulletin. 2007;30:1468–1471.
33. Kim JH, Kim MH, Yang G, Huh Y, Kim S-H, Yang WM. Effects of topical application of *Astragalus membranaceuson* allergic dermatitis. Immunopharmacology and Immunotoxicology. 2013;35:151–156.
34. Zhang WJ, Hufnagl P, Binder BR, Wojta J. Antiinflammatory activity of astragaloside IV is mediated by inhibition of NF-κB activation and adhesion molecule expression. Thrombosis and Haemostasis; 2003.
35. Kim MS, Pyun HB, Hwang JK. Effects of orally administered fingerroot (*Boesenbergia pandurata*) extract on oxazolone-induced atopic dermatitis-like skin lesions in hairless mice. Food Science and Biotechnology. 2013;22:257–264.
36. Lee JK, Ha H, Lee HY, Park SJ, Jeong S, Choi YJ, Shin HK. Inhibitory effects of heartwood extracts of *Broussonetia kazinoki* Sieb on the development of atopic dermatitis in NC/Nga mice. Bioscience, Biotechnology, and Biochemistry. 2010;74: 1802–1806.
37. Lee H, Ha H, Lee JK, Park SJ, Jeong SI, Shin HK. The leaves of *Broussonetia kazinoki* Siebold inhibit atopic dermatitis-like response on mite allergen-treated Nc/Nga Mice. Biomolecules & Therapeutics. 2014;22:438–444.
38. Park S, Lee JB, Kang S. Topical Application of *Chrysanthemum indicum* L. attenuates the development of atopic dermatitis-like skin lesions by suppressing serum IgE levels, IFN-γ, and IL-4 in Nc/Nga mice. Evidence-based Complementary and Alternative Medicine: eCAM. 2012;2012:1–8.
39. Sung YY, Yoon T, Jang JY, Park SJ, Jeong GH, Kim HK. Inhibitory effects of Cinnamomum cassia extract on atopic dermatitis-like skin lesions induced by mite antigen in NC/Nga mice. Journal of Ethnopharmacology. 2011;133:621–628.
40. Shin YK, Son HU, Kim JM, Heo JC, Lee SH, Kim JG. Cinnamomum cassia bark produced by solid-state fermentation with *Phellinus baumii* has the potential to alleviate atopic dermatitis-related symptoms. International Journal of Molecular Medicine. 2015;35:187–194.
41. Hartmann K, Hunzelmann N. Allergic contact dermatitis from cinnamon as an odour-neutralizing agent in shoe insoles. Contact Dermatitis. 2004;50:253–254.
42. Millard LG. Contact sensitivity to toothpaste. Br Med J; 1973.
43. Farkas J. Perioral dermatitis from marjoram, bay leaf and cinnamon. Contact Dermatitis. 1981;7:121.
44. Kern AB. Contact dermatitis from cinnamon. AMA Archives of Dermatology. 1960;81:599–600.
45. Calnan CD. Cinnamon dermatitis from an ointment. Contact Dermatitis. 1976;2:167–170.
46. De Benito V, Alzaga R. Occupational allergic contact dermatitis from cassia

(*Chinese cinnamon*) as a flavouring agent in coffee. Contact Dermatitis. 1999;40:165.
47. García-Abujeta JL, de Larramendi CH, Berna JP, Palomino EM. Mud bath dermatitis due to cinnamon oil. Contact Dermatitis. 2005;52:234.
48. Lee H, Ha H, Lee JK, Seo CS, Lee N, Jung DY, Park SJ, Shin HK. The fruits of *Cudrania tricuspidata* suppress development of atopic dermatitis in NC/Nga mice. Phytotherapy Research. 2011;26:594–599.
49. Han HY, Ryu MH, Lee G, Cheon WJ, Lee C, An WG, Kim H, Cho SI. Effects of *Dictamnus dasycarpus* Turcz., root bark on ICAM-1 expression and chemokine productions *in vivo* and *in vitro* study. Journal of Ethnopharmacology. 2015;159: 245–252.
50. Kim H, Kim M, Kim H, Lee GS, An WG, Cho SI. Anti-inflammatory activities of *Dictamnus dasycarpus* Turcz., root bark on allergic contact dermatitis induced by dinitrofluorobenzene in mice. Journal of Ethnopharmacology. 2013;149:471–477.
51. Jiang S, Nakano Y, Rahman MA, Yatsuzuka R, Kamei C. Effects of a *Dictamnus dasycarpus* T. extract on allergic models in mice. Bioscience, Biotechnology, and Biochemistry. 2008;72: 660–665.
52. Kotani M, Matsumoto M, Fujita A, Higa S, Wang W, Suemura M, Kishimoto T, Tanaka T. Persimmon leaf extract and astragalin inhibit development of dermatitis and IgE elevation in NC/Nga mice. The Journal of Allergy and Clinical Immunology. 2000;106:159–166.
53. Sun G, Zhang Y, Takuma D, Onogawa M, Yokota J, Hamada A, Yoshioka S, Kusunose M, Miyamura M, Kyotani S, Nishioka Y. Effect of orally administered *Eriobotrya japonica* seed extract on allergic contact dermatitis in rats. The Journal of Pharmacy and Pharmacology. 2007;59: 1405–1412.
54. Sun G, Liu Y, Zhu J, Iguchi M, Yoshioka S, Miyamura M, Kyotani S. Immunomodulatory effect of *Eriobotrya japonica* seed extract on allergic dermatitis rats. Journal of Nutritional Science and Vitaminology. 2010;56:145–149.
55. Saeedi M, Morteza-Semnani K, Ghoreishi MR. The treatment of atopic dermatitis with licorice gel. Journal of Dermatological Treatment. 2003;14:153–157.
56. Miller DW, Koch SB, Yentzer BA, Clark AR. An over-the-counter moisturizer is as clinically effective as, and more cost-effective than, prescription barrier creams in the treatment of children with mild-to-moderate atopic dermatitis: A randomized, controlled trial. Journal of Drugs in Dermatology. 2011;10(5):531-7.
57. Zhai H, Villarama CD, Hafeez ZH, Maibach HI. Efficacy of a topical agent, MAS063D (Atopiclair), in the treatment of sodium lauryl sulphate-induced irritant contact dermatitis. Exogenous Dermatology. 2003; 2:301–305.
58. Patrizi A, Capitanio B, Neri I, Giacomini F, Sinagra JL, Raone B, Berardesca E. A double-blind, randomized, vehicle-controlled clinical study to evaluate the efficacy and safety of MAS063DP (ATOPICLAIR TM) in the management of atopic dermatitis in paediatric patients. Pediatric Allergy and Immunology. 2008; 19(7):619-25.
59. Veraldi S, Menter A, Innocenti M. Treatment of mild to moderate seborrhoeic dermatitis with MAS064D (Sebclair®), a novel topical medical device: Results of a pilot, randomized, double-blind, controlled trial. Journal of the European Academy of Dermatology and Venereology. 2008;22: 290–296.
60. Abramovits W, Hebert AA, Boguniewicz M, Kempers SE, Tschen E, Jarratt MT, Lucky AW, Cornelison RL, Swinyer LJ, Jones TM. Patient-reported outcomes from a multicenter, randomized, vehicle-controlled clinical study of MAS063DP (Atopiclair ^{TM}) in the management of mild-to-moderate atopic dermatitis in adults. Journal of Dermatological Treatment. 2009;19:327–332.
61. Teelucksingh S, Mackie AD, Burt D, McIntyre MA, Brett L, Edwards CR. Potentiation of hydrocortisone activity in skin by glycyrrhetinic acid. Lancet (London, England). 1990;335:1060–1063.
62. Ohuchi K, Kamada Y, Levine L, Tsurufuji S. Glycyrrhizin inhibits prostaglandin E2 production by activated peritoneal macrophages from rats. Prostaglandins and Medicine. 1981;7:457–463.
63. Shin YW, Bae EA, Lee B, Lee S, Kim J, Kim YS, Kim DH. *In vitro* and *In vivo* anti allergic effects of *Glycyrrhiza glabra* and its components. Planta Medica. 2007;73: 257–261.

64. Cho YC, Lee SH, Yoon G, Kim HS, Na JY, Choi HJ, Cho CW, Cheon SH, Kang BY. Licochalcone E reduces chronic allergic contact dermatitis and inhibits IL-12p40 production through down-regulation of NF-κB. International Immunopharmacology. 2010;10:1119–1126.
65. Kwon TK, Kim JC. *In vitro* skin permeation and anti-atopic efficacy of lipid nanocarriers containing water soluble extracts of *Houttuynia cordata*. Drug Development and Industrial Pharmacy. 2013;40:1350–1357.
66. Schempp CM, Windeck T, Hezel S, Simon JC. Topical treatment of atopic dermatitis with St. John's wort cream – a randomized, placebo controlled, double blind half-side comparison. Phytomedicine. 2003;10:31–37.
67. Sung YY, Yang WK, Lee AY, Kim DS, Nho KJ, Kim YS, Kim HK. Topical application of an ethanol extract prepared from *Illicium verum* suppresses atopic dermatitis in NC/Nga mice. Journal of Ethnopharmacology. 2012;144:151–159.
68. Sung YY, Kim YS, Kim HK. *Illicium verum* extract inhibits TNF-α- and IFN-γ-induced expression of chemokines and cytokines in human keratinocytes. Journal of Ethnopharmacology. 2012;144:182–189.
69. Matsuda H, Dai Y, Ido Y, Yoshikawa M, Kubo M. Studies on kochiae fructus. IV. Anti-allergic effects of 70% ethanol extract and its component, momordin Ic from dried fruits of *Kochia scoparia* L. Biological & Pharmaceutical Bulletin. 1997;20:1165–1170.
70. Choi YY, Kim MH, Lee JY, Hong J, Kim S-H, Yang WM. Topical application of *Kochia scoparia* inhibits the development of contact dermatitis in mice. Journal of Ethnopharmacology. 2014;154:380–385.
71. Lim H-S, Ha H, Lee H, Lee J, Lee M-Y, Shin HK. *Morus alba* L. suppresses the development of atopic dermatitis induced by the house dust mite in NC/Nga mice. BMC Complementary and Alternative Medicine. 2014;14:139.
72. Chung HC, Kim MS, Mun SY, Sa BK, Chung JY, Kim DU, Hwang JK. Effect of oral administration of nutmeg extract on American house dust mite (*Dermatophagoides farinae*) extract-induced atopic dermatitis-like skin lesions in NC/Nga mice. Food Science and Biotechnology. 2016;21:559–564.
73. Han YS, Kim MS, Hwang JK. Macelignan inhibits histamine release and inflammatory mediator production in activated rat basophilic leukemia mast cells. Inflammation. 2012;35:1723–1731.
74. Nardelli A, D'Hooghe E, Drieghe J, Dooms M, Goossens A. Allergic contact dermatitis from fragrance components in specific topical pharmaceutical products in Belgium. Contact Dermatitis. 2009;60:303–313.
75. Van den Akker TW, Roesyanto-Mahadi ID, van Toorenenbergen AW, van Joost T. Contact allergy to spices. Contact Dermatitis. 1990;22:267–272.
76. Ueda H, Yamazaki M. Anti-inflammatory and anti-allergic actions by oral administration of a perilla leaf extract in mice. Bioscience, Biotechnology, and Biochemistry. 2001;65(7):1673-1675.
77. Ueda H, Yamazaki M. Inhibition of tumor necrosis factor-alpha production by orally administering a perilla leaf extract. Bioscience, Biotechnology, and Biochemistry. 1997;61:1292–1295.
78. Heo JC, Nam DY, Seo MS, Lee SH. Alleviation of atopic dermatitis-related symptoms by *Perilla frutescens* Britton. International Journal of Molecular Medicine. 2011;28:733–737.
79. Morizawa K, Tomobe YI, Suchida M, Nakano Y, Hibino H, Tanaka Y. Dietary oils and phospholipids containing n-3 highly unsaturated fatty acids suppress 2, 4-Dinitro-1-fluorobenzene-induced contact dermatitis in mice. Journal of Japan Oil Chemists' Society. 2000;49(1):59–65,85.
80. Okazaki N, Matsunaka M, Kondo M, Okamoto K. Contact dermatitis due to beefsteak plant (*Perilla frutescens* Britton var. acuta Kudo). Skin Research. 1982;24: 250–256.
81. Kanzaki T, Kimura S. Occupational allergic contact dermatitis from *Perilla frutescens* (shiso). Contact Dermatitis. 1992;26:55–56.
82. Watanabe K, Matsuda M, Furuhashi S, Kimura T. Skin reaction induced by aldehydes for food flavoring agents. Journal of Health; 2001.
83. Kim EJ, Lee HA, Lee BS, Park SJ, Kim J. *Platycodon grandiflorus* alleviates DNCB-induced atopy-like dermatitis in NC/Nga mice. Indian Journal of Pharmacology. 2012;44:469.
84. Choi JH, Han EH, Park BH, Kim HG, Hwang YP, Chung YC, Lee YC, Jeong HG.

Platycodi radix suppresses development of atopic dermatitis-like skin lesions. Environmental Toxicology and Pharmacology. 2012;33:446–452.

85. Kim MS, Hur YG, Kim WG, Park BW, Ahn KS, Kim JJ, Bae H. Inhibitory effect of *Platycodon grandiflorum* on TH1 and TH2 immune responses in a murine model of 2,4-dinitrofluorobenzene–induced atopic dermatitis–like skin lesions. Annals of Allergy, Asthma & Immunology. 2011;106: 54–61.
86. Kim MS, Kim WG, Chung HS, Park BW. Improvement of atopic dermatitis-like skin lesions by *Platycodon grandiflorum* fermented by *Lactobacillus plantarum* in NC/Nga mice. Biological & Pharmaceutical Bulletin; 2012.
87. Park SJ, Kim YS, Kim TJ. Inhibitory effect of PG-Platycodin D on the development of atopic dermatitis-like skin lesions in ICR mice. Journal of Life Science. 2012;22: 1339–1343.
88. Choi JH, Jin SW, Han EH, Park BH, Kim HG, Khanal T, Hwang YP, Do MT, Lee H-S, Chung YC, Kim HS, Jeong TC, Jeong HG. *Platycodon grandiflorum* root-derived saponins attenuate atopic dermatitis-like skin lesions via suppression of NF-κB and STAT1 and activation of Nrf2/ARE-mediated heme oxygenase-1. Phytomedicine. 2014;21:1053–1061.
89. Choi JH, Park BH, Kim HG, Hwang YP, Han EH, Jin SW, Seo JK, Chung YC, Jeong HG. Inhibitory effect of *Psidium guajava* water extract in the development of 2,4-dinitrochlorobenzene-induced atopic dermatitis in NC/Nga mice. Food and Chemical Toxicology. 2012;50:2923–2929.
90. Han EH, Hwang YP, Choi JH, Yang JH, Seo JK, Chung YC, Jeong HG. *Psidium guajava* extract inhibits thymus and activation-regulated chemokine (TARC/CCL17) production in human keratinocytes by inducing heme oxygenase-1 and blocking NF-Ï°B and STAT1 activation. Environmental Toxicology and Pharmacology. 2011;32: 136–145.
91. Sung YY, Yoon T, Jang JY, Park SJ, Kim HK. Topical application of *Rehmannia glutinosa* extract inhibits mite allergen-induced atopic dermatitis in NC/Nga mice. Journal of Ethnopharmacology. 2011;134: 37–44.
92. Yoo KH, Seo SJ, Li K, Hong CK. Ingestion of Rhus chicken causing systemic contact dermatitis in a Korean patient. Clinical and Experimental Dermatology. 2010;35:756–758.
93. Powell SM, Barrett DK. An outbreak of contact dermatitis from *Rhus verniciflua* (*Toxicodendron vernicifluum*). Contact Dermatitis. 1986;14:288–289.
94. Park SD, Lee SW, Chun JH, Cha SH. Clinical features of 31 patients with systemic contact dermatitis due to the ingestion of Rhus (lacquer). British Journal of Dermatology. 2000;142:937–942.
95. Park DK, Lee YG, Park HJ. Extract of *Rhus verniciflua* bark suppresses 2,4-dinitrofluorobenzene-induced allergic contact dermatitis. Evidence-based Complementary and Clternative Medicine: eCAM. 2013;2013:1–11.
96. Goh FY, Upton N, Guan S, Cheng C, Shanmugam MK, Sethi G, Leung BP, Wong WSF. Fisetin, a bioactive flavonol, attenuates allergic airway inflammation through negative regulation of NF-κB. European Journal of Pharmacology. 2012; 679:109–116.
97. Lim HS, Ha H, Lee MY, Jin SE, Jeong SJ, Jeon WY, Shin NR, Sok DE, Shin HK. *Saussurea lappa* alleviates inflammatory chemokine production in HaCaT cells and house dust mite-induced atopic-like dermatitis in Nc/Nga mice. Food and Chemical Toxicology. 2014;63:212–220.
98. Kang YH, Shin HM. Inhibitory effects of *Schizandra chinensis* extract on atopic dermatitis in NC/Nga mice. Immunopharmacology and Immunotoxicology. 2011;34:292–298.
99. Lee HJ, Jo S, Ryu J, Jeong HS, Lee G, Ryu MH, Jung MH, Kim H, Kim BJ. Effects of *Schisandra chinensis* Turcz. fruit on contact dermatitis induced by dinitrofluorobenzene in mice. Mol Med Reports. 2015;12(2):2135–2139.
100. Kim H, Lee MR, Lee GS, An W-G, Cho S-I. Effect of *Sophora flavescens* Aiton extract on degranulation of mast cells and contact dermatitis induced by dinitrofluorobenzene in mice. Journal of Ethnopharmacology. 2012;142:253–258.
101. Jeong SI, Choi BM, Yun YG, Lee JW, Jang SI. A noble therapeutic approach of atopic dermatitis by development of Th2 Chemokine inhibitors from natural products: Inhibitory effect of *Sophora flavescens* extract in atopic dermatitis model mice, NC/Nga. The Korean Journal

of Oriental Medical Prescription. 2009; 2009:1–11.

102. Choi BM, Oh GS, Lee JW, Mok JY, Kim DK, Jeong SI, Jang SI. *Prenylated chalcone* from *Sophora flavescens* suppresses Th2 chemokine expression induced by cytokines via heme oxygenase-1 in human keratinocytes. Archives of Pharmacal Research. 2010;33:753–760.
103. Kim DY, Jung JA, Kim TH, Seo SW, Jung SK, Park CS. Oral administration of *Uncariae rhynchophylla* inhibits the development of DNFB-induced atopic dermatitis-like skin lesions via IFN-γ down-regulation in NC/Nga mice. Journal of Ethnopharmacology. 2009;122:567–572.
104. Choi JK, Oh HM, Lee S, Park JW, Khang D, Lee SW, Lee WS, Rho MC, Kim SH. Oleanolic acid acetate inhibits atopic dermatitis and allergic contact dermatitis in a murine model. Toxicology and Applied Pharmacology. 2013;269:72–80.
105. Ngatu NR, Okajima MK, Yokogawa M, Hirota R, Takaishi M, Eitoku M, Muzembo BA, Sabah AB, Saruta T, Miyamura M, Kaneko T, Sano S, Suganuma N. Anti-Allergic effects of *Vernonia amygdalina* leaf extracts in hapten-induced atopic dermatitis-like disease in mice. Allergology International. 2012;61:597–607.
106. Ngatu NR, Mukuamu M, Hirota R, Nangana LS, Longo-Mbenza B, Suganuma N. Severe, chronic and recalcitrant atopic dermatitis associated with *Tinea capitis*: Diagnostic approach and effects of topical *Vernonia amygdalina* Del. extracts. Annal of Phytomedicine; 2014.
107. Ngatu NR, Hirota R, Okajima MK. Efficacy of leaf extracts of *Vernonia amygdalina* Del. from central Africa on atopic eczema. Annal of Phytomedicine; 2014.
108. Collantes TM, Rho MC, Kwon HJ, Jung BG, Alfajaro MM, Kim DS, Kim HJ, Hosmillo M, Park JG, Son KY, Park SI, Kang MI, Park SJ, Lee SW, Lee WS, Cho KO. Azuki bean (*Vigna angularis*) extract inhibits the development of experimentally induced atopic dermatitis-like skin lesions in NC/Nga mice. Food Chemistry. 2012; 132:1269–1275.
109. Chan YC, Tay YK, Sugito TL, Boediardja SA, Chau DD, Nguyen KV, Yee K-C, Alias M, Hussein S, Dizon MV, Roa F, Chan Y-H, Wananukul S, Kullavanijaya P, Singalavanija S, Cheong WK. A study on the knowledge, attitudes and practices of Southeast Asian dermatologists in the management of atopic dermatitis. Annals of the Academy of Medicine, Singapore. 2006;35:794–803.
110. Baron ED, Barzilai D, Johnston G, Kawashima M, Takigawa M, Nakagawa H, Graham-Brown RA, Stevens SR. Atopic dermatitis management: Comparing the treatment patterns of dermatologists in Japan, U.S.A. and U.K. British Journal of Dermatology. 2002;147:710–715.
111. Sirikudta W. Moisturizers for patients with atopic dermatitis: An overview. Journal of Allergy & Therapy. 2013;04:1–6.
112. Matsuda H. Development of atopic dermatitis-like skin lesion with IgE hyperproduction in NC/Nga mice. International Immunology. 1997;9:461–466.
113. Mansouri Y, Guttman-Yassky E. Immune pathways in atopic dermatitis, and definition of biomarkers through broad and targeted therapeutics. Journal of Clinical Medicine. 2015;4:858–873.
114. Yamanaka K, Mizutani H. The role of cytokines/chemokines in the pathogenesis of atopic dermatitis. Current problems in Dermatology. 2011;41:80–92.
115. Peng W, Novak N. Pathogenesis of atopic dermatitis. Clinical and experimental allergy: Journal of the British Society for Allergy and Clinical Immunology. 2015;45: 566–574.
116. Rios JL, Bas E, Recio MC. Effects of natural products on contact dermatitis. Current Medicinal Chemistry - Anti-Inflammatory & Anti-Allergy Agents. 2005; 4:65–80.
117. Martins S, Mussatto SI, Martínez-Avila G, Montañez-Saenz J, Aguilar CN, Teixeira JA. Bioactive phenolic compounds: Production and extraction by solid-state fermentation. A review. Biotechnology Advances. 2011;29:365–373.
118. Pandey A. Solid-state fermentation. Biochemical Engineering Journal. 2003;13: 81–84.
119. Nghĩa Nam. Giải pháp phát triển thị trường dược liệu [Implications for the development of pharmaceutical materials marker]. Nhân Dân Newspaper; 2016.
120. Ministry of Health. Danh sách các cơ sở và cây dược liệu đã được cấp phiếu tiếp nhận công bố sản xuất dược liệu GACP - WHO - Đợt 1 (01/6/2016) [List of manufacturers and herbal medicines in compliance with GACP-WHO (01/06/2016)]. ydct.moh.gov. vn.; 2016.

121. Danh sách 174 doanh nghiệp ngành dược đạt chứng nhận GMP-WHO [List of 174 pharmaceutical manufacturers in compliance with GMP-WHO] Available:http://gmp.com.vn/danh-sach-174-doanh-nghiep-nganh-duoc-dat-chung-nhan-gmp-who.htm
122. World Health Organization. WHO guidelines for assessing quality of herbal medicines with reference to contaminants and residues. 2008;2008:1–118.
123. Medicinal Plant Specialist Group. International Standard for Sustainable Wild Collection of Medicinal and Aromatic Plants (ISSC-MAP). Bundesamt fur Natur-schutz BfN, MPSGSSCIUCN, WWF Germany, and TRAFFIC, Bonn, Gland, Frankfurt, and Cambridge BfN-Skripten; 2007.
124. Mosihuzzaman M, Choudhary MI. Protocols on safety, efficacy, standardization, and documentation of herbal medicine (IUPAC Technical Report). Pure and Applied Chemistry. 2008;80:1–36.

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